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The Prevalence and Risk Factors of *Clostridioides difficile* Infection in Inflammatory Bowel Disease: 10-Year South Korean Experience Based on the National Database

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ABSTRACT

Background: Few studies evaluate the epidemiology and risk factors of *Clostridioides difficile* infection (CDI) in Asian patients with inflammatory bowel disease (IBD). We investigated the year-end prevalence, cumulative incidence and risk factors of CDI in Asian patients with IBD using a large-scale population-based cohort in Korea.

Methods: Using the National Health Insurance Service database, we identified patients with IBD and sex- and age-matched controls without IBD between 2008 and 2018. The year-end prevalence and cumulative incidence of CDI were compared among patients with Crohn's disease (CD) and ulcerative colitis (UC) with controls. The risk factors for CDI were evaluated.

Results: Among the 54,836 patients with IBD and 109,178 controls, CDI occurred in 293 patients with IBD and 87 controls. The annual year-end prevalence of CDI in patients with IBD increased from 8.6/10,000 persons in 2008 to 22.3/10,000 persons in 2018. The risk of CDI was higher in both patients with CD and UC than that in the matched controls (hazard ratio [HR], 7.285; 95% confidence interval [CI], 5.388–9.851; *P* < 0.001 and HR, 7.487; 95% CI, 5.796–9.670; *P* < 0.001, respectively). Among patients with IBD, the risk factors for CDI included older age, female sex, high Charlson comorbidity index score, and IBD-related medications including oral 5-aminosalicylic acid, immunomodulatory agents, biologics, and steroids used for > 90 days.

Conclusion: The risk of CDI in Korean patients with IBD was approximately seven times higher than that in controls without IBD, and the annual year-end prevalence of CDI continuously increased from 2008 to 2018.

Keywords: *Clostridioides difficile*; Pseudomembranous Enterocolitis; Inflammatory Bowel Diseases; Crohn Disease; Ulcerative Colitis

INTRODUCTION

After the first recognition of *Clostridioides difficile* as a key pathogen of severe colitis in 1978,[1] *Clostridioides difficile* infection (CDI) has become a common cause of diarrhea in hospitalized patients.[2,3] CDI usually involves the large bowel and has a wide range of clinical manifestations, from asymptomatic carriage to mild diarrhea, toxic megacolon, and life-threatening severe colitis.[4-7] An alarming steady global increase of CDI incidence has been reported in Asian countries over the last few decades.[5,8] A territory-wide study in Hong Kong has documented a nearly three-fold increase of CDI incidence from 2006 to 2014.[9] Another Asian population-based study also reported an increase in CDI incidence from 1.43/100,000 persons in 2008 to 5.06/100,000 persons in 2011.[10] While it is acknowledged that the studies conducted on only hospitalized patients or solely based on diagnostic codes, a few previous South Korean studies have also reported an increase in the CDI incidence.[10,11] Patients with inflammatory bowel disease (IBD) often have certain risk factors for CDI, including prior treatment with broad-spectrum antibiotics, frequent hospitalization, and long-term immunosuppression. However, the diagnosis of CDI is particularly difficult in patients with IBD. First, the symptoms of CDI, such as diarrhea, fever, and abdominal pain, are similar to those of IBD flare-ups; therefore, the identification of CDI in these patients is difficult. In addition, several previous studies have reported that pathognomonic endoscopic findings such as thick yellowish plaques are not observed in patients with IBD.[12,13] Owing to these difficulties in diagnosis, diagnostic delay of CDI may occur in patients with IBD, which can result in fatal outcomes such as total colectomy and mortality. Therefore, it is important to understand the prevalence of CDI and the risk factors associated with CDI to appropriately diagnose CDI in patients with symptomatic IBD.

However, limited data describe the epidemiology and risk factors of CDI, especially in Asian patients with IBD. As Asian patients with IBD have distinct epidemiologic, clinical, and genetic characteristics from westerners, larger-scaled studies are needed in this topic.[14-16] Thus, we conducted a population-based study to investigate the prevalence and risk factors of CDI in patients with IBD using data from the National Health Insurance Service (NHIS) in Korea.

METHODS

Data source

We extracted the International Classification of Diseases, 10th revision (ICD-10) diagnostic codes from the NHIS database and V codes from the Rare Intractable Diseases (RID) database. For RID registration of patients with IBD including ulcerative colitis (UC) and Crohn's disease (CD) in Korea, clinical, endoscopic, and pathological diagnoses of IBD are required.

Study population

In total, 55,052 patients with IBD aged 18–79 years were identified from 2008 to 2018, after a washout period of one year. Patients with IBD were defined as those diagnosed with the ICD-10 and the RID registration system (V code). Patients with CD were defined as those with ICD-10 code K50 and V code V130, and patients with UC were defined as those with ICD-10 code K51 and V code V131. Sex- and 10-year age-matched reference populations without IBD (non-IBD controls) were selected from the NHIS database during the study period at a matching ratio of 1:2. Patients with histories of CDI before the index date were excluded. Patients with CDI were defined those with correlating diagnostic codes and
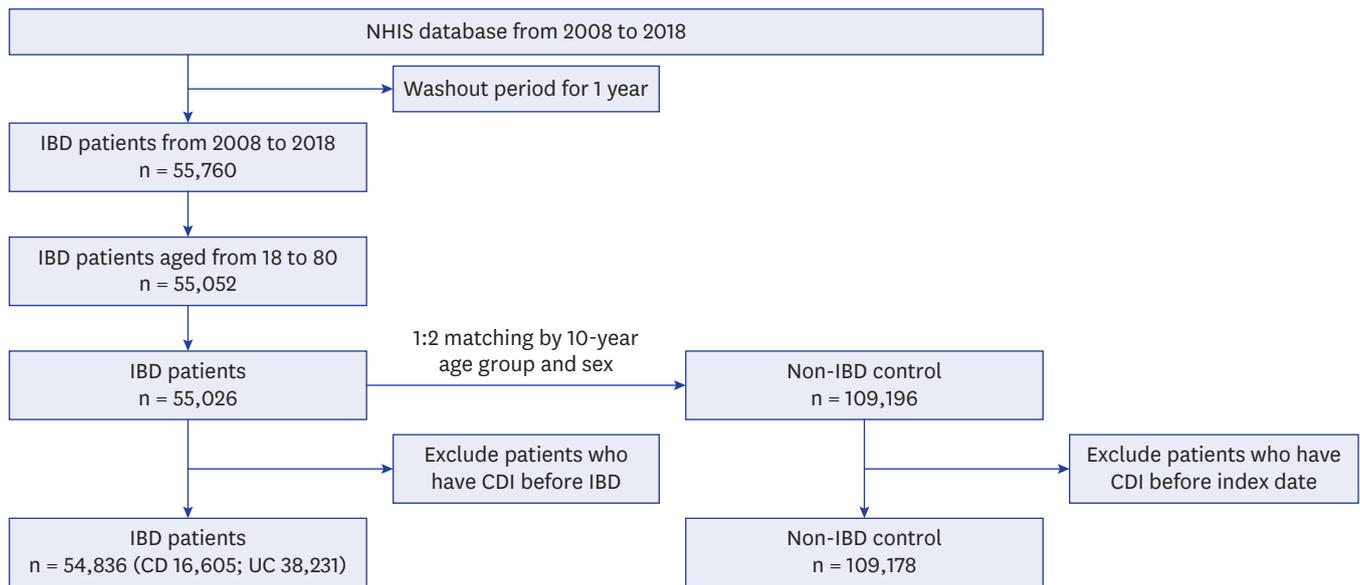
Fig. 1. Flow chart of the study population.
NHIS = National Health Insurance Service, IBD = inflammatory bowel disease, CDI = *Clostridioides difficile* infection, CD = Crohn's disease, UC = ulcerative colitis.

registered medications such as metronidazole per os (PO), vancomycin PO, or metronidazole intravenous. Finally, 54,836 patients with IBD and 109,178 non-IBD controls were eligible for analysis (**Fig. 1**).

Outcomes

Demographic features, comorbidities, and medications used for IBD were analyzed. The Charlson comorbidity index (CCI) was used to assess the severity of underlying comorbidities. Based on the index date, CCI was calculated by observing comorbidities over the previous year and assigning weighted scores of 0, 1, 2, and ≥ 3. Data on IBD medications, including oral 5-aminosalicylic acid (ASA), immunomodulators (azathioprine, mercaptopurine, cyclosporine, tacrolimus, and methotrexate), steroids, and biologics (infliximab, adalimumab, vedolizumab, and ustekinumab), were collected. Regarding the duration of medications, we counted all the days in which the medications were prescribed.

Year-end prevalence and cumulative incidence of CDI in patients with CD and UC were investigated and compared with those in the non-IBD controls. We also examined the risk factors for CDI in patients with IBD.

Statistics

Continuous variables were analyzed using Student's *t*-test and the Mann-Whitney *U* test, and categorical variables were analyzed using the χ^2 test and Fisher's exact test. Continuous variables are presented as means ± standard deviations, and categorical variables are presented as numbers with percentages. The annual year-end prevalence of CDI was compared based on calculations from claims data for patients with IBD and National Statistical Office data. We assessed the cumulative CDI incidence between patients with IBD and non-IBD controls and performed Cox proportional hazards regression analysis to assess several risk factors in patients with IBD. All statistical tests were two-tailed, and a *P* value of < 0.05 was considered significant.

All statistical analyses were performed using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics statement

This study was approved by the Institutional Review Board of Eunpyeong St. Mary's Hospital, Catholic University of Korea (IRB approval number: PC19ZNSE0128). No informed consent was required from patients due to the nature of public data from NHIS.

RESULTS

Demographic characteristics of the study population

Between 2008 and 2018, 54,836 patients with IBD were identified (38,231 with UC and 16,605 with CD) as well as 109,178 non-IBD controls in the reference population. The mean ages at CDI diagnosis of those with CD, those with UC, and the non-IBD control group were 37.5 ± 19.8 years, 49.1 ± 18.6 years, and 62.4 ± 13.9 years respectively ($P < 0.001$). IBD patients with CDI were younger than non-IBD control group with CDI. The participants' characteristics are presented in **Table 1**.

Table 1. Baseline characteristics of enrolled population

| Variables	Non-IBD controls (N = 109,178)		P value[a]	CD (N = 16,605)		P value[a]	UC (N = 38,231)		P value[a]
	Non-CDI (n = 109,096)	CDI (n = 82)		Non-CDI (n = 16,518)	CDI (n = 87)		Non-CDI (n = 38,025)	CDI (n = 206)	
Age, yr	40.6 ± 16.0	62.4 ± 13.9	< 0.001	32.2 ± 15.2	37.5 ± 19.8	0.016	43.6 ± 15.5	49.1 ± 18.6	< 0.001
Male sex	68,268 (62.6)	47 (57.3)	0.385	11,624 (70.4)	52 (59.8)	0.041	22,723 (59.8)	96 (46.6)	< 0.001
Disease duration to occur CDI, yr	-	3.6 ± 2.8		-	2.4 ± 2.5		-	2.7 ± 2.6	
CCI group			< 0.001			0.001			< 0.001
0	71,017 (65.1)	26 (31.7)		7,163 (43.4)	26 (29.9)		17,194 (45.2)	78 (37.9)	
1	20,806 (19.1)	12 (14.6)		5,173 (31.3)	28 (32.2)		10,740 (28.2)	45 (21.8)	
2	8,608 (7.9)	12 (14.6)		2,345 (14.2)	12 (13.8)		5,299 (13.9)	36 (17.5)	
≥ 3	8,667 (7.9)	32 (39.0)		1,837 (11.1)	21 (24.1)		4,792 (12.6)	47 (22.8)	
Use of medications									
Oral 5-ASA	-	-		13,966 (84.6)	79 (90.8)	< 0.001	30,506 (80.2)	190 (92.2)	< 0.001
Immunomodulator	-	-		10,758 (65.1)	60 (69.0)	0.525	7,145 (18.8)	126 (61.2)	< 0.001
Biologics	-	-		4,717 (28.6)	45 (51.7)	< 0.001	2,759 (7.3)	89 (43.2)	< 0.001
Use of steroid	-	-	< 0.001			< 0.001			< 0.001
< 90 days	74,825 (68.6)	52 (63.4)		8,996 (54.5)	37 (42.5)		0	56 (27.2)	
≥ 90 days	6,636 (6.1)	17 (20.7)		4,642 (28.1)	45 (51.7)		10,259 (27.0)	142 (68.9)	
Characteristics of CDI									
Admission	-	72 (87.8)		-	63 (72.4)		-	156 (75.7)	
Hospital type									
Tertiary hospital	-	34 (41.5)		-	57 (65.5)		-	142 (68.9)	
General hospital	-	41 (50.0)		-	28 (32.2)		-	59 (28.6)	
Others	-	7 (8.5)		-	2 (2.3)		-	5 (2.5)	
Treatment									
Metronidazole PO	-	46 (56.1)		-	51 (58.6)		-	101 (49.0)	
Vancomycin PO	-	18 (22.0)		-	13 (14.9)		-	32 (15.5)	
Vancomycin PO and IV metronidazole IV	-	18 (22.0)		-	23 (26.4)		-	73 (35.4)	

Values are presented as mean ± standard deviation or number (%).
IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis, CDI = *Clostridioides difficile* infection, CCI = Charlson comorbidity index, 5-ASA = 5-aminosalicylic acid, PO = per os, IV = intravenous.
[a]P value was calculated by comparing patients with CDI to those without CDI (non-CDI).

Year-end prevalence and cumulative incidence of CDI

Among the patients with IBD, 293 had CDI during the study period. A total of 206 cases occurred in patients with UC, and 87 cases occurred in patients with CD. Among the age- and sex-matched non-IBD controls, 82 cases of CDI occurred. The annual year-end prevalence of CDI in patients with IBD increased from 8.6/10,000 in 2008 to 22.3/10,000 in 2018 (**Fig. 2**). This trend was similarly observed in both patients with CD and UC, as follows: 1.5/10,000 persons in 2008 to 23.7/10,000 persons in 2018 for CD and 11.7/10,000 persons in 2008 to 21.6/10,000 persons in 2018 for UC. The risk of CDI was higher in both patients with CD and UC than that in the matched non-IBD controls (hazard ratio [HR], 7.285; 95% confidence interval [CI], 5.388–9.851; $P < 0.001$ and HR, 7.487; 95% CI, 5.796–9.670; $P < 0.001$, respectively) (**Fig. 3**).
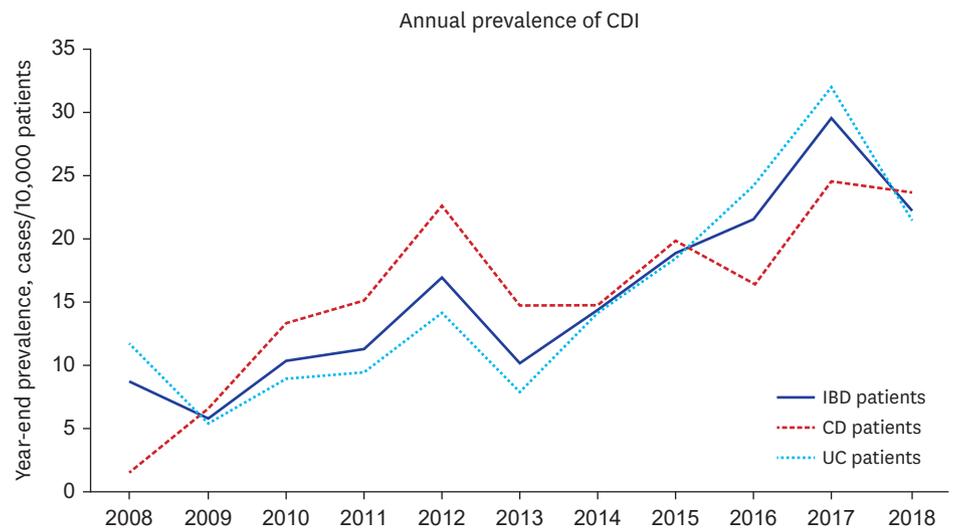
Fig. 2. Annual year-end prevalence of CDI in patients with IBD and in non-IBD controls.
CDI = *Clostridioides difficile* infection, IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis.
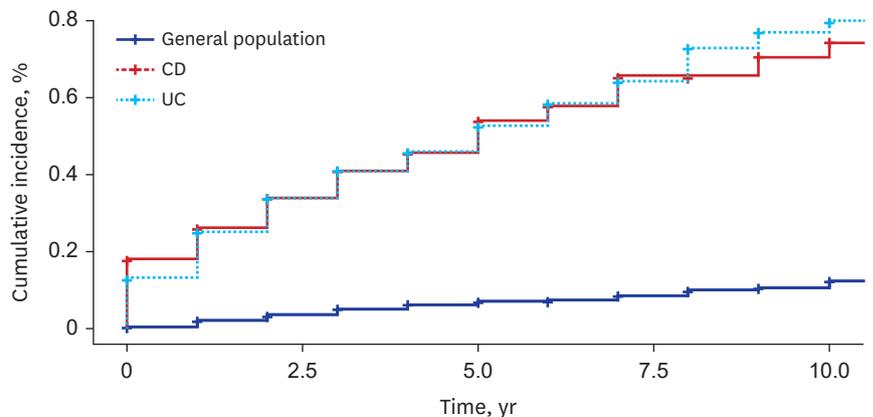
No. at risk					
General population	109,178	85,709	65,263	38,489	22,305
CD	16,605	12,616	9,435	5,134	2,578
UC	38,231	28,440	21,473	12,618	6,908

Fig. 3. Cumulative incidence of *Clostridioides difficile* infection in patients with IBD and in non-IBD controls.
IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis.

Risk factors for the occurrence of CDI

Cox regression analysis was performed to investigate the factors influencing the incidence of CDI. In the general population, the risk factors significantly associated with the occurrence of CDI were IBD (CD and UC), older age, female sex, and high CCI scores in both univariate and multivariate analyses (**Table 2**). Among patients with IBD, the risk factors that were significantly associated with the occurrence of CDI were older age, female sex, high CCI scores, and IBD-related medications (e.g., oral 5-ASA, immunomodulatory agents, biologics, and steroids). In particular, steroid use for > 90 days was significantly associated with CDI incidence (**Table 3**).

Table 2. Risk factors for CDI in general population

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Presence of IBD						
Non-IBD controls	Reference			Reference		
CD	7.285	5.388–9.851	< 0.001	8.552	6.269–11.668	< 0.001
UC	7.487	5.796–9.670	< 0.001	6.511	5.028–8.432	< 0.001
Age, yr	1.032	1.025–1.038	< 0.001	1.025	1.018–1.032	< 0.001
Sex						
Male	Reference			Reference		
Female	1.495	1.221–1.830	< 0.001	1.365	1.113–1.674	0.003
CCI group						
0	Reference			Reference		
1	1.712	1.302–2.250	< 0.001	1.074	0.814–1.417	0.615
2	2.730	2.010–3.707	< 0.001	1.395	1.016–1.914	0.039
≥ 3	4.765	3.671–6.184	< 0.001	2.050	1.529–2.750	< 0.001

CDI = *Clostridioides difficile* infection, HR = hazard ratio, CI = confidence interval, IBD = inflammatory bowel disease, CD = Crohn's disease, UC = ulcerative colitis, CCI = Charlson comorbidity index.

Table 3. Risk factors for CDI in patients with IBD

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Type of IBD						
CD	Reference			Reference		
UC	1.029	0.801–1.322	0.825	0.938	0.697–1.264	0.677
Age, years	1.019	1.012–1.026	< 0.001	1.020	1.011–1.029	< 0.001
Sex						
Male	Reference			Reference		
Female	1.607	1.278–2.021	< 0.001	1.458	1.150–1.848	0.002
CCI group						
0	Reference			Reference		
1	1.085	0.804–1.463	0.594	0.810	0.596–1.100	0.178
2	1.486	1.056–2.092	0.023	0.876	0.603–1.272	0.486
≥ 3	2.385	1.757–3.238	< 0.001	1.497	1.057–2.120	0.023
IBD treatment						
Oral 5-ASA	2.638	1.738–4.006	< 0.001	1.643	1.063–2.54	0.025
Immunomodulator	3.482	2.746–4.419	< 0.001	1.825	1.318–2.528	< 0.001
Biologics	5.176	4.113–6.515	< 0.001	2.514	1.871–3.376	< 0.001
Use of steroid						
< 90 days	Reference			Reference		
≥ 90 days	3.903	3.073–4.957	< 0.001	1.403	1.044–1.885	0.025

CDI = *Clostridioides difficile* infection, IBD = inflammatory bowel disease, HR = hazard ratio, CI = confidence interval, CD = Crohn's disease, UC = ulcerative colitis, CCI = Charlson comorbidity index, 5-ASA = 5-aminosalicylic acid.

DISCUSSION

In the present study, we evaluated the annual year-end prevalence and risk factors for CDI in Korean patients with IBD using a large population-based cohort. In this nationwide population-based cohort, the annual year-end prevalence of CDI in patients with CD and UC increased continuously from 2008 to 2018, and the risk of CDI was approximately seven times higher than that in the age- and sex-matched non-IBD control group. The risk of CDI was significantly increased in individuals with IBD, advancing age, female sex, and higher comorbidity burdens (CCI score of ≥ 3). In patients with IBD, the risk of CDI increased in those who were prescribed oral 5-ASA, immunomodulators, biologics, and steroids for > 90 days.

Our study demonstrated a CDI year-end prevalence of 23.6/10,000 persons with CD and 21.6/10,000 persons with UC in 2018 and an almost seven-fold increased risk of CDI in patients with IBD, compared with that of the non-IBD control group. Population-based studies on the epidemiology of CDI in patients with IBD are limited, particularly in Asian populations. Most nationwide studies from North America have evaluated the incidence of CDI in hospitalized patients with IBD using hospital discharge databases. A study by Nguyen et al.[17] conducted in Canada reported a CDI prevalence of 10.9/1,000 hospitalizations in patients with CD and 37.3/1,000 hospitalizations in patients with UC. In addition, they reported a nearly eight-fold increased risk of CDI in patients with IBD, compared with that of the all-hospital discharge population.[17] In a study in the United States by Barber et al., the incidence of CDI was 32.1/1,000 hospitalizations in patients with CD and 84.7/1,000 hospitalizations in patients with UC in 2014, showing a significant increase in both of these values compared with those of 1998.[18] In a recent study by Singh et al.,[19] the incidence of CDI in patients with IBD was evaluated in both hospitalized and ambulatory care settings. They reported that the annual incidences of CDI per 100,000 person-years of follow-up were 377 for CD and 512 for UC, approximately five times higher than that in the non-IBD population. In Asian populations, only a few hospital-based cohort studies have analyzed the risk factors and outcomes of CDI in patients with IBD.[20-23] To the best of our knowledge, this is the first large-scale population-based study to evaluate the year-end prevalence of CDI in Asian patients with IBD. According to the results of our study, the risk of CDI in Korean patients with IBD was significantly higher than that in the non-IBD population (CD: HR, 7.285; 95% CI, 5.388–9.851; P < 0.001; and UC: HR, 7.487; 95% CI, 5.796–9.670; P <0.001). This overall trend was comparable to that observed in Western patients with IBD.

In our study, the annual year-end prevalence of CDI in patients with IBD increased from 2008 to 2018, and this trend was similar in both CD and UC patients. Whether the incidence of CDI is increasing in patients with IBD remains unclear, and the findings of previous studies on this topic are inconsistent. Two earlier large cohort studies from the United States reported a steady increase of CDI in patients with IBD, especially in patients with UC and colonic CD.[13,24] However, more recent studies from the United Kingdom and Canada have reported either a decreasing or unchanged incidence of CDI in patients with IBD.[19,25] Given that our study identified CDI cases with a combination of diagnostic codes and treatment medications for CDI, our results suggest that true CDI cases have increased in Korean patients with IBD, rather than those with a previous history of CDI. Although the reason for this increase in CDI in Korean patients are unclear, the potential causes may be multifactorial. First, the increasing awareness of the importance of CDI infection in the acute exacerbation of IBD has led physicians to suspect and test for CDI. In addition, the wider use of diagnostic tests with higher sensitivities, such as nucleic acid amplification

tests, may contribute to higher detection rates of CDI in patients with IBD. However, further studies are needed to elucidate the exact underlying causes of this increasing trend and to investigate whether the increasing trend in CDI among patients with IBD will plateau or decline, as observed in Western populations.

In our study, the significant risk factors for the occurrence of CDI in patients with IBD were advancing age, female sex, higher comorbidity burden (CCI score of ≥ 3), and IBD medication (e.g., immunomodulators, biologics and steroids prescribed for > 90 days). Considering that other risk factors such as advancing age and higher CCI scores are similar to those in the general population, the use of IBD medications may specifically increase the risk of CDI. Although conflicting evidence exists on the impact of IBD medications on CDI, the significant association between the use of biologics and the risk of CDI was demonstrated in a recent large-scale nationwide study (HR, 2.69; 95% CI, 1.13–6.40) and a meta-analysis (odds ratio [OR], 1.65; 95% CI, 1.18–2.30), consistent with our study (HR, 2.514; 95% CI, 1.871–3.376).[2,19] As in the study of Singh et al., the use of steroids was a significant risk factor for the development of CDI in our study.[19] Especially, the risk of CDI was found to be approximately 1.5 times higher with the long-term use of steroids for > 90 days, compared with steroid use for < 90 days. The use of immunomodulators was also a significant risk factor of CDI, as determined in a Western study.[13] Interestingly, our results showed a significant association between the use of oral 5-ASA and the risk of CDI, which is not confirmed in previous Western studies; therefore, further investigation may be needed to determine if this finding is unique to Asian patients with IBD.[2,26] Considering the risk of CDI associated with IBD medications in our study, patients with IBD and these risk factors, especially the use of biologics or prolonged steroid use for > 90 days, should be investigated early for CDI when the symptoms associated with CDI occur.

The strengths of our study include its large sample size and population-based design, which minimized the effects of referral bias. However, our study had some limitations that should be addressed. First, owing to the limitations of claim data, our study could not include the performance and results of laboratory tests for CDI such as *C. difficile* toxin A/B immunoassay, *C. difficile* real-time polymerase chain reaction assay, and *C. difficile* agar culture. Therefore, misclassified CDI cases may have been included in this study. Since the diagnostic tests for CDI have been reimbursed by the Korean government since September 1, 2019, which did not encompass our study period, we could not include the frequency of these tests of each group in our results. Additionally, we were unable to confirm the results of these diagnostic tests for CDI as they were not available in the claims data. To mitigate this potential misclassification bias, we combined diagnostic codes and treatment medications to select CDI cases, as described in the METHODS section. Second, although the overall diagnostic and treatment policies for CDI were similar between patients with and without IBD, specific treatment situations may differ. For example, because *C. difficile* is a risk factor for acute exacerbation in patients with IBD, this factor may have influenced doctors to adopt a more proactive approach for treating CDI in patients with IBD compared to those without it. Third, the NHIS database does not include information about disease behavior and the extent of IBD; therefore, we did not evaluate the risk of CDI according to these subtypes of IBD. Fourth, because of the impossibility of establishing temporal precedence, especially in patients who did not develop CDI, we could not include prior antibiotic use as a risk factor for CDI. Fifth, although we evaluated risk according to the use of IBD medications, we did not include information regarding the doses of IBD medications.

In conclusion, our study, using a large-scale nationwide population-based cohort, demonstrated an approximate seven-fold increased risk of CDI in Korean patients with IBD, compared with that of the age- and sex-matched non-IBD controls. In addition, the annual year-end prevalence of CDI in patients with CD and UC increased continuously from 2008 to 2018. Among patients with IBD, the risk of CDI further increased with the use of IBD medications, including oral 5-ASA, immunomodulators, biologics, and steroids prescribed for > 90 days. Although our study showed a continuous increase of 156% in the annual year-end prevalence of CDI in patients from 2008 to 2018, further studies are needed to determine whether this trend will persist or shift toward a plateau or downward trend, as observed in Western studies.[19,25,27,28]

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