의학석사 학위논문

국민건강보험 빅데이터를 이용한 초조기발병 염증성 장질환의 전국 인구 기반 역학 연구 (2005-2016)

Nationwide Population-Based Epidemiologic Study of Very-Early Onset IBD Using Health-Care Big Data, 2005-2016

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이 논문을 의학석사 학위 논문으로 제출함

2021년 2월

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Abstract

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Title: Nationwide Population-Based Epidemiologic Study of Very-Early Onset IBD Using Health-Care Big Data, 2005-2016

Purpose: Children diagnosed with IBD under 6 years, called very early onset (VEO)-IBD, represent atypical manifestations including isolated and extensive colonic involvement and poor response to the conventional therapies compared to older children. We aimed to investigate the incidence and changes in the incidence rate of IBD over time in Korea in each age group including VEO-IBD using the National Health Insurance Service (NHIS) database.

Methods: We analyzed data from the NHIS of the Korean government and the Korean Statistical Information Service from 2005 to 2016. New incident cases of pediatric IBD aged under 17 were retrospectively identified according to validated diagnostic algorithm. In the prior study, the combination of the experience of colonoscopy, use of the IBD-specific medication at least 3 months, and the ICD-10 and RID (Rare and intractable disease) codes for CD and UC was chosen as the best diagnostic algorithm. We divided the age at diagnosis into infantile (0-1 year), VEO (2-6 years), early onset (EO, 6-9 years), and PIBD (10-16 years). Study region was divided into metropolitan and non-metropolitan areas.

Results: From 2005 to 2016, 2,763 children (1833 males and 930 females) were diagnosed with IBD before the age of 17 years. Among them, 43 (1.6%) were diagnosed before the age of 6. In the overall population, the incidence of IBD over the entire study period (2005-2016) was $2.248/10^5$. In each age group, the incidence of IBD over the entire study period was $0.124/10^5$, $0.132/10^5$, $0.347/10^5$, and $4.888/10^5$, respectively. The overall incidence rate of pediatric IBD increased from $1.001/10^5$ in 2005 to $3.701/10^5$ in 2016. In the infantile and VEO group, the incidence remained stable during the whole period, whereas the incidence of EO-IBD and PIBD was increased. There was no difference in the incidence rates of CD and UC between metropolitan and non-metropolitan areas except the incidence

rate of CD in the PIBD group.

Conclusion: We found that the incidence of PIBD and EO-IBD increased in Korea whereas the incidence of infantile- and VEO-IBD remained stable. When comparing the incidence rates of VEO-IBD of metropolitan and non-metropolitan areas, there was no significant difference between regions.

Key Words: VEO-IBD, incidence rate

차 례

표 및 그림 차례

Introduction

The incidence of pediatric inflammatory bowel disease (PIBD) has been increasing worldwide [1, 2]. Children diagnosed at a very young age represent different phenotypes compared to older children [1-4]. Ulcerative colitis (UC) and IBD-undetermined (IBD-U) were more common at diagnosis, isolated colonic diseases are more common in Crohn's disease (CD), pancolitis is more common in UC, and rectal bleeding is common in young children [1-5]. Based on these differences, Paris modification of the IBD Montreal classification divided the age at diagnosis into A1a (younger than 10 years) and A1b (older than 10 years). In addition, some physicians have suggested very early onset (VEO)-IBD (younger than 6 years) as a clinically distinct form [6]. Because of atypical manifestations of VEO-IBD including extensive colonic involvement in CD and poor response to the conventional therapies [5, 6], further studies to investigate the pathogenesis of VEO-IBD and new treatment strategies are needed.

Recent studies in Canada and France reported the incidence of VEO-IBD and the temporal trend of the incidences using population-based data [1, 2]. Several epidemiologic studies in East-Asia have assessed the incidence of PIBD and included children under 6 years, but did not analyzed temporal trend of the incidence of IBD in this age group separately nor include the whole nation-wide pediatric population [7, 8]. We aimed to investigate the incidence and changes in the incidence rate of IBD over time in Korea in each age group including VEO-IBD using the National Health Insurance Service (NHIS) database. In addition, we compared the outcomes between metropolitan and non-metropolitan areas.

Method

Patient population and data collection

We analyzed data from the National Health Insurance Service (NHIS) of the Korean government and the Korean Statistical Information Service from 2002 to 2017, which includes medical information of all Korean patients. New incident cases of pediatric IBD aged under 17 were retrospectively identified according to validated diagnostic algorithm. We analyzed the data using washout periods of three year before and one year after of the study period

For detailed analysis, we divided the data into four groups according to the age of the patients; Infantile was defined as 0-1 year of age, VEO was defined as 2-5 years of age, EO was defined as 6-9 years of age, and PIBD was defined as 10-16 years of age.

Study region was divided into metropolitan and non-metropolitan areas. Metropolitan areas included Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan. Non-metropolitan areas included Gyeonggi-do, Gangwon-do, Chungcheongbuk-Do, Chungcheongnam-Do, Jeollanam-do, Jeollabuk-do, Gyeongsangbuk-do, Gyeongsangnam-do, and Jeju-do.

Approval was obtained from the Institutional Review Board of Asan Medical Center (2018-1577).

Diagnostic algorithm development and validation

We used the health administrative data from NHIS including age, sex, treatment, medication, procedures such as endoscopy, and billing claims. Diagnosis codes for CD and UC were referenced from the 6th and 7th Korean Classification of Disease (KCD) which modified the 10th International Classification of Diseases (ICD). The rare and intractable disease (RID) codes were used which were established to provide national support for the people with RID including IBD.

To develop the diagnostic algorithm for identifying the people with IBD, we assessed the accuracy of the combination of ICD-10 codes (K50 for CD and K51 for UC), RID codes (V130 for CD and V131 for UC), prescription of IBD-specific medications, and diagnostic procedures. Diagnosis codes for CD and UC were used when the ICD-10 and RID codes were matched and people with code

for both CD and UC were excluded. The date of diagnosis was defined as the initial date when the ICD-10 code for CD or UC was registered. Diagnostic procedures included colonoscopy or sigmoidoscopy performed within a year before and three months after diagnosis. The IBD-specific medications included 5-aminosalicylic acid (5-ASA), immunomodulators (methotrexate, azathioprine, or 6-mercaptopurine), and anti-tumor necrosis factor drugs (infliximab or adalimumab) prescribed only after the diagnosis codes were registered.

Finally, the most accurate combination which produced the closest results to the reference incidences in previous population-based data was selected. The reference incidences were verified in a prior study [9] which was regional population-based study of Kangdong-Songpa district of Seoul. As a result, the combination of the experience of colonoscopy, use of the IBD-specific medication at least 3 months, and the ICD-10 and RID codes for CD and UC was chosen as the best diagnostic algorithm.

Statistical analyses

Incidence rates were calculated as the number of incident cases divided by the population at risk. Age- and sex-adjusted annual incidence rates per 100,000 population were determined in the overall population and each age subgroups for each year of the study period (2005-2016). Korean population data for calculating incidence and standardization were referred from the KOrean Statistical Information Service (KOSIS). The incidence rates were directly standardized to the 2017 Korean population.

Temporal trends of incidence rate over time and comparison between metropolitan and non-metropolitan areas were analyzed using linear Poison regression analysis. Chi-square test was used to compare qualitative variables between age groups or genders.

Statistical analyses were performed using SPSS version 24th. Statistical significance was accepted at p value of < 0.05.

Results

Incidence rates and temporal trend

From 2005 to 2016, 2,763 children (1833 males and 930 females) were diagnosed with IBD before the age of 17 years. Among them, 43 (1.6% of all pediatric IBD cases) were diagnosed before the age of 6 [VEO-IBD]. (Figure 1, Table 1)

In the overall population, the incidence of IBD over the entire study period (2005-2016) was $2.248/10^5$. In the infantile group, the incidence of IBD over the entire study period was $0.124/10^5$ including $0.088/10^5$ for CD and $0.036/10^5$ for UC. In the VEO group, the incidence of IBD over the entire study period was $0.132/10^5$ including $0.084/10^5$ for CD and $0.048/10^5$ for UC. In the EO and PIBD group, the incidence of IBD was $0.347/10^5$ and $4.888/10^5$ respectively, during the same period.

The overall incidence rate of pediatric IBD increased from $1.001/10^5$ in 2005 to $3.701/10^5$ in 2016 (Table 2, Figure 2). In the infantile ($0.227/10^5$ in 2005 and $0.000/10^5$ in 2016, p=0.611) and VEO group ($0.192/10^5$ in 2005 and $0.268/10^5$ in 2016, p=0.17), the incidence remained stable during the whole period. On the other hand, the incidence rates of EO-IBD ($0.079/10^5$ in 2005 and $0.683/10^5$ in 2016, p=0.022) and PIBD ($2.052/10^5$ in 2005-2008 and $7.744/10^5$ in 2016, p <0.001) were increased (Table 2, Figure 2).

In subgroup analysis of CD and UC, the incidence rate of CD was increased in PIBD and remained stable in infantile, VEO, and EO groups. The incidence rates of UC were increased over time in EO and PIBD group, whereas the incidence rates remained stable in infantile and VEO group as shown in IBD (Table 2, Figure 3).

Figure 1. Patient number and proportion of infantile, VEO, EO, and PIBD group

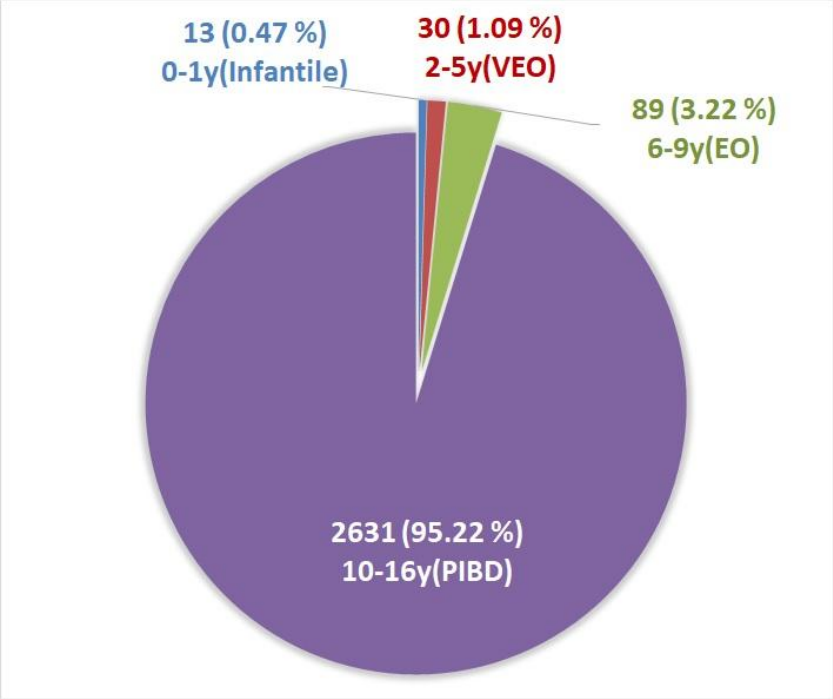


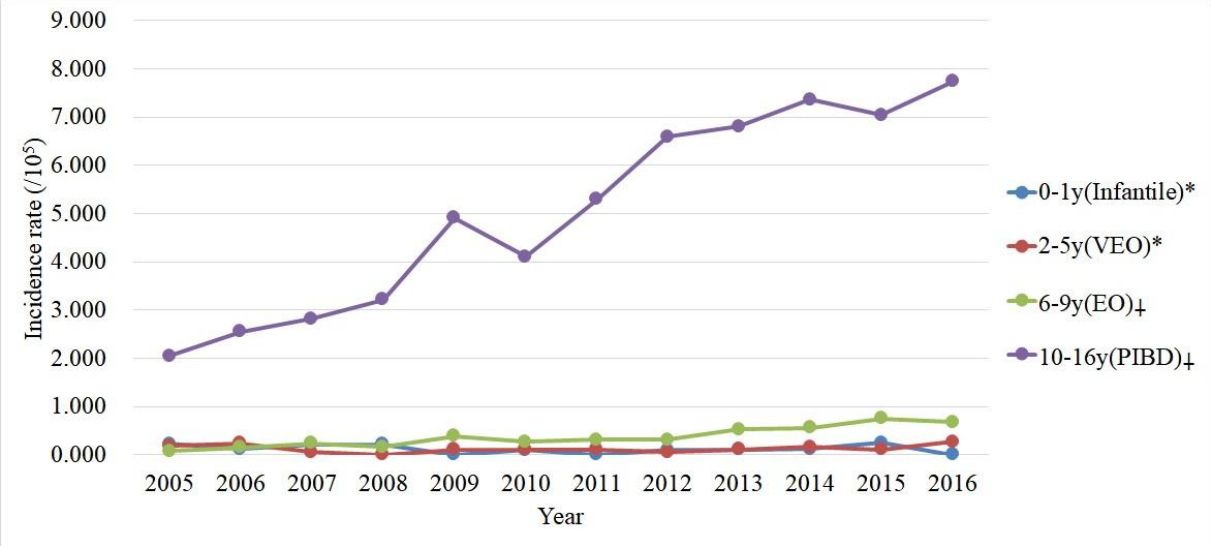
Table 1. Comparison of CD and UC cases according to age groups and gender

Variables	**IBD(%), N=2763(100%)**	**CD(%), N= 1952(71%)**	**UC(%) N= 811(29%)**	CD:UC ratio	*P* value
Age at diagnosis (year)					
0-1(infantile)	13	9 (69%)	4 (31%)	2.25:1	
2-5(VEO)	30	19 (63%)	11 (37%)	1.73:1	0.004
6-9(EO)	89	48 (54%)	41 (46%)	1.17:1	
10-16(PIBD)	2631	1876 (71%)	755 (29%)	2.48:1	
Gender					
Males	1833	1386 (76%)	447 (24%)	3.10:1	< 0.001
Females	930	566 (61%)	364 (31%)	1.55:1	

Table 2. Age- and sex- standardized incidence rates of IBD, CD, and UC from 2005 to 2016

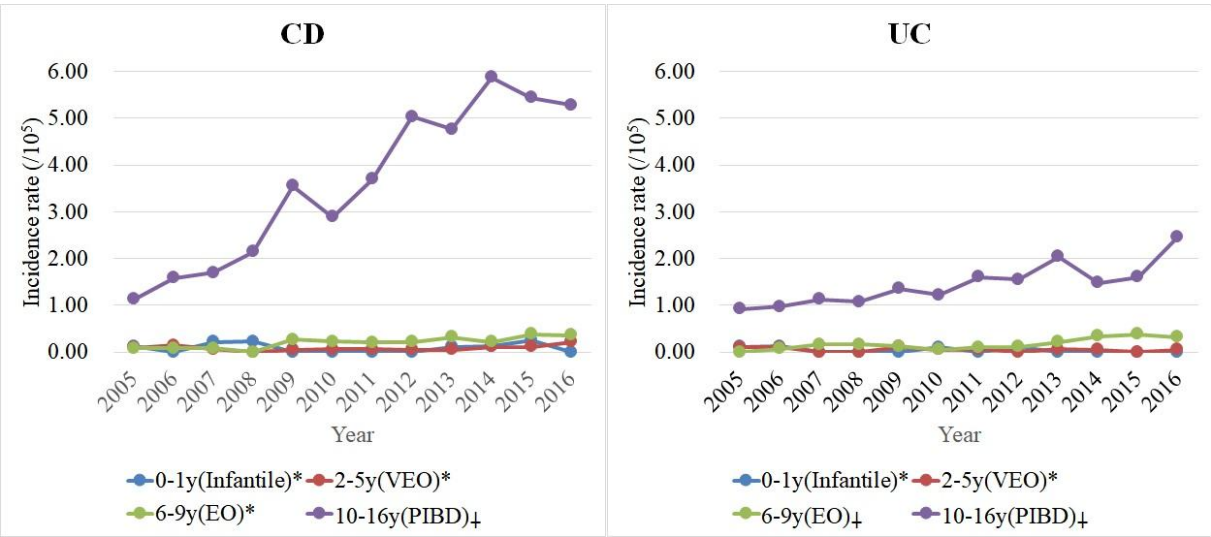
Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2005-2016	P value
All ages														
IBD	1.001	1.248	1.354	1.497	2.330	1.931	2.466	3.042	3.204	3.472	3.372	3.701	2.248	<0.001
CD	0.542	0.738	0.790	0.953	1.619	1.320	1.668	2.251	2.170	2.643	2.501	2.431	1.578	<0.001
UC	0.447	0.492	0.546	0.521	0.672	0.581	0.762	0.736	0.986	0.766	0.810	1.210	0.670	<0.001
0-1y(infantile)														
IBD	0.227	0.127	0.220	0.221	0.000	0.102	0.000	0.099	0.111	0.124	0.248	0.000	0.124	0.611
CD	0.117	0.000	0.220	0.221	0.000	0.000	0.000	0.000	0.111	0.124	0.248	0.000	0.088	0.844
UC	0.110	0.127	0.000	0.000	0.000	0.102	0.000	0.099	0.000	0.000	0.000	0.000	0.036	0.243
2-5y(VEO)														
IBD	0.192	0.244	0.056	0.000	0.111	0.108	0.115	0.054	0.112	0.162	0.114	0.268	0.132	0.170
CD	0.093	0.144	0.056	0.000	0.049	0.055	0.060	0.054	0.054	0.111	0.114	0.219	0.084	0.068
UC	0.099	0.099	0.000	0.000	0.111	0.053	0.055	0.000	0.058	0.051	0.000	0.050	0.048	0.806
6-9y(EO)														
IBD	0.079	0.151	0.242	0.161	0.389	0.274	0.314	0.318	0.527	0.557	0.758	0.683	0.347	0.022
CD	0.079	0.076	0.079	0.000	0.270	0.228	0.210	0.210	0.314	0.213	0.378	0.363	0.189	0.331
UC	0.000	0.075	0.163	0.161	0.120	0.045	0.104	0.108	0.213	0.343	0.380	0.320	0.158	0.021
10-16y(PIBD)														
IBD	2.052	2.553	2.825	3.224	4.914	4.104	5.300	6.588	6.809	7.361	7.043	7.744	4.888	<0.001
CD	1.128	1.580	1.696	2.145	3.554	2.885	3.694	5.038	4.770	5.880	5.436	5.282	3.465	<0.001
UC	0.924	0.973	1.129	1.079	1.359	1.218	1.606	1.550	2.038	1.481	1.606	2.462	1.422	0.033

Figure 2. Temporal trends in the incidence rates of IBD by age groups



*: not significant, †: $p < 0.05$

Figure 3. Temporal trends in the incidence rates of CD and UC by age groups



*: not significant, †: $p < 0.05$

CD to UC ratio according to age groups

Over the study period, 1952 (71%) and 811 (29%) children were diagnosed with CD and UC, respectively.

The CD to UC ratio was 2.25:1 in infantile group, 1:73:1 in VEO-IBD group. In the EO and PIBD group, the ratio was 1.17, 2.48, respectively (Table 1). The CD: UC ratio was significantly different between children under 10 years old and older children (p=0.004), but not significantly different among each age groups.

Gender differences

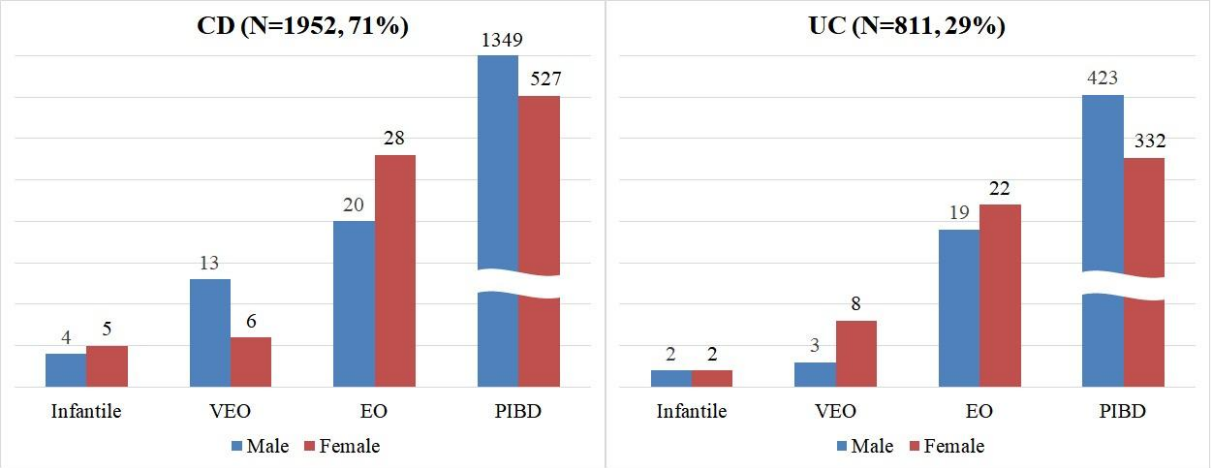
Overall, 66% of the patients were male; 46% were male in infantile-IBD, 53% in VEO, 44% in EO, and 67% in PIBD. In CD, the male to female ratio was 2.45:1 whereas the ratio was 1.23:1 in UC (Table 3, Figure 4).

CD: UC ratio was 3.1:1 in males and 1.55:1 in females. CD was significantly dominant in male (p<0.001, Table 1).

Table 3. Male: female ratio in CD and UC

	Male	**Female**	**total**	**M:F**
CD				
Infantile	4	5	9	0.8:1
VEO	13	6	19	2.17:1
EO	20	28	48	0.71:1
PIBD	1349	527	1876	2.56:1
all	1386	566	1952	2.45:1
UC				
Infantile	2	2	4	1.00:1
VEO	3	8	11	0.38:1
EO	19	22	41	0.86:1
PIBD	423	332	755	1.27:1
all	447	364	811	1.23:1

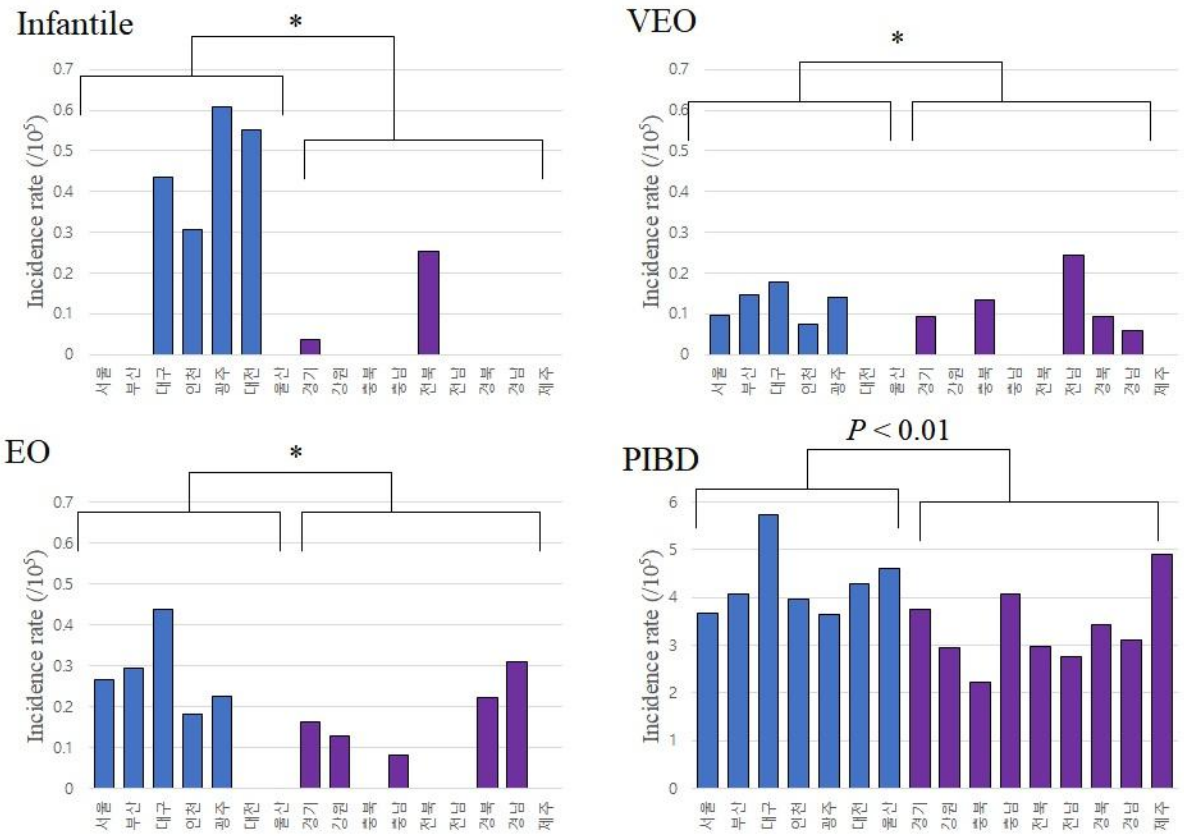
Figure 4. The number of male and female in each age group in CD and UC



Comparison of incidence rates between metropolitan and non-metropolitan areas

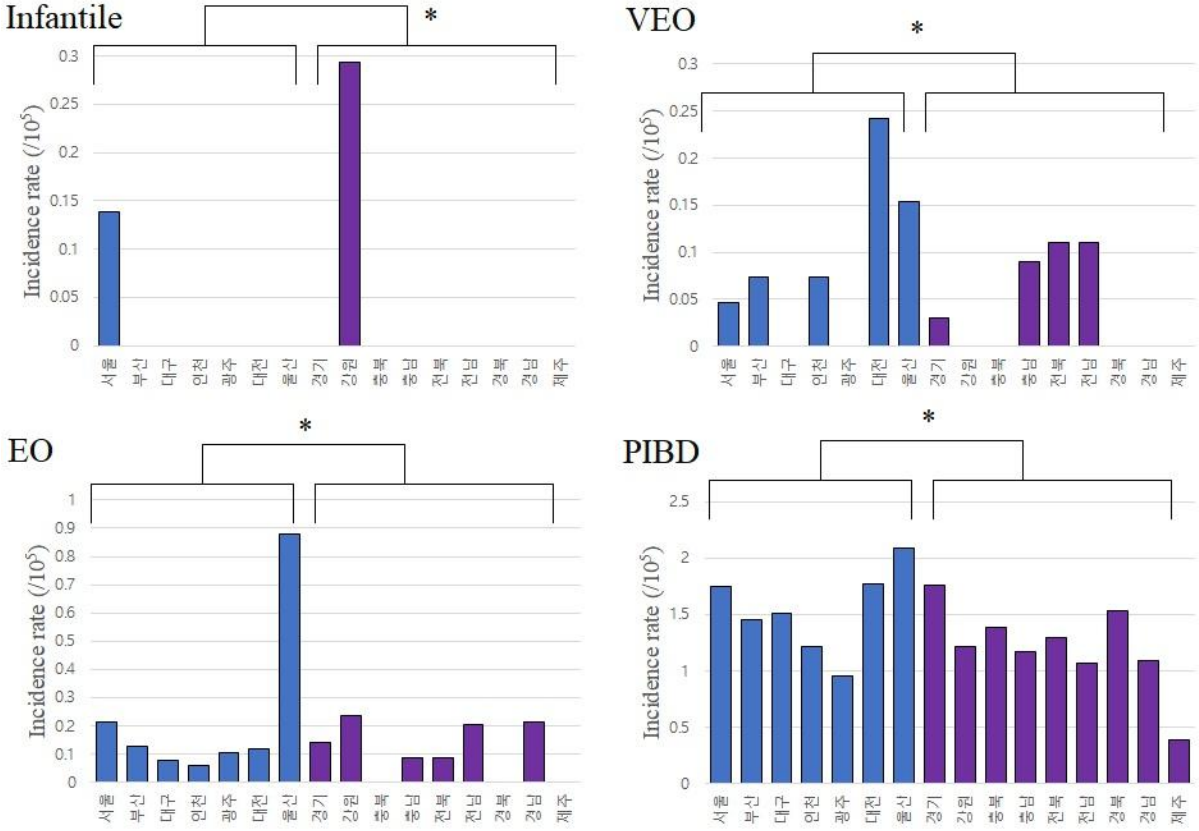
We compared the age- and sex- standardized incidence rates for the entire study period between metropolitan (N=1337) and non-metropolitan areas (N=1426). There were no statistical differences in the incidence rates of CD and UC between the two regions in all age groups, except the incidence of the CD in the PIBD group (Figure 5 and 6).

Figure 5. Comparison of incidence rates of CD between metropolitan and non-metropolitan areas



*: not significant

Figure 6. Comparison of incidence rates of UC between metropolitan and non-metropolitan areas



*: not significant

Discussion

This population-based nation-wide study using health-care big data showed that the incidence of PIBD and EO-IBD increased in Korea from 2005 to 2016 whereas the incidence of infantile and VEO-IBD remained stable during the same period.

Recent studies in Canada and France reported the incidence of VEO-IBD and the temporal trend of the incidences using population-based data [1, 2]. In a prospective population-based study in Northern France, the incidence of VEO-IBD was $0.4/10^5$/year from 1988 to 2011. The trend in incidences over time was analyzed using log-linear Poisson regression analysis. The incidence of VEO-IBD remained stable over the study period, whereas that of EO-IBD increased [1]. In contrast, the rate of incidence increase per year was 7.4% of VEO-IBD, which was faster compared with the children older than 10 years reported by the study in Ontario, Canada [2]. This result may be secondary to increased interests and awareness of VEO-IBD, improved access to pediatric gastroenterologists, or more prompt diagnosis of childhood-onset disease. The difference between two studies may be attributed to the method to include the study population, study area, and environmental factors such as food and lifestyles [1, 10].

In East Asia, there were few population-based epidemiologic studies of VEO-IBD. In study of Wang et al., the annual incidence of IBD was analyzed using data of the total resident population in Shanghai, China [7]. It showed an increasing incidence of IBD over time in children under 14 years. It was supposed that all PIBD patients in Shanghai were treated in 4 hospitals participating in the study. However, it might not cover all IBD patients in this area and the result cannot reflect the whole Chinese pediatric population. In addition, the age groups were divided every 4 years, not reflecting the VEO-IBD age criteria and age-specific temporal trend analysis was not conducted.

In Japan, the study by Ishige et al. [8] used the nation-wide IBD registry and showed the age-standardized prevalence of IBD in each age group, the number of patients in each age group, and the characteristics of PIBD in Japan. However, they did not assess the incidence or the temporal trends of each age group.

In Korea, the study by Hong et al. [11] estimated the incidence rate and trend of pediatric IBD from 2011 to 2016 in Daegu-Kyungpook Province. It showed the increasing incidence of PIBD but did not analyzed the patients under 6 years of age separately.

In this point of view, our study is the first population-based study to report the nation-wide incidence and the temporal trend of VEO-IBD in East-Asia whereas previous studies in East-Asia did not analyze the incidence and the temporal trend of IBD in this age group separately nor include the whole nation-wide pediatric population.

In this study, the overall incidence rate of IBD in children under 17 years was $2.248/10^5$ from 2005 to 2016. It was comparable to the study by Bequet et al. [1] which was a population-based study and included the same age group (under 17 years). The incidence was relatively low compared to the study by Benchimol et al. [2] which included older children and used different algorithm for selecting the patients. It might be also affected by different genetic and local environmental factors such as food and lifestyle. Epidemiology studies in Asia and the Middle East have reported the incidence from 0.5 to $11.4/10^5$, reflecting these varieties [12] (Table 4).

In point of VEO-IBD, the incidence was also relatively low compared to other studies. In our study, the proportion of VEO-IBD in pediatric-onset IBD was 1.6%. It is lower than previous population-based studies in Western countries which reported 3 to 5% [1, 2, 13] (Table 4). In addition, it is opposite to previous studies which showed that the proportion of VEO-IBD in pediatric-onset IBD was higher and mean age of onset of pediatric IBD was younger in Asian countries than European countries [14]. The study in Singapore which used the same definition of VEO-IBD reported the proportion of VEO-IBD was 17.5% [15]. The proportion of VEO-IBD was much higher (26.1%) in the Chinese study which used a lower age cut-off of 4 years [7]. It might be influenced by the characteristics of single or multicenter cohort study. On the other hand, the study by Ishige et al [8] reported the proportion of CD and UC in children under 9 years of age were 2.6% and 2.5%, respectively. This study used the nationwide IBD registry and it is one of the reasons why the result was closest to the result of our study, whereas other epidemiologic studies in East-Asia used center- or

cohort-based data. It means that the multi-national study is necessary to evaluate and compare the epidemiology of pediatric IBD and VEO-IBD among the Asian countries.

The IBD is a multifactorial disease, influenced by both genetic and environmental factors. The differences in the incidence of IBD across the regions and the increment of the incidence over the years mean that the environmental factors have a significant effect to development of IBD [16]. Risk factors associated with a higher risk of IBD are smaller family size, early life exposure to antibiotics [17]. Early-life exposure to farm animals was associated with a lower risk of IBD [17, 18]. The rural and urban environments also have been suggested as the factor affecting the development of the IBD and investigated by many studies. A systematic review and meta-analysis by Soon IS, et al. [19] showed the pooled incidence rate ratios for urban compared to the rural environment were 1.43 for CD and 1.17 for UC respectively. Benchimol et al. demonstrated that rural residence at diagnosis and at birth has a protective association in childhood-onset IBD [17]. On the other hand, we cannot observe the difference in the incidence rates of CD and UC between metropolitan and non-metropolitan areas except the incidence rate of CD in the PIBD group in our study. We used the region at diagnosis, not at birth, which affect the different result. It also may be because there is no significant difference in early life exposure to environmental factors such as lifestyle, food, antibiotics, or air pollution between metropolitan and non-metropolitan areas in Korea. In the retrospective multicenter cohort study including 1,002 Korean patients diagnosed with CD, there was no difference in clinical manifestations between rural and urban regions [16]. In addition, heterogeneity observed in studies might be derived from the differences in the study design and the definition of rural and urban regions [19].

We found that the incidence of infantile- and VEO-IBD was stable and there was no difference between the two regions. Furthermore, it was demonstrated that phenotypes of VEO-IBD are distinct from those of older children by several multicenter cohort studies [5, 6]. These findings suggest that the pathogenesis of VEO-IBD may be influenced by genetic factors rather than environmental factors [1, 17]. Recently several gene mutations such as interleukin (IL) 10RA/B, IL10, XIAP, and ADAM17 were identified to be important in the pathogenesis of VEO-IBD [6]. Further studies are needed to understand the genetic origin of VEO-IBD and apply it to early diagnosis and

treatment of very young IBD patients.

The strength of this study is that it could include a large number of patients and longitudinal data by using nationwide population-based data.

This study has some limitations by the fact that it used the population-based health administrative databases. First, we could not analyze the clinical manifestations such as symptoms, behaviors, location, severity, endoscopic findings, or treatment responses. This may affect all research using health administrative data [2]. The study by Bequet et al. overcame this limitation by using the EPIMAD registry which prospectively recorded all children diagnosed with definite or probable IBD before 17 years of age [1]. Data including age at diagnosis, gender, the interval between the onset of symptoms and diagnosis, and clinical, radiological, endoscopic, and histological findings at the time of diagnosis, extraintestinal manifestations, location, phenotype, and information on the management were collected. We suggest that the National registry for pediatric IBD is needed for further investigation of epidemiologic and clinical characteristics in Korean pediatric IBD.

Second, inappropriate medication use, disease codes, or healthcare utilization may create misclassification biases [2]. Our study used the combination of the experience of colonoscopy, use of the IBD-specific medication at least 3 months, and the ICD 10^{th} and RID codes for CD and UC, and this algorithm was validated in the previous study.

Third, we excluded the children who had the ICD or RID code for both CD and UC. They might be diagnosed with IBD-U or classified to CD or UC after following examinations. Initial diagnosis changes in the significant number of young children with IBD [2, 4]. Furthermore, some studies reported that the proportion of IBD-U was high in young patients [1, 5]. Thus, the incidence rate of IBD might be underestimated. However, it was validated that the diagnostic algorithm we used showed the closest results to the reference incidences by the previous study.

Table 4. Comparison of incidence rate and proportion of VEO-IBD

Study	Year	Age (years)	Incidence (/10^5/year)	Proportion of VEO-IBD	Study population
South Korea (this study)	2005-2008 2013-2016	0-1	0.200 0.120	1.6%	Nation-wide, data from National Health Insurance Service
	2005-2008 2013-2016	2-5	0.125 0.165		
	2005-2008 2013-2016	6-9	0.157 0.632		
	2005-2008 2013-2016	10 – 16	2.674 7.217		
South Korea [11]	2011 2016	<18	0.86 3.33	CD: 5.1% (5/98, <10 years) UC: 8.3% (2/24, <10 years)	4 university hospitals in Daegu-Gyeongbuk province cohort-based, retrospective (Medical record review)
South Korea [20]	-	-	-	CD: 3.3% (1/30, <6 years) UC: 3.03% (1/33, <8 years)	5 university hospitals, cohort-based, retrospective (Medical record review)
Northern France [1]	1988-1990 2009-2011	0-16	3.0 6.3	3%	Population-based, EPIMAD registry, prospective
	1988-2011 1988-1990 2009-2011	0-5	0.4 0.44 0.36		
Canada, Ontario [2]	1994 2002 2009	0-17	9.4 8.1 13.2	5.4%	Population-based, Using validated algorithm, Health administrative data
	1994 2002 2009	0-5	1.3 0.6 2.1		

Great Britain and Ireland [13]	1998-1999	<16	-	4%	Prospective, cohort-based (monitoring registry)
China, Shanghai [7]	2000-2010	<4 5-9 10-14 15-18 0-18	0.66 0.46 0.78 0.32 0.55	26.1 % (< 4 years)	4 hospitals, chart review
Japan [8]	2013	0-19	7.2 (CD) 15.0 (UC) (prevalence)	CD: 2.6% (< 9 years) UC: 2.5% (< 9 years)	Nationwide registry
		0-9	0.4 (CD) 0.8 (UC)		
Singapore [15]	1994-1997 2013-2015	0-18	0.05 4.29	17.5% (< 6 years)	South-east Asian cohort in two tertiary pediatric hospitals, prospective (case review)
Kingdom of Saudi Arabia(KSA) [12]	2003-2012 2003-2007 2008-2012	0-14yr	0.47 0.35 0.59	15.9% (< 4 years)	Retrospective, national multicenter cohort study
	2003-2007 2008-2012	0-4yr	0.27 0.19		
Taiwan [21]	2000-2010	10-19 yr	CD: 0.117 (female) 0.211 (male) UC: 0.193 (female) 0.233 (male)	-	Retrospective, The Taiwan Health Insurance Research Dataset (NHIRD)
	2000-2010	0-9 yr	CD: 0.075 (female) 0.138 (male) UC: 0.038 (female) 0.062 (male)		

Conclusion

We found that the incidence of PIBD and EO-IBD increased in Korea whereas the incidence of infantile- and VEO-IBD remained stable. When comparing the incidence rates of VEO-IBD of metropolitan and non-metropolitan areas, there was no significant difference between regions.

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국문요약

제목: 국민건강보험 빅데이터를 이용한 초조기발병 염증성 장질환의 전국 인구 기반 역학 연구 (2005-2016)

목적: 6세 미만에 염증성 장질환으로 진단된 환아들은 연장아들과 비교하였을 때 대장 단독 침범 또는 대장 전체 침범이 흔하고, 기존의 약물에 반응이 좋지 않은 등의 비전형적 임상 양상을 보인다. 이에 6세 미만을 초조기발병 염증성 장질환(VEO-IBD)으로 구분하고 있다. 최근 캐나다와 프랑스의 인구 기반 자료를 이용한 역학 연구를 통해 VEO-IBD의 발생률과 변화 추이를 보고하였다. 동아시아 지역에서의 역학 연구에서도 6세 미만의 연령군을 포함한 소아 염증성 장질환의 발생률을 보고한 바 있으나, VEO-IBD 연령군만 따로 분류하여 분석한 전국 인구 대상 연구는 없었다. 우리 나라에서도 전국 인구 자료를 이용한 VEO-IBD의 역학 연구 및 이를 바탕으로 한 병인론에 대한 고찰이 필요한 실정이다. 이에 본 연구에서는 국가 보건 자료를 이용하여 전국의 VEO-IBD 발생률과 변화 추이를 분석하고, 도시와 비도시에서의 발생률을 비교하고자 하였다.

방법: 2005년부터 20016년까지의 국민건강보험 및 국가통계포털 자료를 이용하여 이 기간동안 새로 염증성 장질환을 진단받은 17세 미만의 소아를 분류하였고, 이들을 연구 대상으로 하였다. 연구 대상의 연령군을 infantile(0-1세), VEO(2-6세), EO(6-9세), PIBD(9-16세) 세 군으로 나누어 전체 발생률 및 각 연령군의 연도별 발생률, 발생률 변화 추이를 분석하였다. 염증성 장질환을 진단받은 환아들을 분류하기 위한 진단 알고리즘을 개발하기 위해 국민건강보험 자료에서 각 개인의 연령, 성별, 치료, 처방된 약, 내시경 등의 시술, 비용 청구 내역 등의 정보를 이용하였고, 이들의 다양한 조합들을 비교하였다. 그 중 기존 인구 기반 자료 연구에서 보고한 발생률과 가장 가까운 결과를 보여

주는 조합인 ICD-10 진단 코드, 희귀난치등록 코드, 6개월 이상의 염증성 장질환 약물 처방, 내시경 시행의 조합이 최종 진단 알고리즘으로 선정되었다. 이 알고리즘을 이용하여 전국의 17세 미만의 인구 중 해당 년도에 새로이 염증성 장질환을 진단받은 환아들을 분류하였고, 성별 및 연령을 보정한 표준화 발생률을 구하였다. 또한 연도에 따른 발생률의 변화를 분석하여 VEO-IBD의 발생률이 증가하는지, 일정한지 확인하고자 하였다. 그리고 도시, 비도시로 나누어 크론병 및 궤양성 대장염의 발생률을 비교하였다.

결과: 2005년부터 2016년까지 2763명(남자 1833명, 여자 930명)이 17세 이전에 염증성 장질환으로 진단받았다. 이들 중 43명(1.6%)이 6세 이전에 진단받은 VEO-IBD에 해당되었다. 전체 연령에서 전체 연구 기간(2005-2016년) 동안의 염증성 장질환 발생률은 $2.248/10^5$ 이었다. 동일기간의 각 연령군별 염증성 장질환 발생률은 각각 $0.124/10^5$(infantile), $0.132/10^5$ (VEO), $0.347/10^5$ (EO), $4.888/10^5$ (PIBD)이었다. 전체 소아 염증성 장질환의 발생률은 2005년에 $1.001/10^5$에서 2016년에 $3.701/10^5$ 로 증가하였다. Infantile과 VEO 그룹에서는 전체 기간동안 염증성 장질환 발생률이 일정했던 반면, EO 및 PIBD 그룹에서는 발생률이 증가하였다. 또한 도시, 비도시의 발생률은 PIBD 그룹의 크론병을 제외하고는 차이가 없었다.

결론: 한국의 염증성 장질환의 발생률은 PIBD, EO 그룹에서는 증가한 반면 infantile, VEO 그룹에서는 일정하였다. 또한 VEO-IBD의 발생률을 비교하였을 때 지역 간 차이가 없었다.

중심단어: 초조기발병 염증성 장질환, 발생률