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Original Article

Gastrointestinal complications and extraintestinal manifestations of inflammatory bowel disease in Taiwan: A population-based study

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Abstract

Background: Despite a rising incidence of inflammatory bowel disease (IBD) in Taiwan, the clinical presentation of IBDs in this population has yet to be well characterized. Therefore, the aim of our study was to identify and describe the clinical features of gastrointestinal (GI) complications and extraintestinal manifestations (EIMs) of IBDs in the Taiwanese population.
Methods: We conducted a retrospective study between 1998 and 2011, with relevant medical information extracted from the National Health Insurance Research Database. The diagnoses of IBD, GI complications, and EIMs were defined from the health registry using the appropriate International Classification of Diseases 9 codes.
Results: A total of 3153 patients with IBDs were identified: 611 with Crohn's disease (CD) and 2542 with ulcerative colitis, with GI complications and EIMs identified in 22.2% and 11.9% of cases, respectively. CD was associated with an increased incidence of intestinal fistula, perforation, obstruction, peritonitis and perianal disease, and ulcerative colitis with benign neoplasm of the colon. Colorectal cancer developed in 0.35% of patients. Children with CD characteristically have more complex intestinal complications. The prevalence of EIMs was higher in females and in CD, with peripheral arthritis identified as the most common EIMs, overall. The rate of major EIMs affecting the articular, cutaneous, and visual systems was lower than the rate reported in Western countries.
Conclusion: Our study found that CD had a more complicated course, with a higher incidence of GI complications and EIMs. However, the prevalence of intestinal complications, perianal disease, and major EIMs was less common than in Western countries. This study provided a distinct clinical feature of IBD in Taiwan.

Keywords: Crohn's disease; extraintestinal manifestations; inflammatory bowel disease; ulcerative colitis

1. Introduction

Inflammatory bowel disease (IBD) is a multifactorial disorder comprising two major disorders, ulcerative colitis (UC) and Crohn's disease (CD). Dysregulation of the immune interaction between enteric antigens and the enteral mucosa results in chronic, immune-mediated inflammation.[1−3] IBD is associated with several gastrointestinal (GI) symptoms that can vary widely in severity of presentation, and can include any or all of the following: abdominal pain, diarrhea, GI bleeding, intestinal fistula, intra-abdominal abscess, and perianal disease (PD).[1] IBD can also present with a large number of extraintestinal manifestations (EIMs),[4] with the major EIM symptoms involving the musculoskeletal, cutaneous, hepatobiliary, and ocular systems.

Historically, although IBDs have commonly been found in Western countries, they have remained a rare occurrence in Asia. However, the incidence of IBDs in Japan, Hong Kong,

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China, and Korea has increased over the past two decades.[5−7] Taiwan, which shares similar regional and cultural characteristics with these areas, has also experienced an increasing incidence of IBD. A nationwide study in Taiwan revealed an increase in the annual incidence of UC and CD of 0.58−1.07 and 0.17−0.27 per 10^5 inhabitants, respectively, from 1998 to 2010.[8] Despite the increasing numbers of patients with IBD, however, the current level of knowledge regarding IBD presentation and prevalence of associated EIMs in Taiwan is limited.

The aim of our retrospective study was to conduct a nationwide review of medical records of patients having received a diagnosis of IBD between January 1998 and December 2011, to evaluate the current state of IBDs in Taiwan. The prevalence of GI complications and EIMs was calculated to define the clinical features of IBD. A secondary aim was to determine associations of clinical features with the type of IBD, namely CD or UC; age of presentation; and sex.

2. Methods

2.1. Data source

This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (TPEVGH IRB No.: 2015-10-008CC; Taipei, Taiwan). Medical data were extracted from the National Health Insurance Research Database (NHIRD) for the years 1998−2011. The National Health Insurance (NHI) is a social health insurance system with almost 100% of Taiwanese citizen enrolled (i.e., 94.7% of the national population in 1998 and 99.9% in 2011).[9] Approximately 23 million people are registered in the NHI system,[10] with the NHIRD providing a comprehensive health database including, but not limited to, diagnostic codes, date of registration, sex, birthday, and dates of hospitalization.

2.2. Study patients

IBDs are classified as catastrophic illnesses by the NHI, and patients receive financial support to cover medical costs. To receive a catastrophic illness certificate (CIC), the medical data of patients with suspected IBD are thoroughly reviewed by a gastroenterologist commissioned by the Bureau of the NHI. Evaluation is based on thorough documentation of the clinical course, laboratory tests, imaging studies, endoscopic pictures, and pathological findings. Patients with a CIC with International Classification of Diseases 9 (ICD-9) codes of 555 for CD and 556 for UC were identified for our study, and their medical records, including outpatient and hospitalization records, were extracted from the database and reviewed.

2.3. Epidemiology and clinical presentations

Annual incidence rates were calculated by dividing the number of newly registered IBD patients in the CIC database each year by the group at risk (per 100,000 persons). The "at-risk" group consisted of the total inhabitants in Taiwan, each year between 1998 and 2011, according to the records of the Department of Household Registration.[9]

The diagnosis of GI complications and EIMs was confirmed by the associated ICD-9 code registered in the outpatient and hospitalization records in NHIRD. GI complications associated with IBDs, defined as "complicated GI presentations," including intestinal lesions (abscess: 569.5; fistula: 569.81; perforation: 569.83), intestinal obstructions (560.*X*), peritonitis (567.*X*), PD (anal fissure: 565; anal fistula: 565.1; perianal abscess: 566), and benign and malignant neoplasm of colon (211.3), were identified. A series of EIMs were identified and included in our analysis[11] (associated ICD codes are mentioned in Table 1). GI complications and EIMs diagnosed before the registration of an IBD were excluded from our analysis.

2.4. Statistical analysis

Statistical evaluation was conducted using the Chi-square test, Fisher's exact test, and Yates' correction or Pearson's Chi-square test, depending on the nature and distribution of the data. All analyses were performed using the SPSS version 20.0 statistical package (SPSS Inc., Chicago, IL, USA), with $p < 0.05$ determined to be statistically significant.

Table 1
Prevalence of extraintestinal manifestations in Crohn's disease and ulcerative colitis in Taiwan.

Extraintestinal manifestations	ICD-9-CM	Crohn's disease	Ulcerative colitis	p[a]
		n (%)	*n* (%)	
Musculoskeletal diseases				
Peripheral arthritis	713.1, 715.0−715.9	37 (6.1)	155 (6.1)	>0.99
Ankylosing spondylitis	720	11 (1.8)	44 (1.7)	>0.99
Bone manifestations				
Osteoporosis	733.0	14 (2.3)	40 (1.6)	0.292
Hepatobiliary diseases				
Cholangitis	576.1	13 (2.1)	20 (0.8)	0.007
Pancreatic diseases				
Pancreatitis	577.0, 577.1	12 (2.0)	17 (0.7)	0.006
Mucocutaneous diseases				
Erythema nodosum	695.2	11 (1.8)	7 (0.3)	<0.001
Pyoderma gangrenosum	686.0	0 (0)	11 (0.4)	—
Blood & vascular diseases				
Venous/arterial thromboembolism	453, 453.2−453.9 444	9 (1.5)	18 (0.7)	0.072
Renal diseases				
Glomerulonephritis	580, 581, 582, 583	8 (1.3)	22 (0.9)	0.434
Neurological diseases				
Peripheral neuropathy	356.8	3 (0.5)	7 (0.3)	0.652
Ocular diseases				
Iritis/uveitis	364.0−364.3	2 (0.3)	4 (0.2)	0.727
Scleritis/episcleritis	379.0	1 (0.2)	2 (0.1)	>0.99
Bronchopulmonary diseases				
Bronchiectasis	494	0 (0)	13 (0.5)	—

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.
[a] The p value is from Chi-square test.

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3. Results

3.1. Patient characteristics and incidence

A total of 3153 patients with IBDs, 611 with CD and 2542 with UC, were registered in the CIC database between January 1, 1998, and December 31, 2011 (Table 2). The incidence of CD and UC was higher in men as compared with that in women. The median age at registration was 36.6 years for CD and 43.6 years for UC. Of newly registered patients with an IBD, 62% were between 30 years and 60 years of age. The median duration of follow-up was 64.3 months (range, 0.07–167.2 months).

The mean annual incidence of CD and UC, for the period of 1998–2011, was 0.19 (95% confidence interval, 0.15–0.23) and 0.80 (95% confidence interval, 0.68–0.91) per 10^5 inhabitants, respectively. The incidence of CD increased gradually from $0.13/10^5$ inhabitants in 1998 to $0.33/10^5$ inhabitants in 2011. The incidence of UC also increased from $0.51/10^5$ inhabitants in 1998 to $0.84/10^5$ inhabitants in 2011, with its highest incidence rate of $1.10/10^5$ inhabitants recorded in 2010 (Fig. 1).

3.2. GI complications

The prevalence of GI complications of IBDs is summarized in Table 3. Of all patients with an IBD, 699 (22.2%) presented with at least one GI complication. The prevalence of GI complications was higher in patients with CD, compared with UC (33.6% and 19.4%, respectively; $p < 0.001$), and in males, compared with females (24.7% and 18.0%, respectively; $p < 0.001$). Changes of GI complications with the duration of follow-up are shown in Fig. 2. At 14 years of follow-up, UC patients were found to have a steadily increasing prevalence of GI complications, while CD patients were found to reach the peak prevalence of GI complications at the 9th year and thereafter reach a plateau.

Intestinal lesions, including abscesses, fistula, and perforation, were more common in patients with CD. However, it was noted that age at CD onset affected the disease presentation. Pediatric patients with CD registered before 16 years of age were at the highest risk for developing intestinal lesions, compared with two other age groups (younger than 16 years, 17.2%; 17–40 years, 13.8%; older than 40 years, 8.2%; $p = 0.04$).

PDs, such as anal fissure, fistula, and perianal abscess, were more common in patients with CD compared UC. The occurrence of anal fistulas was significantly higher in patients with CD, with a higher prevalence in males (7.1% and 3.9%, respectively; $p = 0.008$). Benign neoplasms of the colon were more frequent in patients with UC compared with those with CD, with males, again, being at higher risk (7.0% and 4.1%, respectively; $p = 0.039$).

A total of 11 patients, one with CD and 10 with UC, were diagnosed with colorectal cancer (CRC), with the majority of these patients being male (male, 9; female, 2). The overall prevalence of CRC in patients with IBDs was 0.35%, with a prevalence of 0.39% in patients with UC and 0.16% in patients with CD. The median age of CRC diagnosis was 51.3 years in patients with UC and 66.7 years in patients with CD. The median duration of IBD prior to CRC diagnosis was 94.7 months in patients with UC and 96.7 months in patients with CD.

Table 2
Demographic characteristics of patients with IBD in Taiwan.

	Crohn's disease	Ulcerative colitis	IBD
	n (%)	*n* (%)	*n* (%)
No. of patients	611 (19.4)	2542 (80.6)	3153 (100)
Male/female	411 (13.0)/ 200 (6.4)	1551 (49.2)/ 991 (31.4)	1962 (62.2)/ 1191 (37.8)
Age (y) at registration			
≤16	64 (10.5)	52 (2.0)	116 (3.7)
17–40	290 (47.5)	1001 (39.4)	1291 (40.9)
>40	257 (42.0)	1489 (58.6)	1746 (55.4)

IBD = inflammatory bowel disease.

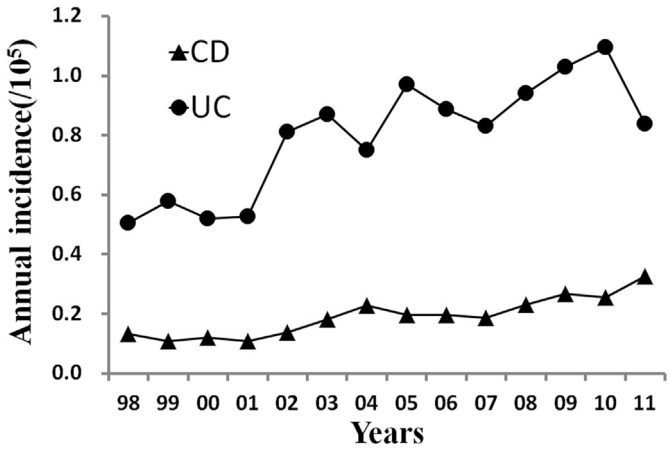

Fig. 1. Annual incidence of CD and UC in Taiwan, from 1998 to 2011. CD = Crohn's disease; UC = ulcerative colitis.

Table 3
Prevalence of gastrointestinal complications in Crohn's disease and ulcerative colitis in Taiwan.

Anatomic lesions	ICD-9-CM	Crohn's disease	Ulcerative colitis	p[a]
		n (%)	*n* (%)	
Intestinal obstruction	560, 560.8, 560.9	109 (17.8)	140 (5.5)	<0.001
Intestinal lesions		72 (11.8)	55 (2.2)	<0.001
Fistula	569.81	48 (7.9)	17 (0.7)	<0.001
Perforation	569.83	29 (4.7)	40 (1.6)	<0.001
Abscess	569.5	12 (2.0)	6 (0.2)	<0.001
Perianal disease		57 (9.3)	175 (6.9)	0.038
Anal fistula	565.1	34 (5.6)	75 (3.0)	0.002
Perianal abscess	566	26 (4.3)	86 (3.4)	0.355
Anal fissure	565	16 (2.6)	51 (2.0)	0.432
Peritonitis	567.2, 567.9	54 (8.8)	67 (2.6)	<0.001
Benign neoplasm of colon	211.3	25 (4.1)	161 (6.3)	0.036
Colorectal cancer	153.0–153.9 154.0–154.8	1 (0.4)	10 (0.2)	0.402

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.
[a] The p value is from the Chi-square test.

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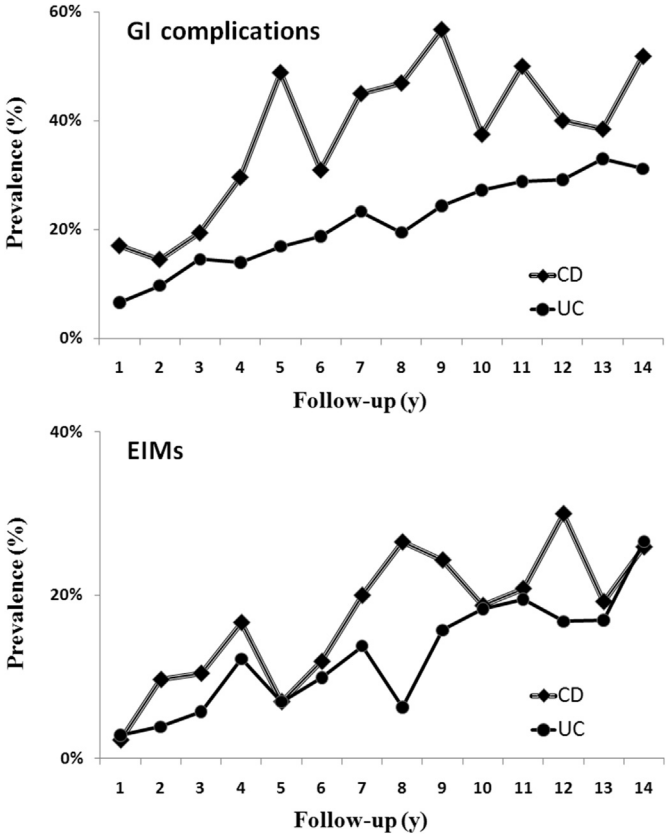

Fig. 2. Change of the prevalence of GI complications and EIMs by CD and UC patients over a 14-year follow-up period. CD = Crohn's disease; EIM = extraintestinal manifestation; GI = gastrointestinal; UC = ulcerative colitis.

3.3. Extraintestinal manifestations

The prevalence of EIMs is summarized in Table 1. In our study group, EIMs were reported in 11.9% of cases (375 patients). Peripheral arthritis was the most common EIM reported in both CD and UC patient groups. Overall, EIMs were more frequently associated with CD, compared with UC (14.9% and 11.2%, respectively; $p = 0.011$), with more frequent presentation in females than in males (14.6% and 10.2%, respectively; $p < 0.001$). After 14 years of follow-up, the prevalence of EIMs increased from 2.3% to 25.9% and from 2.8% to 26.6% in patients with CD and UC, respectively (Fig. 2). Among the major EIMs affecting the articular, cutaneous, biliary, and visual systems, the prevalence of peripheral arthritis increased steadily throughout the follow-up period, whereas that of other EIMs remains relatively constant (Fig. 3).

Joint manifestations were comparable between CD and UC, with the incidence of associated peripheral arthritis being higher for females than for males in both groups (CD: 10.5% and 3.9%, respectively, $p = 0.002$; UC: 7.9% and 5.0%, respectively, $p = 0.003$). In the UC group, 11 (0.4%) patients had pyoderma gangrenosum, with a higher incidence in females, compared with males (0.8% and 0.2%, respectively; $p = 0.034$), with no cases identified in the CD group. By contrast, erythema nodosum was more commonly associated with CD than with UC. Cholangitis, including primary sclerosing cholangitis (PSC), was diagnosed in 13 (2.1%) patients with CD and 20 (0.8%) with UC. Pancreatitis was also more frequently noted in CD than in UC. Other EIMs involving the ocular, respiratory, renal, vascular, and neurological systems appeared less frequently (Table 1). Generally, there was no significant difference in the prevalence of these rare EIMs between the CD and UC groups.

4. Discussion

Analyzing the large population-based IBD cohort, the present study has three main findings. First, the incidence of IBD in Taiwan increased almost two-fold from 1998 to 2011. Second, patients with CD presented with more complex disease, with more GI complications and EIMs. Third, age of IBD presentation affected the development of GI complications, and patients with an early onset of CD were at higher risk to have complicated intestinal disease. Moreover, this retrospective study represents comprehensive information about IBD presentation, useful for understanding the different manifestations of these diseases in Taiwan and Western countries.

Owing to the characteristics of transmural inflammation in CD, intestinal complications including stricture, fistula, abscess, and perforation were more common in CD. Ramadas et al[12] reported an increase in the incidence of mucosal lesions, from 15% at the time of diagnosis to 32% at 5 years post-diagnosis for strictures, and an increase from 4% to 23% for penetrating mucosal lesions. The incidence of intestinal lesions was relatively low in our study group, with an incidence rate of 11.8% over a mean 5.8-year follow-up.

Previous studies have provided evidence that the development of CD in children and adolescents is more severe and extensive, compared with that in adults, often resulting in significant intestinal complications, including strictures and perforation.[13,14] Our study also demonstrated a significantly higher incidence of intestinal lesions among patients who developed CD before 16 years of age. Therefore, age of onset is a critical factor in estimating the rate of developing a complex disease progression of CD.

PD in patients with IBD has usually been considered to be related to CD. Our study also demonstrated the increasing frequency of PD, especially anal fistula, in patients with CD. In CD, anal fissures had been identified in 21−35% of cases and abscesses, usually accompanied with fistulas, in 23−62% of patients.[15] Our study revealed a low incidence (10.5%) of PD in patients with CD, similar to the findings of a study in China in which PD was identified in only 5.6% of patients with CD.[16]

The most common benign tumors in the colon are colorectal polyps. In a general Taiwanese population, Wang et al[17] reported a prevalence of 11.1% for hyperplastic polyps and 16.1% for adenomatous polyps. Our study demonstrated a relatively low prevalence of colorectal polyps of 6.3% in patients with UC and 4.1% in patients with CD. Kitiyakara et al[18] also found that only 4% of UC patients had dysplastic

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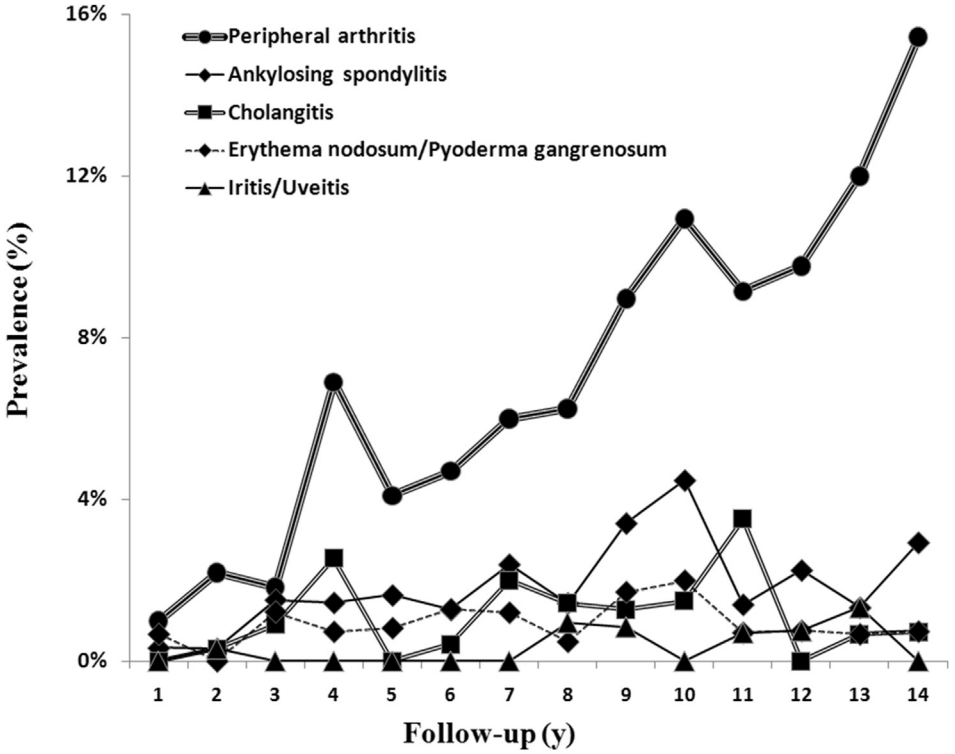

Fig. 3. Change of the prevalence of major EIMs in patients with IBD over a 14-year follow-up period. EIM = extraintestinal manifestation; IBD = inflammatory bowel disease.

colonic polyps, while 12% of the control patients had adenomatous polyps. It is possible that the use of 5-aminosalicylic acid in the treatment of IBDs may prevent the formation of adenomas.

Patients with IBD are considered to be at increased risk for CRC. A meta-analysis of 116 studies estimated the prevalence of CRC in patients with UC to be 3.7% in Western countries.[19] The annual incidence of CRC in patients with UC was reported to range between 0.13% and 0.3%.[19,20] The risk for CRC in patients with CD was found to be similar to that in patients with UC, and approximately two- to three-fold greater than that in the general population.[21] A series of studies in Asia revealed a relatively low prevalence of UC-associated CRC of 0.0−2.2%, which was comparable with the prevalence in our study.[7]

The reported prevalence of EIMs in patients with IBDs has been reported to vary between 25% and 47% in Western countries.[7,22,23] By contrast, an overall lower rate of EIMs (6−14%) have been reported in East Asia.[24] Owing to differences in the definition of EIMs, the true prevalence of EIMs is difficult to define. In our study, we included only EIMs with an immunological background and not with other symptoms secondary to the complication of IBD. The overall prevalence of EIMs in our study (11.9%) was similar to that reported in East Asia, with a higher incidence among females and patients with CD, comparable with previous studies.[25]

Two types of joint involvement are associated with IBD, peripheral arthritis and axial arthropathy. A previous study of 1459 patients with IBDs reported a prevalence of peripheral arthritis of 10% in patients with CD and 6.1% in patients with UC.[26] Axial arthropathy was identified in 10−20% of patients with IBD, and a final diagnosis of ankylosing spondylitis (AS) in 2−10% of patients.[27] Comparing the epidemiology of joint involvement in IBD with that in previous studies, the prevalence of peripheral arthritis was relatively low in our study, including a low occurrence of AS. However, the prevalence of AS in patients with IBDs may be underestimated in Taiwan due to the time required to fulfill the diagnostic criteria of AS.

We found that the prevalence of peripheral arthritis increased from 1% to 15.4% after 14 years of follow-up. Palm et al[28] also described a three-fold increase of peripheral arthritis after 6 years of IBD (3.5−12%), whereas Vavricka et al[29] found 46% and 17% patients with CD and UC, respectively, developed peripheral arthritis after 30 years of disease duration. “Gut synovial-axis” hypothesis may explain the increasing rate of peripheral arthritis.[30] Damage to the intestinal epithelial cell leads to contact of the gut flora with the antigen-presenting cells, thus activating innate immunity.[31] As the disease course goes on, repeated exposure of microbial antigens in the gut may trigger stronger immune response and subsequent development of arthritis.

Pyoderma gangrenosum is a neutrophilic dermatosis and often occurs in association with a systemic disease.[32] Pyoderma gangrenosum has been reported in 1−10% of patients with UC and 1−2% of patients with CD, with a slight predilection for females.[33,34] Erythema nodosum is the most common cutaneous manifestation of IBD. In a cohort study of 2402 patients in France, erythema nodosum was found to affect 5.6% of

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patients with CD and 1.2% with UC.[35] Several putative genes were identified in the association of erythema nodosum, pyoderma gangrenosum, and IBD.[36] Our study revealed a low prevalence of skin manifestation associated with both CD and UC. The difference in genotypes between ethnic groups could influence the clinical presentation of IBDs.

PSC is closely associated with IBD, particularly UC. In Western countries, PSC is estimated to affect 2−7.5% of patients with IBD, with a lower prevalence in Asia (0−1.7%).[7,11,37] In our study, the diagnosis of PSC was based on the ICD code 576.1. However, the ICD code 576.1 is not specific to PSC, but rather includes a spectrum of cholangitis. Therefore, evaluation of the prevalence of IBD-associated PSC is limited to using the NHIRD. Further studies are needed to investigate the clinical features of PSC in Taiwan.

In Taiwan, studies focusing on the clinical features of GI complications and EIMs in patients with IBD are rare. A single medical center-based study between 1988 and 2008 revealed EIMs in 4.5% of 406 UC patients.[38] Any disparity between Wei et al's[38] study and our report may be due to the different inclusion criteria of EIMs and the patient number. In the same study, Wei et al[38] also found that colon cancer was noted in six of 406 patients (1.5%), which was higher than that in our study (0.2%). This may be because the patients in Wei et al's[38] study were collected from a tertiary referral center, with more complicated disease. Another study detailing the clinical features of CD in Taiwan revealed that intra-abdominal abscess and intestinal perforation were noted in 5.5% and 3.6%, respectively, of 110 patients with CD in the same medical center between 1988 and 2008. The result corresponded to our report, which demonstrates that patients with CD in Taiwan have a relatively benign disease course compared with those in Western countries.

There are some limitations to this study. First, collected information was derived from an administrative database, using ICD-9 diagnosis code, and the accuracy of diagnoses cannot be assessed fully. In order to maximize case ascertainment, we included patients with IBD who were registered in the CIC database. Second, age of registration in the database may not represent the real age of disease onset in some patients with IBD; there may have been a time lag in registration. Third, NHIRD lacked clinical symptoms and laboratory data. Therefore, further analyses by disease behavior, activity in IBD, and the association with comorbidity could not be demonstrated. However, even with these intrinsic limitations of NHIRD, the information is comprehensive and valuable regarding the presentation of IBD.

In conclusion, this is the first nationwide population-based study focusing on the clinical features of IBD in Taiwan. Our study revealed distinct differences in the epidemiology of GI complications and EIMs associated with IBDs, compared with rates reported in Western countries. Generally, the risk for GI complications and EIMs was higher in patients with CD. The prevalence of intestinal lesions, PD, and major EIMs affecting the articular, cutaneous, and ocular systems was less common than the prevalence reported in Western countries. Both genetic and environmental differences may contribute to these unique epidemiological differences between Taiwan and Western countries. Age at disease presentation and sex also affect the clinical presentation of IBDs. Future studies investigating other associated factors may help establish a predictive model of the clinical course of IBDs in Taiwan.

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