

Original Article

## Long-term follow-up of ulcerative colitis in Taiwan

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Received August 29, 2011; accepted December 15, 2011

### Abstract

**Background:** The incidence of ulcerative colitis (UC) has been increasing in Asia recently, but little long-term follow-up data is available. We aimed to understand the clinical characteristics of UC patients in the National Taiwan University Hospital (NTUH), a tertiary referral center in Taiwan.

**Methods:** A retrospective study was conducted to review data from January 1, 1988 through December 31, 2008 compiled at NTUH. Patients' clinical information, demographic data, endoscopic pictures, treatment regimens, pathologic, and outcome details were reviewed, recorded, and analyzed.

**Results:** A total of 406 patients were included (233 males and 173 females; median age at diagnosis was 36 years). The follow-up period ranged from 0.25 to 40.8 (mean, 7.3) years. The prevalence of UC in Taiwan was at least 7.4/100,000 in 2008. Bloody stool was the most common presentation (77.3%). Total colon was the most common (41.0%) disease involvement and proctitis the least common (21.1%). Six patients (1.5%) died during the follow up. Most of the UC patients (72.4%) could be controlled with 5-aminosalicylic acid alone, but about one third (30.9%) were admitted for treating the UC or UC-related complications. Twenty-three patients (5.5%) were treated surgically. Extra-gastrointestinal tract manifestations were noted in 4.5% of the UC patients, with primary sclerosing cholangitis (6 in 406, 1.5%) the most common. Colon cancer/severe dysplasia occurred in six (1.5%) of the patients.

**Conclusion:** The incidence of UC has increased in Taiwan. Interestingly, CRC/dysplasia and PSC occur more frequently here than in other Asian nations.

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**Keywords:** colorectal cancer; primary sclerosing cholangitis; Taiwan; ulcerative colitis

### 1. Introduction

The inflammatory bowel diseases (IBDs) Crohn's disease (CD) and ulcerative colitis (UC) are common causes of chronic gastrointestinal disease in the developed world. Initially regarded as a Western style disease, IBD is increasing in both incidence and prevalence in many parts of the Asia Pacific area.<sup>1–8</sup> The reason for this increasing trend has not been established but is most likely related to environment factors, including

improved hygiene and “Westernization” of diet.<sup>9</sup> We previously showed that CD has increased in both incidence and prevalence in Taiwan.<sup>10</sup> However, the status of UC in Taiwan has not been reported.

In Asia, ulcerative colitis has been reported to be milder in severity (lower surgical rate, less colorectal cancer (CRC) and fewer extraintestinal manifestations) than that seen in Western countries. However, most of the reports lacked long term follow-up. The National Taiwan University Hospital (NTUH) is a tertiary referral center in Taipei, Taiwan, with the first case of ulcerative colitis being diagnosed in 1969. Here, we present a summary of UC cases treated in our hospital from 1989 to 2008, which adds to the previous reports from other Asian countries.

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2. Methods

We searched the database of chart records from January 1988 through December 2008 in NTUH, a tertiary medical center in Taiwan. We used the International Classification of Disease (2001 version) for disease coding, UC as 556.9, CD as 555.9, respectively, at NTUH. All data were reviewed completely by the same gastroenterologist, and only those cases that have received more than 3 months of treatment and follow-up after the original UC diagnosis were included in this study. The definition and criteria for UC diagnosis included the combination of clinical, endoscopic, and histologic features and the exclusion of an infectious etiology. This study was approved by the institutional review board of ethics committee of NTUH.

To analyze the clinical characteristics of UC patients in Taiwan, the anatomic distribution of the disease at the time of diagnosis and during clinical follow-up was determined by endoscopic evaluation. We collected clinical data including age at diagnosis, the symptom/sign and the disease course of UC. History of surgery, presence of fistula, extragastrointestinal tract manifestations and the clinical course of the patients were recorded and analyzed. The follow-up duration of our patients started at the time of diagnosis and ended at the last date recorded in the chart.

3. Results

A total of 406 patients diagnosed with UC were included in this analysis. The median age at diagnosis was 36 years (range, 1.2–82 years). The age of disease onset in our UC patients is shown in Fig. 1. There were 233 men and 173 women included in the study, with a man-to-woman ratio of 1.35:1. The follow-up period ranged from 0.25–40.83 years, with a mean follow-up period of 7.3 years. Six of the 406 patients had a family history of UC (1.5%); three involved two generations and three involved the same generation. The number of newly diagnosed

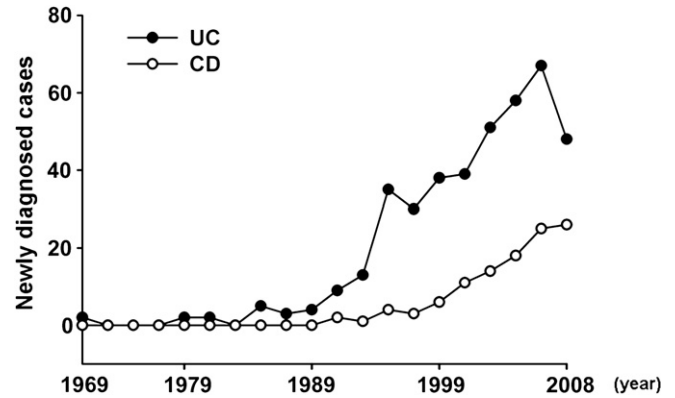


Fig. 2. Comparison of newly diagnosed UC and CD cases. CD = Crohn's disease; UC = ulcerative colitis.

UC patients per year from 1969–2008 is shown in Fig. 2. When we arbitrarily grouped the 406 patients according to the year of diagnosis starting with pre-1989, then at 5-year intervals from 1989 until 2008, the number of UC patients doubled every 5 years from pre-1989 to 1998 (2.2- and 2.0-fold, respectively). Subsequently, the slope of the number of increasing cases decreased gradually from 1999 to 2008 (1.4- to 1.2- fold). We also compared the newly diagnosed rate of UC with that of CD during the same period in the same hospital (Fig. 2). This showed that both types of IBD had gradually increased in Taiwan. According to the registration record in the National Health Insurance of Taiwan, 1560 UC patients had been registered till 2008. The prevalence of UC in Taiwan is at least 7.4/100,000 in 2008, as there are UC patients who have not as yet been registered.

The clinical characteristics of the UC patients seen at NTUH are summarized in Table 1. Blood in the stool was the most common presentation of UC (314/406, 77.3%) in Taiwan. Total colon-type involvement (Montreal classification E3) was the most common (166/406, 41.0%) and proctitis (Montreal classification E1) was the least commonly (86/406,

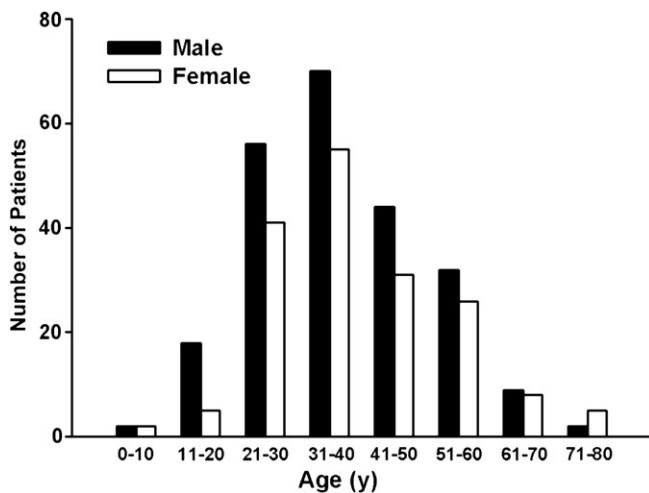


Fig. 1. Distribution of sex and age at diagnosis of 406 patients with UC. UC = ulcerative colitis.

Table 1  
Clinical characteristics of patients with UC.

Patients	(n = 406)
Sex	
Men	233 (57.4%)
Women	173 (42.6%)
Age at diagnosis (y)	
Range	1.2–82
Median	36
Follow-up period (y)	
Range	0.25–40.83
Mean	7.3
Family history of UC	6 (1.5%)
Extent of disease	
Proctitis (E1)	86 (21.1%)
Left-side colon (E2)	154 (37.9%)
Total colon (E3)	166 (41%)

UC = ulcerative colitis; y = year.

21.1%) seen disease involvement. Among the proctitis and left-side colon type patients, only 7.4% have been recorded to have proximal extension during the follow-up period. Stenosis occurred in 3.9% (16/406) of patients. Perforation happened to 1% (4/406) of patients. Six patients (6/406, 1.5%) died during the follow-up period, two of sepsis, two of advanced rectal cancer, one of multiorgan failure after surgery for massive bleeding, and one of primary sclerosing cholangitis (PSC)-related cholangiocarcinoma with lung metastasis.

The majority of our UC patients (294/406, 72.4%) could be controlled with 5-aminosalicylic acid (5-ASA) alone. About a one-fourth of the UC patients (108/406, 26.6%) received steroids for disease management and 4% became steroid-dependent. A small percentage of UC patients were treated with immunosuppressive agents: methotrexate, 4.6%; tacrolimus, 0.8%; hydroxychloroquine sulfate, 1.0%; cyclosporine A, 0.3%. Among these patients, about one-third (125/406, 30.8%) were admitted for treating UC or UC-related complications. Most of these admissions were one (220/406, 54.2%) or two (69/406, 17.0%) times, but there was one patient who had to be admitted 15 times for treating UC.

A total of 23 patients (5.5%) were operated on for UC-related conditions. The reasons for surgical intervention are listed in Table 2. The most common was failure of medical treatment (43.5%). Associated extragastrointestinal tract manifestations were noted in 4.5% of our UC patients (Table 3), the most common of which was PSC (six in 406, 1.5%). Two of the six PSC patients received liver transplants due to liver failure and remain in our outpatient clinic follow-up. One patient died of cholangiocarcinoma.

Colon cancer (adenocarcinoma)/severe dysplasia was noted in six of our patients (1.5%). Most of them were women (man-to-woman ratio, 0.2:1). By location, the cancers were all distal-type (four at the rectum and two at the sigmoid colon). Two patients were referred for suspicious lesions; therefore, no long-term records could be traced for them. One was referred for an anal stricture lesion, which was confirmed by endoscopic biopsy as poorly differentiated rectal cancer and with advanced disease status. Following consultation, the patient preferred to receive supportive treatment at the original hospital as her general condition was poor. Another referral patient was also confirmed to have sigmoid colon cancer. Surgery was

Table 2  
Surgical indications of patients with UC.

Indications	Number
Refractory to medical treatment	10
Stenosis	2
Perforation	2
Massive bleeding	2
Fistula	1
Perianal abscess	1
Cancer	3
Adenocarcinoma	2
Lymphoma	1
Liver transplant	2
Total	23

UC = ulcerative colitis.

Table 3  
Extragastrintestinal manifestations of patients with UC.

Manifestations	Number
Sicca syndrome	1
Primary sclerosing cholangitis	6
Erythema nodosum	2
Spondyloarthropathy	2
Immunoglobulin M mesangial nephropathy	1
Autoimmune hemolytic anemia	1
Uveitis	1
Antiphospholipid syndrome	2
Grave disease	1
Reiter syndrome	1
Deep venous thrombosis	1
Total	19

UC = ulcerative colitis.

performed and pathological staging of Stage 3 was noted. This patient also received postoperative chemotherapy. Sixteen months post surgery, she returned to the original hospital for further follow-up.

Of the other four patients diagnosed with UC and receiving follow-up care in our hospital, three presented with early lesions (two tubulovillous adenoma with focal intraepithelial carcinoma and one dysplasia). All lesions were removed by polypectomy. The final case was diagnosed with UC in 1979 and received subtotal colectomy in 1985 due to poor response to medical treatment, then was lost to follow-up. However, in 2002, this patient returned due to bloody stool, at which time rectal cancer was diagnosed. She had surgery and received chemotherapy but later died due to cancerous peritonitis. Of the four patients diagnosed with cancer/dysplasia in our hospital, the cancer diagnosis occurred 10.3, 15, 17.8, and 22.5 years, respectively, after the diagnosis of UC. We calculated the cumulative CRC rate in our UC patients, although the rate would be lower than the exact condition (we are omitting the two CRC patients without complete follow-up). Fig. 3 showed that the 10-, 20-, and 30-year cumulative CRC rate was

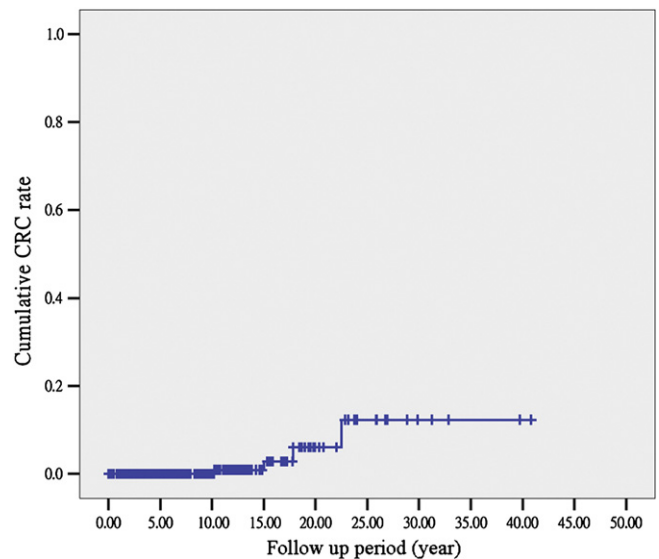


Fig. 3. Cumulative probability of colorectal cancer in patients with UC. UC = ulcerative colitis.

0%, 6%, and 12.3%, respectively. In addition to the six CRC patients, the biopsy of another patient revealed a poorly differentiated carcinoma of the ascending colon, while the final report from the surgical specimen confirmed it to be a plasmacytoid lymphoma. Adenoma was recorded in 15 patients (15/406, 3.6%). Thirteen were tubular adenoma and two were tubulovillous adenoma. They were mostly located in the sigmoid colon (8/15, 53.3%), followed by the ascending colon (4/15, 26.7%), and the other three were located at the cecum, transverse colon, and rectum, respectively.

Being in an endemic area for hepatitis B, we also reviewed the hepatitis B status in our UC patients. Among them, two were hepatitis B carriers (both were hepatitis B surface antigen-positive and Hepatitis B e antigen (HBeAg) antibody-positive) had acute exacerbation of hepatitis B while receiving immunosuppressive therapy. Both cases occurred before it was deemed necessary to prescribe prophylactic treatment. Fortunately, the hepatitis could be controlled with nucleoside analog treatment (one patient with lamivudine and the other with entecavir).

#### 4. Discussion

Our results clearly show that in recent decades, the incidence of UC in Taiwan has markedly increased. In addition to our previous reports on CD patients,<sup>10,11</sup> our results show that the incidence of IBD in general in Taiwan has also increased. According to the registration record in the Bureau of National Health Insurance of Taiwan, 1560 UC patients had been registered before 2008. The prevalence of UC in Taiwan is greater than 7.4/100,000, as a number of UC patients have yet to be registered. The prevalence of UC in Taiwan is slightly greater than that in China (6.99/100,000) but much less than in Korea (30.87/100,000) and Japan (63.6/100,000).<sup>6</sup> It has been noted that there is a trend toward an increased incidence of UC in the Asia-Pacific area, according to reports from Japan, Korea, Singapore, and China.<sup>1,4,5,7,8,12</sup> Our results provide further evidence to support this condition. According to the chart records, the first case to be diagnosed as IBD (UC) in our hospital was in 1969, earlier than the first case from most of the other Asian countries except Japan.<sup>2,4,6,7,13</sup> This permitted us to have a relatively longer follow-up than most of the other studies from Asia.

The clinical presentation of our UC patients was most commonly “bloody stool,” the same as in the Korean report.<sup>14</sup> The sex ratio (man-to-woman, 1.35:1) was similar to that of the report from China (1.34:1)<sup>15</sup>; however, our patients tended to be diagnosed at a younger age, i.e., 36 years of age in our series compared with 44 or 49 years of age in the Chinese studies.<sup>4,15</sup> Our age at diagnosis is similar to reports from Japan and Korea (34 and 35 years of age, respectively).<sup>1,12</sup> Total colon involvement was the most common type of disease, seen in 41% patients, followed by left-side colon type (38%), with proctitis the least common (21%). The ratio of each subtype was almost the same as reported from Japan,<sup>12</sup> with less proctitis than Korea and China.<sup>1,4,15</sup> Proximal extension rate (7.5%) was lower in

our series, probably because we already have more patients as total colon type.

The severity of disease in our UC patients was evaluated by the following criteria: the admission ratio, the proportion needing immunosuppressive treatment, the surgical rate, and the complication rate. About one-third (30.9%) of our patients were admitted to hospital for treatment of UC or UC-related complications. Most of them were admitted only once (54.3%) or twice (17.1%), but there was one patient admitted 15 times for treatment of UC. The majority of our UC patients (72.4%), as in the reports from Japan<sup>12</sup> and Korea,<sup>14</sup> could be controlled by using 5-ASA alone. About one-fourth of our UC patients (26.5%) received steroids for disease control, and 4% became steroid-dependent. The need to use other immunosuppressive agents was also seen in a small population of our patients, (methotrexate, 4.6%; tacrolimus, 0.8%; hydroxychloroquine sulfate, 1.0%; cyclosporin A, 0.3%). Twenty-three patients (5.5%) required surgery for UC-related conditions. The colectomy rate was about 5%, which was within the range seen in other Asian countries (3% from Korea, 6.4% from Hong Kong China).<sup>1,4</sup>

CRC and dysplasia occurred in our patients at a higher rate (1.5%), than in Korea (0.36%)<sup>16</sup> and Hong Kong (0.6%).<sup>4</sup> The CRC and dysplasia rate in our series was comparable to rates reported in Western countries (1%–2%).<sup>17</sup> Furthermore, CRC contributed to 33.3% of our UC mortality rate, which was higher than the 15% reported in Western countries.<sup>17</sup> Earlier diagnosis of CRC and dysplasia and improvement of the prognosis are two goals of our future practice. The two cases of CRC in our series resulting in patient death included a history of colectomy then loss to follow-up. In both cases, the patients returned to hospital only when the cancer occurred. We, therefore, emphasize the importance to our UC patients of regular follow-up, even after they have received colectomy, thereby increasing the chances of early detection of malignant lesions.

Risk factors of UC-associated CRC have been reported as PSC, severe and longstanding disease, and male predominance.<sup>4,18</sup> Interestingly, none of our five PSC patients have developed CRC to date. Five of the six patients with UC-associated CRC and dysplasia were women, but of the four patients for whom we have complete clinical records, all developed CRC and dysplasia at least 10 years after UC diagnosis (10.3, 15, 17.8, and 22.5 years after diagnosis). These cases support the recommendation for colonoscopic surveillance of UC patients after 8–10 years of extensive colitis and 12–15 years of left-side colitis.<sup>19</sup> The standard diagnostic procedure in long-lasting UC is to take four biopsies every 10 cm. Image enhancement methods, such as chromoendoscopy and virtual histology using endomicroscopy, have greatly improved neoplasia detection rates and may contribute to reduced random biopsies by taking targeted “smart” biopsies.<sup>20</sup>

Extraintestinal manifestations of UC occurred in 4.5% of our patients. Among them, PSC was most commonly seen in Taiwan (six in 406 UC patients, 1.5%). Previously, only scant reports of PSC in UC patients have been published, but no prevalence of such a condition has been reported in the Asia Pacific area. The incidence of PSC in UC patients in Western

countries was reported to be 2%–7%.<sup>21</sup> Two of our PSC patients required liver transplants for decompensated liver function. Both of them now have good liver function. The cause of death of one of our UC patients with PSC complications was cholangiocarcinoma with lung metastasis. From our study, we conclude that PSC is not so rare and not as mild as previously thought in Taiwan.

Zeitz and colleagues<sup>22</sup> have reported a case of hepatic failure due to hepatitis B reactivation in a UC patient treated with prednisone. The Asia-Pacific consensus on ulcerative colitis has suggested that UC patients in the highly endemic areas of hepatitis B virus infection require stringent screening before initiating immune-suppressive agents.<sup>8</sup> As Taiwan is an endemic area of hepatitis B, and we have accumulated vast experience managing hepatitis B patients while they are receiving the immunosuppressive agents or chemotherapy.<sup>23</sup> In accordance with the American Association for the Study of Liver Diseases guidelines,<sup>24</sup> antiviral treatment should continue for 6 months after completion of immunosuppressive therapy or until end points for chronic hepatitis B virus infection in immunocompetent patients have been reached. In highly endemic areas, profound immunosuppression may increase the risk of hepatitis B virus reactivation not only in carriers of hepatitis B virus surface antigen (HBsAg) but also in patients with resolved HBV infection. For HBsAg-negative and anti-hepatitis B virus core antigen (Hepatitis B core antibody (anti-HBc))-positive patients who are candidates to receive immunosuppressive agents, monitoring and follow-up of hepatitis B virus DNA levels can enable earlier detection of reactivation and earlier treatment with the necessary antiviral agent.

In conclusion, much like what has been reported for CD in Taiwan, the incidence of UC in Taiwan has also increased. Although most patients in our study could be managed by medical treatment alone, one-third required hospital admission during the course of disease and 5.5% required surgical treatment. CRC and dysplasia and PSC occurred more frequently than previously reported from other Asian countries. In order to decrease CRC and dysplasia-related mortality, we recommend follow-up colonoscopy surveillance for detecting CRC and dysplasia after 8–10 years of extensive colitis and after 12–15 years of left-side colitis.

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