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Original Article

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Prevalence of Inflammatory Bowel Disease Unclassified, as Estimated Using the Revised Porto Criteria, among Korean Pediatric Patients with Inflammatory Bowel Disease

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ABSTRACT

Purpose: Few studies have reported the prevalence of inflammatory bowel disease unclassified (IBDU) among Korean pediatric IBD (PIBD) population. To address this gap, we used two tertiary centers and nationwide population-based healthcare administrative data to estimate the prevalence of Korean pediatric IBDU at the time of diagnosis.
Methods: We identified 136 patients aged 2–17 years with newly diagnosed IBD (94 Crohn's disease [CD] and 42 ulcerative colitis [UC]) from two tertiary centers in Korea between 2005 and 2017. We reclassified these 136 patients using the revised Porto criteria. To estimate the population-based prevalence, we analyzed Korean administrative healthcare data between 2005 and 2016, which revealed 3,650 IBD patients, including 2,538 CD and 1,112 UC. By extrapolating the reclassified results to a population-based dataset, we estimated the prevalence of PIBD subtypes.
Results: Among the 94 CD, the original diagnosis remained unchanged in 93 (98.9%), while the diagnosis of one (1.1%) patient was changed to IBDU. Among the 42 UC, the original diagnosis remained unchanged in 13 (31.0%), while the diagnoses in 11 (26.2%), 17 (40.5%), and one (2.4%) patient changed to atypical UC, IBDU, and CD, respectively. The estimated prevalences of CD, UC, atypical UC, and IBDU in the Korean population were 69.5%, 9.4%, 8.0%, and 13.1%, respectively.
Conclusion: This study is the first in Korea to estimate the prevalence of pediatric IBDU. This prevalence (13.1%) aligns with findings from Western studies. Large-scale prospective multicenter studies on PIBDU are required to examine the clinical features and outcomes of this condition.

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The authors have no financial conflicts of interest.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal (GI) tract that typically includes Crohn's disease (CD) and ulcerative colitis (UC). However, certain cases cannot be readily classified as CD or UC based on clinical, endoscopic, radiological, and pathological criteria. Thus, a postcolectomy specimen-based pathological diagnosis was traditionally employed as the criterion for diagnosing indeterminate colitis in a narrow sense. Currently, even without a colectomy specimen, the term "IBD unclassified (IBDU)" has been introduced in a broad sense [1]. IBDU is not a misclassification but rather a true overlap of diagnoses within the spectrum of phenotypes between UC and Crohn's [2-5]. As the prevalence of pediatric IBD (PIBD) has increased, the development of accurate diagnostic criteria and subtype classification is also increasingly important [6-8].

To meet the need for establishing objective and accurate diagnoses of PIBD, the Porto criteria were introduced in 2005 and enabled doctors to make objective diagnoses and classify PIBD [9]. Subsequently, the revised Porto criteria published in 2014 were used to not only diagnose PIBD but also to classify IBD subtypes, including CD, UC, and IBDU, based on the Paris classification through an evidence-based approach [9,10]. In 2017 and 2020, the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) issued revised and simplified criteria for PIBD diagnosis and subtype classification. These criteria consisted of 19 items and categorized PIBD into CD, colonic CD, UC, atypical UC, and IBDU. These criteria have enabled pediatric gastroenterologists to make precise and objective clinical assessments [11].

Although the prevalence of PIBD in Asia [12] and South Korea [8] has been rapidly increasing, few studies have investigated PIBD subtype classification in Asian populations. Among these studies is a prospective multicenter study in Japan aimed at classifying and revealing PIBD subtypes [13]. However, no studies in Korea have focused on PIBD subtype classification, including the prevalence of IBDU. Therefore, we conducted the present population-based study to estimate the prevalence of IBD subtypes in Korean patients with PIBD.

MATERIALS AND METHODS

Patients

This study on PIBD re-classification included a total of 136 pediatric patients (94 with CD and 42 with UC) aged 2–17 years who underwent complete initial evaluations. The patients were treated between January 2005 and December 2017 at two centers: Asan Medical Center Children's Hospital and Seoul National University Children's Hospital. Patients with monogenic IBD or suspected monogenic diseases were excluded from the study. Only patients who met 17 pretreatment criteria required by the revised Porto criteria [11], including clinical manifestations, upper and lower endoscopic findings, and radiological and histological data, were included.

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All patients had undergone serological testing for anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) (**Supplementary Data 1**), as well as esophagogastroduodenoscopy (EGD) and ileocolonic fiberscopy (CFS). Small bowel evaluation was performed using computed tomography (CT), magnetic resonance enterography (MRE), or capsule endoscopy (**Supplementary Data 2**). Biopsies were obtained from multiple sites in the terminal ileum and colon. Stomach and duodenal samples were collected based on mucosal condition. Finally, two pathologists at each center reviewed the slides twice using defined criteria (**Supplementary Data 3**) [14-19].

To determine the prevalence of PIBD subtypes, data from 3,650 pediatric patients aged 2–17 years were analyzed, including 2,538 patients with CD and 1,112 with UC. These data were obtained from the National Health Insurance Service (NHIS) gathered between 2005 and 2016. IBD was diagnosed using the International Classification of Diseases, 10th revision (ICD-10) codes and previously validated algorithms [8].

The primary objective of this study was to estimate the prevalence of each IBD subtype in Korean patients with PIBD, including those with IBDU. The secondary objective was to identify the factors contributing to a shift in diagnosis from CD or UC to IBDU. The study was approved by the ethical committe of the Asan Mecial Center Institutinal Review Board (no. S2018-2487-0001) and the Institutional Review Board at Seoul National University Hospital (no. 2012-163-1184).

Statistical analysis

Between 2005 and 2017, we assessed the pediatric cases of CD and UC in the two centers. We tallied the instances and frequencies of classes 2 and 3 according to the revised Porto criteria. These were then adjusted to estimate the expected prevalence with a 95% confidence interval (CI) for a nationwide population-based cohort between 2005 and 2016 using the NHIS data. Finally, we compared the expected prevalence of Korean pediatric IBDU (PIBDU) with the Porto group data using a two-sided z-test.

RESULTS

Patients

Among patients with CD, the male-to-female ratio was 2.8:1 (69 males vs. 25 females), and the median age at diagnosis was 12.9±2.7 years. The median follow-up duration was 2.3±1.3 years. Among patients with UC, the male-to-female ratio was 1.21:1 (23 males vs. 19 females), and the median age at diagnosis was 13.4±2.3 years. The median follow-up duration was 4.5±4.3 years (**Table 1**).

Reclassification results based on the revised Porto criteria

Among the 94 patients with CD, the original diagnosis remained unchanged in 73 (98.9%) patients, while the diagnosis of one (1.1%) patient was changed to PIBDU. Among the 42 patients with UC, the original diagnosis remained unchanged in 13 (31.0%) patients, meanwhile, the diagnoses of 11 (26.2%), 17 (40.5%), and one (2.4%) patients were changed to atypical PUC, PIBDU, and PCD, respectively. The factors associated with each alteration are listed in **Table 2** [10,20].

Estimated prevalence of PIBD subtypes in the Korean population

The estimated prevalence rates, when extrapolated to the Korean NHIS data of 2,538 pediatric patients with CD and 1,112 with UC, were 69.5% (95% CI, 61.0–76.6%) for CD, 9.4% (95% CI, 4.5–14.3%) for UC, 8.0% (95% CI, 3.43–12.5%) for atypical UC, and 13.1% (95% CI, 7.4–18.7%) for IBDU (**Table 3**).

Table 1. Clinical characteristics and reclassification of patients with pediatric inflammatory bowel disease, 2005–2017

	IBD	UC	CD
No. of patients	136	42	94
Sex, male	92 (67.6)	23 (54.8)	69 (73.4)
Median age at initial diagnosis (yr)	13.1±2.6	13.4±2.3	12.9±2.7
Median follow-up duration (yr)	3.0±2.2	4.5±4.3	2.3±1.3
Reclassification			
UC	13 (9.6)	13 (31.0)	0 (0.0)
Atypical UC	11 (8.1)	11 (26.2)	0 (0.0)
IBDU	18 (13.2)	17 (40.5)	1 (1.1)
Colonic CD	0 (0.0)	0 (0.0)	0 (0.0)
CD	94 (69.1)	1 (2.4)	93 (98.9)

Values are presented as number only, number (%), or mean±standard deviation.
IBD: inflammatory bowel disease, UC: ulcerative colitis, CD: Crohn's disease, IBDU: inflammatory bowel disease unclassified.

Table 2. Factors related to the change in diagnosis based on the revised Porto criteria algorithm

	Feature		PUC to			PCD to
			Atypical PUC	PIBDU	PCD	PIBDU
Class 1	1 (1-1)	At least one well-formed granuloma anywhere in the GI tract, remote from ruptured crypts	0	0	1	0
	2 (1-2)	At least one of the following: deep ulcerations, cobblestone appearance, or stenosis anywhere in the small bowel or UGI tract (excluding the stomach)	0	0	0	0
	3 (1-3)	Fistulizing disease (internal or perianal)	0	0	0	0
	4 (1-4)	Thickened jejunal or ileal bowel loops on radiology or other evidence of significant small bowel inflammation on capsule endoscopy not compatible with backwash ileitis	0	0	0	0
	5 (1-5)	Any ileal inflammation in the presence of a normal cecum (i.e., incompatible with backwash ileitis)	0	0	0	0
Class 2	6 (2-6)	Macroscopically and microscopically normal-appearing skip lesions in untreated IBD (excluding rectal sparing and cecal patch)	0	3	-	1
	7 (2-7)	Complete (macroscopic and microscopic) rectal sparing	0	1	-	1
	8 (2-8)	Macroscopically normal colon in between inflamed mucosa but with microscopic inflammation (i.e., relative patchiness)	0	0	-	0
	9 (2-9)	Significant growth delay (height velocity<minus 2SD) not explained by other causes (e.g., celiac disease, prolonged steroids, or growth hormone deficiency)	0	1	-	0
	10 (2-10)	Transmural inflammation of the colon in the absence of severe colitis	0	0	-	0
	11 (2-11)	Presence of any small and shallow ulcers in the small bowel and esophagus, or ≥5 small and shallow ulcers in the stomach or colon, with background normal mucosa, not explained by other causes (e.g. Helicobacter pylori, NSAIDs, and celiac disease)	0	3	-	0
	12 (2-12)	Positive ASCA in the presence of negative pANCA	0	3	-	0
	13 (2-13)	Reverse gradient of mucosal inflammation (proximal>distal [except rectal sparing])	0	1	-	1
	14 (2-14)	Deep ulcerations or severe cobblestoning in the stomach or scalloping of the duodenum, not explained by other causes (e.g., celiac disease, NSAIDs, H. pylori)	0	0	-	0
Class 3	15 (3-15)	Focal chronic duodenitis on histology	0	1	-	0
	16 (3-16)	Focal active colitis on histology in more than one biopsy	0	0	-	1
	17 (3-17)	Several (<5) aphthous ulcerations in the colon or stomach	1	3	-	0
	18 (3-18)	Non-bloody diarrhea	2	1	-	1
	19 (3-19)	Focally enhanced gastritis on histology	2	3	-	0

Values are presented as number only.
PUC: pediatric ulcerative colitis, PCD: pediatric Crohn's disease, PIBDU: pediatric inflammatory bowel disease unclassified, GI: gastrointestinal, UGI: upper gastrointestinal, IBD: inflammatory bowel disease, SD: standard deviation, NSAIDs: nonsteroidal anti-inflammatory drugs, ASCA: anti-*Saccharomyces cerevisiae* antibodies, pANCA: perinuclear antineutrophil cytoplasmic antibodies.
Adapted from Levine et al. (J Pediatr Gastroenterol Nutr 2014;58:795-806) [10]. Adapted from Birimberg-Schwartz et al. (J Crohns Colitis 2017;11:1078-84) [20].

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Table 3. Observed pediatric inflammatory bowel disease cases and estimated Korean pediatric inflammatory bowel disease subtype classifications

	Observed PIBD cases at AMC and SNUH		Estimated PIBD from the NHIS		
	CD	UC	CD	UC	Total PIBD (%, 95% CI)
Total	94	42	2,538	1,112	3,650
Changed to PUC	0 (0.0%)	13 (31.0%)	0 (0.0%)	345 (31.0%)	344 (9.4, 4.5–14.3)
Changed to atypical UC	0 (0.0%)	11 (26.2%)	0 (0.0%)	291 (26.2%)	291 (8.0, 3.4–12.5)
Changed to PCD	93 (98.9%)	1 (2.4%)	2,511 (98.9%)	26 (2.3%)	2,537 (69.5, 61.0–76.6)
Changed to PIBDU	1 (1.1%)	17 (40.5%)	27 (1.1%)	450 (40.5%)	477 (13.1, 7.4–18.7)

PIBD: pediatric inflammatory bowel disease, AMC: Asan Medical Center, SNUH: Seoul National University Hospital, NHIS: National Health Insurance Service, CD: Crohn's disease, UC: ulcerative colitis, CI: confidence interval, PUC: pediatric ulcerative colitis, PCD: pediatric Crohn's disease, PIBDU: pediatric inflammatory bowel disease unclassified.

Factors related to the changes in diagnosis to PIBDU

Among patients with CD, the factors leading to a change in diagnosis to IBDU included macroscopically and microscopically normal findings in the treatment-naïve skipped mucosa (n=1), complete rectal sparing (n=1), a reverse gradient of mucosal inflammation (n=1), focal active colitis on histology in more than one biopsy sample from a macroscopically inflamed site (n=1), and non-bloody diarrhea (n=1).

Among patients with UC, the factors leading to a change in diagnosis to IBDU were macroscopically and microscopically normal-appearing skip lesions in untreated IBD (n=3); complete rectal sparing (n=1); significant growth delay (n=1); small ulcers in the small bowel and esophagus, or more than five small ulcers in the stomach or colon, with normal background mucosa (n=3); ASCA positivity without pANCA positivity (n=3); a reverse gradient of mucosal inflammation (n=1); focal chronic duodenitis on multiple biopsies (n=1); several (<5) aphthous ulcerations in the colon or stomach (n=3); non-bloody diarrhea (n=1); and focally enhanced gastritis (n=3) (**Table 4**).

DISCUSSION

This is the first study to estimate the prevalence of PIBDU in pediatric patients with IBD in Korea. We retrospectively applied the revised Porto criteria to multicenter data from tertiary medical centers in Korea collected between 2005 and 2017, a period when the revised Porto criteria were not available in Korea. During this period, most patients diagnosed with IBD were categorized as having either CD or UC, with only a few instances of indeterminate colitis being identified, as surgical pathology was required for diagnosing indeterminate colitis at that time. Therefore, analyzing data from patients during this period provides an accurate prediction of IBDU among Korean patients with PIBD.

Understanding IBDU is increasingly crucial for a comprehensive understanding of IBD, primarily because IBDU prevalence is rising over time [20,21]. Studies have demonstrated increases from 9% to 14% between 2006 and 2014 in Western populations [21] and a nearly ten-fold increase in Singapore [22,23]. In addition, PIBDU is more prevalent than adult-onset IBDU, with prevalence rates of 12.7% among children compared with 6.0% in adults (p<0.001) [24,25]. PIBDU is estimated to affect approximately 5–25% of all pediatric patients with IBD [1,4,5,25–28]. Consequently, the significance of understanding PIBDU can be emphasized.

The predicted prevalence of IBDU in Korean children in the present study was approximately 13.1%, which is consistent with previously reported PIBDU prevalence rates ranging from 5% to 25% [1,4,5,25–28]. Additionally, in the present study, the frequency of reclassification

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Table 4. Factors related to the change in diagnosis to inflammatory bowel disease unclassified

	Observed data from two centers (AMC+SNUH)	
	CD	UC
Total	94	42
Observed/estimated IBDU, n (%)	1 (1.1)	17 (40.5)
Feature distribution in IBDU		
2-6	1	3
2-7	1	1
2-8	0	0
2-9	0	1
2-10	0	0
2-11	0	3
2-12	0	3
2-13	1	1
2-14	0	0
3-15	0	1
3-16	1	0
3-17	0	3
3-18	1	1
3-19	0	3

AMC: Asan Medical Center, SNUH: Seoul National University Hospital, IBDU: inflammatory bowel disease unclassified, CD: Crohn's disease, UC: ulcerative colitis, 2-6: Macroscopically and microscopically normal-appearing skip lesions in untreated inflammatory bowel disease (IBD) (excluding rectal sparing and cecal patch), 2-7: Complete (macroscopic and microscopic) rectal sparing, 2-8: Macroscopically normal colon in between inflamed mucosa but with microscopic inflammation (i.e., relative patchiness), 2-9: Significant growth delay (height velocity<minus 2 standard deviations [SD]) not explained by other causes (e.g., celiac disease, prolonged steroid use, or growth hormone deficiency), 2-10: Transmural inflammation of the colon in the absence of severe colitis, 2-11: Presence of any small and shallow ulcers in small bowel and esophagus, or ≥5 small and shallow ulcers in stomach or colon, with background normal mucosa, not explained by other causes (e.g. *Helicobacter pylori*, nonsteroidal anti-inflammatory drugs [NSAIDs], and celiac disease), 2-12: Positive anti-*Saccharomyces cerevisiae* antibodies (ASCA) in the presence of negative perinuclear antineutrophil cytoplasmic antibodies (pANCA), 2-13: Reverse gradient of mucosal inflammation (proximal>distal [except for rectal sparing]), 2-14: Deep ulcerations or severe cobblestoning of the stomach or scalloping of the duodenum, not explained by other causes (e.g., celiac disease, NSAIDs, *H. pylori*), 3-15: Focal chronic duodenitis on histology, 3-16: Focal active colitis on histology in more than one biopsy, 3-17: Several (<5) aphthous ulcerations in the colon or stomach, 3-18: Non-bloody diarrhea, 3-19: Focally enhanced gastritis on histology.

from UC to IBDU was higher than that from CD to IBDU (40.5% vs. 1.1%). This finding aligns with the notion that IBDU more closely resembles UC than CD in terms of clinical features [23,29]. Furthermore, considering the different prevalence trends observed between CD and UC in Korea [8], the actual prevalence of IBDU may be underestimated in the present study. Presently, the reported prevalence of PUC in Korea is lower than that of PCD, unlike in Western populations [30,31], where the ratio of pediatric UC to CD ranges from approximately 1:1 to 1:1.5, compared with 1:2.5 in Korean studies [32,33].

Intriguingly, the differences in the frequency and patterns of features within classes 2 and 3 led to a change in the diagnosis of IBDU in Korean patients with PIBDU compared with European patients with PIBDU. These disparities may be attributed to ethnic variations. As no published studies have elucidated the characteristic differences and potential causes of variations between Asian and Western patients, future larger-scale studies are required. Thus, the present study plays a pivotal role in providing comprehensive insights into racial disparities among Korean and Western patients with PIBD, particularly concerning PIBDU, based on the revised Porto criteria (**Table 4**).

A previous report suggested that IBDU is a distinct disease entity rather than merely existing within an ambiguous spectrum between CD and UC [20,23]. This notion is supported by evidence indicating that the frequency of adult IBDU remained relatively consistent at approximately 10% throughout the study period despite the implementation of new

diagnostic methods [20,34]. However, in Korea, data on the prevalence of adult IBDU or longitudinal PIBDU follow-up results are lacking, both of which are essential for confirming the hypothesis that the prevalence of PIBDU continues into adulthood. Thus, additional studies are needed to explore the natural course and future behavior of patients, who were thoroughly examined in this study with a complete diagnostic workup, and ensure adherence to the diagnostic algorithm to minimize the risk of misdiagnosis due to inadequate evaluations. This will allow us to determine whether these patients maintain their PIBDU diagnosis over time or if the transition to other diseases occurs. Additionally, the results of the present study provide an opportunity to investigate the differences in PIBDU response to IBD treatment as well as PIBDU prognosis and outcome in Korea.

Our study has several limitations. This was a retrospective analysis conducted at tertiary medical centers and only included patients who completed all evaluation workup modalities and those with moderate-to-severe conditions. Consequently, patient selection bias was possible. Additionally, this study, conducted based on diagnoses at the time of diagnosis, lacks long-term follow-up outcomes. Therefore, future research should be conducted to include long-term follow-up results. Therefore, we extrapolated the calculated data to the NHIS database.

Estimating the prevalence of PIBDU in the Korean population is of paramount importance to meet the increasing demand for a comprehensive understanding of PIBD. Now, we can enhance our understanding of PIBDU by longitudinally tracking and examining the disease course and its varied behavior based on the type of intervention, including medication, among the patients with PIBDU identified in this study. Prospective large-scale population-based studies are needed to broaden our understanding of PIBDU and its relationship with overall PIBD in South Korea.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1

Measurement of anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA)

Supplementary Data 2

Imaging studies

Supplementary Data 3

Pathologic criteria

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