Original Article

Surgical Experience of Crohn's Disease – A Single-center 30-year Case Analysis

Chih-Tien Chen
Hwei-Ming Wang
Joe-Bin Chen
Hsiu-Feng Mar
Chou-Chen Chen
Feng-Fan Chiang
Kuan-Min Lin
Te-Hsin Chao
Department of Surgery, Colorectal Section,
Taichung Veterans General Hospital,
Taichung, Taiwan

Background. Crohn's disease is a relatively rare disease in Asian. An increasing incidence has been observed but domestic data for Crohn's disease was still lacking. The aim of this study was to assess the clinical course of Crohn's disease and the role of surgery in the treatment of Crohn's disease, in the intension to provide reference on clinical judgements.

Methods. This study used data obtained from the Taichung Veterans General Hospital (VGHTC) Clinical Informatics Research and Development Center (CIRDC) database. The patients with diagnosis of Crohn's disease from 1984 to 2014 in VGHTC were screened. Sixty-four patients with Crohn's disease were identified and included in this study. Clinical records (age, location of the lesion and initial symptoms) and surgery records were reviewed for each patient.

Results. The female/male ratio was 0.39:1, and the mean age at diagnosis was 37.73 years. Overall, the incidence peaked in those aged 21-30 years, with two peaks in the male patients and one peak in the female patients. In Montreal classification, L2 (37.5%) was the most common location of Crohn's disease, followed by L1, L3, and L4.

Gastrointestinal bleeding was the most common clinical symptom (29.69%). In the initial diagnosis, 67.19% of the patients were diagnosed with other entities. Only 32.81% of the patients were proven to have or suspected of having Crohn's disease. 79.69% of the patients underwent surgery for a complication of Crohn's disease, 94.11% of whom underwent intestinal resection. 35.2% of the patients who underwent surgery required a second surgery within seven years.

Conclusion. Due to the rarity of Crohn's disease in Taiwan, the diagnosis was often missed and most of the patients received surgery for late complications. Improved diagnostic modalities are needed to decrease the requirement for surgical interventions.
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Crohn's disease (CD) is a chronic gastrointestinal disease of unknown cause, and it is a relatively rare disease in Asian compared to Western populations.[1] In Europe, the standardized prevalence of Crohn's disease was reported to be 75.8/100,000 in 1993.[2] In Taiwan, the prevalence of CD increased

from 0.19/100,000 in 1998 to 1.78/100,000 in 2008, however this is still low compared with Western countries.[3] Although more than 75% of the patients with CD will require surgery at least once, early aggressive medical therapy has been proven to decrease this rate and also lower the complication rate.[4,5]

The difference in incidence between Asian and Western populations may be due to ethnic differences or simply a delayed diagnosis due to the physician's lack of awareness and experience.[6] Even though the incidence has increased in Taiwan over the past few decades, Taiwan is still a low-endemic area for CD.[7] The best way to optimize both medical and surgical treatment is an important issue for patients with CD. The aim of this study was to present the disease characteristics, clinical symptoms, surgical procedures and time to recurrence in incident cases of Crohn's disease from a single medical center over the past 30 years, hoping to offer a reference in clinical judgements of this disease entity and achieve early diagnosis.

Materials and Methods

This study used data obtained from the CIRDC database of VGHTC. The diagnostic codes in the CIRDC database are based on the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM).[8]

The patients with an ICD-9-CM code 555 (CD) from 1984 to 2014 in VGHTC (N = 139) were screened. The patients who did not have pathological reports were excluded from analysis (N = 75). Sixty-four patients with Crohn's disease were identified and included in this study, of whom 60 had proven CD or suspected inflammatory bowel disease by pathology. The other four patients whose clinical symptoms strongly suggested CD were found to have ulcers with fistulas or perforations on pathology. Clinical records and pathological reports were reviewed for each patient (Fig. 1). The histological diagnosis of all patients was confirmed at the Department of Pathology of Taichung Veterans General Hospital. The age of the patients and location of CD were classified according to the Montreal classification,[9] with the ad-

dition of an another age group as follows: 0-10, 11-20, 21-30, 31-40, 41-50, 51-60 and > 60 years.

Statistical analysis

Continuous variables were expressed as the median and interquartile range, and the subgroups were compared using the Mann-Whitney U test. Categorical variables, expressed as percentages, were analyzed using the chi-square test or Fisher's exact test. All statistical tests were 2-sided, and a *p* value of less than 0.05 was considered to indicate statistical significance. All analyses were performed using SAS version 9.1.3 software (SAS Institute, Cary, NC).

Results

The female/male ratio was 0.39:1 (18/46, $p = 0.0251$) (Table 1). The mean age at diagnosis was 37.73 years (males 40.96 years; females 29.5 years). Most patients were aged 17-40 years (N = 32, 50.00%). Overall, the incidence peaked in those aged 21-30 years
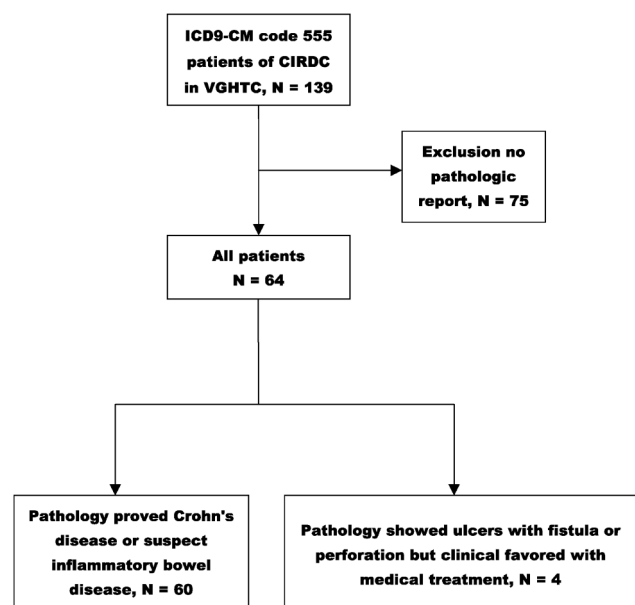

Fig. 1. Flowchart of recruitment of the subjects with an ICD-9CM code of 555 from the Clinical Informatics Research and Development Center (CIRDC) database from 1984 to 2014 in Taichung Veterans General Hospital (VGHTC).

Table 1. Characteristics of the patients with Crohn's disease (n = 64)

	Total (n = 64)		Gender				p-value
			Male (n = 46)		Female (n = 18)		
Age[t]							0.0251*
Mean (SD)	37.73	18.55	40.96	18.60	29.50	16.13	
0-10	2	(3.13%)	1	(2%)	1	(6%)	0.2993
11-20	9	(14.06%)	5	(11%)	4	(22%)	
21-30	17	(26.56%)	10	(22%)	7	(39%)	
31-40	11	(17.19%)	9	(20%)	2	(11%)	
41-50	9	(14.06%)	8	(17%)	1	(6%)	
51-60	5	(7.81%)	3	(7%)	2	(11%)	
> 60	11	(17.19%)	10	(22%)	1	(6%)	
Age by Montreal classification							0.0868
A1 ≦ 16 years	7	(10.94%)	3	(7%)	4	(22%)	
A2 17-40 years	32	(50.00%)	22	(48%)	10	(56%)	
A3 > 40 years	25	(39.06%)	21	(46%)	4	(22%)	
Location							0.6208
L1 (terminal ileum)	20	(31.25%)	13	(28%)	7	(39%)	
L2 (colon)	24	(37.50%)	17	(37%)	7	(39%)	
L3 (ileocolon)	11	(17.19%)	8	(17%)	3	(17%)	
L4 (upper gastrointestine)	9	(14.06%)	8	(17%)	1	(6%)	

[t] T test. Chi-square test. * $p < 0.05$.

(N = 17, 26.56%), with two peaks in the male patients (21-30 years, N = 10, 22%; and > 60 years, N = 10, 22%), and one in the female patients (21-30 years, N = 7, 39%). About 78% of the female patients were diagnosed before 40 years of age, and only 22% after 40 years of age. According to the Montreal classification, L2 (37.5%) was the most common location of Crohn's disease, followed by L1 (31.25%), L3 (17.19%), and L4 (14.06%) (Table 1).

Gastrointestinal bleeding was the most common initial clinical symptom of Crohn's disease (29.69%), followed by intestinal obstruction (21.88%) and abdominal mass (20.31%). Other symptoms included diarrhea, fever, enteroenteric fistula and peritonitis. Anal fistulas occurred in three patients (4.69%).

In the initial clinical diagnosis, 43 patients (67.19%) were diagnosed with other entities including diverticulitis, intestinal obstruction, appendicitis, and suspected tuberculosis of the colon. 39 patient (60.9%) received colonoscopy examination and biopsy and 3 (7.69%) of these patients received terminal ileum checkup. 25 patient (39.1%) did not undertake colo-noscopy due to acute abdomen or suspected other disease entity. Overall, 21patients (32.81%) were clinically favored inflammatory bowel disease initially (Table 2). Only two patients was proved Crohn's disease by colonoscopic biopsy and the others19 were suspected inflammatory bowel disease. One patient presented bowel obstruction and was diagnosed on abdominal CT.

Among all cases, 79.69% (N = 51) of the patients underwent surgery for a complication of Crohn's disease, and 20.31% (N = 13) received conservative treatment. With regards to the first surgery, 39.22% (N = 20) of the patients underwent right hemicolectomy, laparoscopic right hemicolectomy or right hemicolectomy with end-ileostomy, followed by intestinal resection 35.25% (N = 18), and seven cases who underwent major bsurgery including total (N = 4, 7.84%) or subtotal (N = 3, 5.88%) colectomy with or without ileostomy. Overall, 35.2% (N = 18) of the patients who underwent surgery required a second surgery within seven years. With regards to the second surgery, 88.89% (N = 16) of the patients underwent

Table 2. Initial clinical presentations

	Total (n = 64)		First operation				p-value
			No operation (n = 13)		Operation (n = 51)		
Initial clinical symptom (n = 64)							0.7824
Abdominal mass	13	(20.31%)	10	(22%)	3	(17%)	
Anal fistula	3	(4.69%)	3	(7%)	0	(0%)	
Diarrhea	7	(10.94%)	4	(9%)	3	(17%)	
Enteroenteric fistula	1	(1.56%)	1	(2%)	0	(0%)	
Fever	1	(1.56%)	1	(2%)	0	(0%)	
GI bleeding & LGI bleeding#	19	(29.69%)	12	(26%)	7	(39%)	
Intestinal obstruction	14	(21.88%)	11	(24%)	3	(17%)	
Peritonitis	6	(9.38%)	4	(9%)	2	(11%)	
Initial diagnosis (n = 64)[f]							0.4709
Others	43	(67.19%)	8	(62%)	35	(69%)	
Crohn's disease	21	(32.81%)	5	(38%)	16	(31%)	
Initial diagnosis (n = 64)							0.2958
Colitis with ulcer	7	(10.94%)	2	(15%)	5	(10%)	
Perforation & peritonitis	7	(10.94%)	0	(0%)	7	(14%)	
Crohn's disease	17	(26.56%)	4	(31%)	13	(25%)	
Diverticulitis	1	(1.56%)	0	(0%)	1	(2%)	
Fever, unkown origin	1	(1.56%)	1	(8%)	0	(0%)	
GI bleeding	7	(10.93%)	4	(31%)	3	(6%)	
Intestinal obstruction	9	(14.06%)	0	(0%)	9	(18%)	
Malabsorption syndrome	2	(3.12%)	1	(8%)	1	(2%)	
Peptic ulcer	1	(1.56%)	0	(0%)	1	(2%)	
Appendicitis	2	(3.12%)	0	(0%)	2	(4%)	
Colon ca	1	(1.56%)	0	(0%)	1	(2%)	
Lymphoma	4	(6.25%)	0	(0%)	4	(8%)	
T.B colitis	1	(1.56%)	0	(0%)	1	(2%)	
IBD (UC or Crohn's disease)*	4	(6.25%)	1	(8%)	3	(6%)	

[f] Fisher's Exact Test. * $p < 0.05$.
LGI: lower gastrointestinal.
* IBD: inflammatory bowel disease, UC: ulcerative colitis.

major surgery, including seven cases of intestinal resection, four of right colectomy and one total colectomy. Only two patients underwent minor surgery (fistulectomy) (Table 3).

Discussion

This study reports 30 years of experiences of Crohn's disease in a single medical center. Age distribution, gender ratio, initial clinical presentations, and surgeries were concluded in this study. Ethnic differences in gender ratio have been reported, with three major studies in the United States reporting a female/male ratio ranging from 1.2~1.4:1.[10-12] In contrast, studies on Asian patients tend to show an opposite trend in gender ratio. The female/male ratio in the current study was 0.39:1 (18/46), while Hirohashi et al. reported a female/male ratio of 0.45:1 in a Japanese population,[13] and a report from China found an overall female/male ratio of 0.7:1.[14]

According to the Montreal classification, the age distribution in the current study was quite similar to reports from Western countries. The most common age at diagnosis was 17-40 years, which accounted for more than 50% of the cases. However, when age was stratified by ten-year groups, the age distribution of CD showed a bimodal pattern.[15] Our data showed

Table 3. Surgical procedures for Crohn's disease

	Total (n = 64)		Gender				*p*-value
			Male (n = 46)		Female (n = 18)		
First operation[f]							0.1646
No	13	(20.31%)	7	(15%)	6	(33%)	
Yes	51	(79.69%)	39	(85%)	12	(67%)	
First operation type (n = 51)							0.5735
Intestine resection	18	(35.29%)	14	(36%)	4	(33%)	
Fistulectomy	2	(3.92%)	2	(5%)	0	(0%)	
Hartmann	1	(1.96%)	1	(3%)	0	(0%)	
Ileocolon bypass	1	(1.96%)	1	(3%)	0	(0%)	
Left hemicolectomy	1	(1.96%)	1	(3%)	0	(0%)	
Right hemicolectomy with or without end-ileostomy	20	(39.22%)	14	(36%)	6	(50%)	
Sigmoidectomy	1	(1.96%)	0	(0%)	1	(8%)	
Subtotal colectomy with or without end-ileostomy	3	(5.88%)	2	(5%)	1	(8%)	
Total colectomy and J pouch, Total colectomy with or without ostomy	4	(7.84%)	4	(10%)	0	(0%)	
Low anterior resection	0	(0.00%)	0	(0%)	0	(0%)	
Time to secondary operation (n = 13 vs. 5)[t]							
Mean (SD)	6.94	3.51	6.50	3.48	8.25	3.77	0.4067
Second operation (n = 18)							0.7280
Intestine resection	7	(38.89%)	6	(43%)	1	(25%)	
Fistulectomy	2	(11.11%)	1	(7%)	1	(25%)	
Hartmann	1	(5.56%)	1	(7%)	0	(0%)	
Ileocolon bypass	0	(0.00%)	0	(0%)	0	(0%)	
Left hemicolectomy	1	(5.56%)	1	(7%)	0	(0%)	
Right hemicolectomy with or without end-ileostomy	4	(22.22%)	2	(14%)	2	(50%)	
Sigmoidectomy	0	(0.00%)	0	(0%)	0	(0%)	
Subtotal colectomy with or without end-ileostomy	1	(5.56%)	0	(0%)	1	(5.56%)	
Total colectomy and J pouch, Total colectomy with or without ostomy	1	(5.56%)	1	(7%)	0	(0%)	
Low anterior resection	1	(5.56%)	1	(7%)	0	(0%)	

[t] T test. [f] Fisher's exact test. * *p* < 0.05.

that age-distribution was characterized by a large peak (21-30 years) in the younger patients, followed by a small peak in the older patients (> 60 years). The males in particular had a typical bimodal pattern, however there were fewer females in the > 60 age group, which may be due to the low total number of females (N = 18). We found that female patients tended to be diagnosed earlier than the male patient. More than 78% of the female patients with CD were diagnosed before the age of 40 years, while only 55% of the male patients were diagnosed before 40 years of age (Table 1). Canavan et al. reported a shorter life expectancy in those diagnosed with Crohn's disease

at a younger age compared to those diagnosed later in life and to the general population.[16] Further studies are needed to elucidate whether male patients have a longer life expectancy and better prognosis than female patients.

With regards to the diagnosis of Crohn's disease, our results showed that an initial definite or suspected diagnosis was only made in 21 (32.81%) of the patients, while 43 (67.19%) patients had a delay in the diagnosis. Schoepfer et al. showed that a diagnostic delay in Crohn's disease was associated with a complicated disease course and increased operation rate.[17] Patients would benefit most from early aggressive therapy as it

will reduce the development of complications and is associated with improved medical response and remission rate.[18] The European Crohn's and Colitis Organization guidelines suggested that prophylaxis treatment should be started within 2 weeks after surgery.[19] Some literature even proposed that treatment strategy iniciated immediately after surergy.[20]

The low diagnostic ability of endoscopic specimens, possibly due to difficulties in making a pathological diagnosis with the small amount of specimen obtained from a colonoscopy may be one of the reasons for the delay in diagnosis.[21] Therefore, if a suspicious lesion is noted in a colonoscopic examination, we suggest that more specimens be obtained during the examination to increase the likelihood of a successful pathological diagnosis. According to European Crohn's and Colitis Organization (ECCO) guideline, a reliable diagnosis of CD was from multiple biopsies from six segments (terminal ileum, ascending, transverse, descending, sigmoid and rectum). Multiple biopsies imply a minimum of two representative samples from each segment including macroscopically normal segment. Therefore, the colonoscope should be inserted into the terminal ileum.[19] Checking the ileum during colonoscopy should be considered as far as possible with the intension of making an early diagnosis of CD.

With regards to the distribution of the location of Crohn's lesions, a wide difference between our study and Western studies was found. In the current study, 31.25% of the patients had Crohn's lesions in the ileum, and 14.06% in the upper intestine. This means that the diagnosis of CD can easily be missed. A review by Lujan-Sanchis showed that the early use of capsule endoscopy helps to make an early diagnosis of Crohn's disease.[22] Esaki indicated that capsule endoscopy was useful in the detection of CD and that it should be given to patients with suspected CD, although caution should be taken over the possibility of stricture-induced capsule retention.[23] Surgical treatment for CD has been evolving towards bowel conservation surgery such as limited bowel resection and stricturoplasty. However, this is often not sufficient for complicated bowel diseases.[24] In our study, 51 patients with CD received surgery, including 48 cases (except for two fistulectomy and one ileocolonic bypass) of large or small intestine resection. Furthermore, 35.2% of the patients needed a second operation, 88.89% (N = 16) of whom underwent a major operation (including bowel resection of any kind), with an average 6.94 years between surgeries (Table 3). Nearly 35.2% of the patients with CD who undergo surgery will require a second surgery within seven years. Hesham et al. pointed out that both conventional and nonconventional stricturoplasty techniques are beneficial for both jejunoileal and ileocolonic anastomotic strictures after primary surgery.[25] Therefore, a more conservative secondary surgery should be considered. In the absence of treatment, around 65-90% of the patients with CD will experience endoscopic recurrence within 12 months after curative surgery, and 80-100% within three years of the operation.[19,26] Therefore, maintenance therapy after surgery and frequent endoscopic examinations within one year should be considered after the primary surgery. The maintenance therapy should be considered according to the risk of recurrence. For those at very low risk of recurrence, no therapy may be needed; however, for patients at moderate risk, immunomodulators should be considered. For those at highest risk of recurrence, biologic therapy, especially antitumor necrosis factor agents, have emerged as appropriate treatment.[27]

Conclusion

Due to the rarity of CD in Taiwan, the diagnosis was often missed and most of the patients received surgery for late complications. Physicians and surgeons should keep this disease entity in mind so that treatment can be given in the early stage. Improved diagnostic modalities are needed to decrease the requirement for surgical interventions and to lower the complication rate.

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原　　著

克隆氏症的外科經驗 — 單一醫學中心
三十年之資料分析

陳志典　王輝明　陳周斌　陳周誠　馬秀峰　蔣鋒帆　林冠名　趙德馨

台中榮民總醫院　大腸直腸外科

背景　克隆氏症在亞洲是一個相對罕見的疾病。本篇研究旨在探討台灣克隆氏症的臨床特性，進而達到早期診斷及改善預後之目的。

方法　本篇資料蒐集自台中榮總臨床研究中心資料庫。 我們整理了從 1984 年到 2014 年的 64 個患者，並檢視了包括年齡、病灶處、初始症狀及手術紀錄等病歷資料。

結果　在所有病人中，女男比例為 0.39:1，平均年齡為 37.73 歲。整體年齡分布最多在 21~30 歲，男性是有兩個好發年齡層而女性只有一個。以蒙特婁分類來區分的話，L2 是病灶處最常出現的位置，然後依序是 L1，L3 和 L4。

消化道出血是最常見的臨床症狀 (29.69%)。至於初始診斷，有 67.19% 的病人被診斷為其他疾病，只有 32.81% 的病人被證實或是懷疑是克隆氏症。79.69% 的病人因為克隆氏症的併發症而手術，其中 94.11% 的病人接受了腸道切除的手術。這些病人之中有 35.2% 的人在 7 年內必須再經歷一次手術治療。

結論　因為克隆氏症在台灣比較罕見，大部分的病人診斷容易被延誤，而多數病人因此必須接受手術處理晚期的併發症。我們有必要改良診斷方式以減少手術介入的必要性。

關鍵詞　克隆氏症、延遲診斷、克隆氏症手術。