

Risk Factors for Repeat Abdominal Surgery in Korean Patients with Crohn's Disease: A Multi-Center Study of a Korean Inflammatory Bowel Disease Study Group

Kil Yeon Lee, Chang Sik Yu¹, Kang Young Lee², Yong Beom Cho³, Kyu Joo Park⁴, Gyu-Seog Choi⁵, Sang Nam Yoon⁶, Hanna Yoo⁷; IBD Study Group, Korean Society of Coloproctology

Department of Surgery, Kyung Hee University School of Medicine, Seoul; ¹Department of Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul; ²Department of Surgery, Yonsei University College of Medicine, Seoul; ³Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; ⁴Department of Surgery, Seoul National University College of Medicine, Seoul; ⁵Department of Surgery, Kyungpook National University School of Medicine, Daegu; ⁶Department of Surgery, Hansol Hospital, Seoul; ⁷Department of Statistics, College of Political Science and Economics, Korea University, Seoul, Korea

Purpose: The purpose of this study was to assess the risk factors for repeated abdominal surgery in Crohn's disease (CD) patients after the first abdominal surgery. Prior studies have tried to identify the risk factors for postoperative recurrence in CD patients, but the results of the studies have been inconsistent. Furthermore, few data on the risk factors for repeated abdominal surgery are available.

Methods: Clinical data on CD patients who underwent abdominal surgery from January 2000 to December 2009 were collected from seventeen university hospitals and one colorectal clinic. Data from a total of 708 patients were analyzed to find the risk factors for repeated abdominal surgery in CD patients. The mean follow-up period was 72 months.

Results: The risk of repeated abdominal surgery was 3 times higher in young patients (below 16 years old) than in older patients (odds ratio [OR], 3.056; 95% confidence interval [CI], 1.021 to 9.150; $P = 0.046$). Stricture behavior at diagnosis was also a risk factor for repeated abdominal surgery (OR, 2.438; 95% CI, 1.144 to 5.196; $P = 0.021$). Among operative indications, only intra-abdominal abscess was associated with repeated abdominal surgery (OR, 2.393; 95% CI, 1.098 to 5.216; $P = 0.028$). Concerning type of operation, an ileostomy might be a risk factor for repeated abdominal surgery (OR, 11.437; 95% CI, 1.451 to 90.124; $P = 0.021$). Emergency surgery (OR, 4.994; 95% CI, 2.123 to 11.745; $P < 0.001$) and delayed diagnosis after surgery (OR, 2.339; 95% CI, 1.147 to 4.771; $P = 0.019$) also increased the risk of repeated abdominal surgery.

Conclusion: Young age (below 16 years), stricturing behavior, intra-abdominal abscess, emergency surgery, and delayed diagnosis after surgery were identified as possible risk factors for repeated abdominal surgery in CD patients.

Keywords: Crohn's disease; Recurrence; Surgery

INTRODUCTION

Crohn's disease (CD) is heterogeneous in nature; consequently, its

clinical course is relatively unpredictable. The only consistent factor in CD is its inconsistency [1]. Some patients have a relatively mild form, but others experience a severe form of CD requiring surgery or have postoperative recurrence. Over 80% of CD patients will undergo surgery, and approximately one-third of those patients will require reoperation [2]. Reported reoperation rates range from 20 to 25% at 5 years after resection and 34 to 39% at 10 years [3, 4]. Several studies have reported the risk factors of an initial intestinal resection or recurrence after the primary operation. Different studies have revealed numerous risk factors for postoperative recurrences, but the results are often not comparable because of differing patient populations and clinical manifestations [5, 6]. In addition, no consistent risk factors for surgery or

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Correspondence to: Chang Sik Yu, M.D.

Department of Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea

Tel: +82-2-3101-3494, Fax: +82-2-3101-6701

E-mail: csyu@amc.seoul.kr

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recurrence, except smoking, have been identified [7, 8]. Furthermore, few studies have evaluated the risk factors for reoperation after the primary surgery in CD patients. Therefore, the aim of the present study was to evaluate the probability of reoperation and to assess the risk factors for reoperation after the primary surgery for CD.

METHODS

Data management

The data for biopsy-proven CD patients who underwent abdominal surgery from January 2000 to December 2009 were collected retrospectively. The operations were performed at 18 different hospitals (17 university hospitals and one colorectal clinic). The factors included in the study protocol were decided at a meeting held before data collection. The data of 754 patients were collected initially, and 46 cases were excluded because of data duplication or unmet criteria (Fig. 1). Data from a total of 708 CD patients were analyzed to determine the risk factors for repeated abdominal surgery. The mean follow-up period was 72 months. The variables that were analyzed were gender, family history, age at diagnosis, disease behavior at diagnosis, and disease location at diagnosis ac-

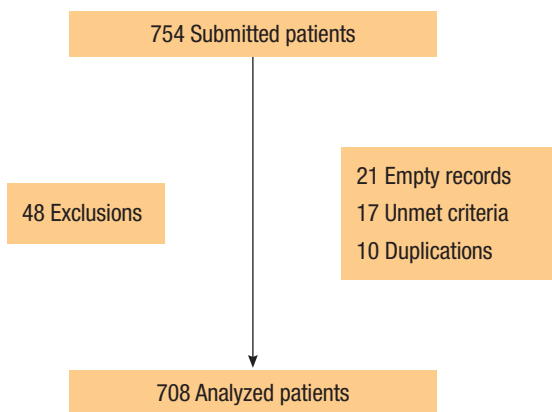


Fig. 1. Study selection flow chart.

ording to the Montreal classification. Other variables were indications, type of first abdominal surgery, and the time interval between diagnosis and surgery.

Statistical analysis

For the continuous variables, normality was tested first. When the normality assumption was satisfied, a one-way analysis of variance was used; otherwise, a Kruskal-Wallis test was utilized to test whether a mean difference between the number of operations existed (1, 2, ≥ 3). In addition, for the categorical variables, a Pearson chi-square test or a Fisher's exact test was used as appropriate to evaluate the association between the number of operations (1, 2, ≥ 3). In order to evaluate the relationships between the number of operations and the risk factors, we used univariate and multivariate logistic regression modeling. Since the percentage of patients who had more than three operations was only 6.2%, the number of the operations was divided into two categories (1, ≥ 2). Additionally, within the independent variables of surgery type, indication for surgery and main symptoms, a few categories had a low percentage of patients; thus, for the stability of the analysis, those categories were eliminated/merged. For the goodness-of-fit, Hosmer-Lemeshow statistics were utilized, and the area under the receiver operating characteristic curve was used to assess the model discrimination. All statistical analyses were performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Twenty-four percent of the CD patients with primary abdominal surgery experienced repeated abdominal surgery, and 25% of that 24% underwent one additional abdominal surgery. The male-to-female ratio of the CD patients with abdominal surgery was 2.27:1, and the mean ages of male and female patients were 34.0 and 34.16 years, respectively (Table 1). Family history was confirmed in only 2.2% of the patients. Gender and family history were not associated with repeated abdominal surgery in CD patients. All patients were classified according to the Montreal classification (Table 2). Patients between 17 and 40 years of age (A2), ileal location (L1),

Table 1. Baseline population characteristics

Characteristic	No. of abdominal surgeries			Total	P-value
	1	2	≥ 3		
Gender					0.853
Male	374 (70)	87 (67)	31 (70)	492 (70)	
Female	161 (30)	42 (33)	13 (30)	216 (30)	
Age (yr)	34.0 \pm 12.4	34.4 \pm 11.7	33.6 \pm 10.5	34.0 \pm 12.1	0.571
Family history					0.999
Yes	12 (2)	2 (2)	0 (0)	14 (2.2)	
No	486 (98)	108 (98)	36 (100)	630 (97.8)	

Values are presented as number (%) or mean \pm SD.

and stricturing behavior (B2) were the most common subgroups in the CD patients who underwent primary abdominal surgery

Table 2. Montreal classification of Crohn's disease

Age at diagnosis (yr)	
A1 (≤16)	
A2 (17-40)	
A3 (≥41)	
Location	
L1 (ileal)	
L2 (colonic)	
L3 (ileocolonic)	
L4 (isolated upper disease ^a)	
Behavior	
B1 (non-stricturing, non-penetrating)	
B2 (stricturing)	
B3 (penetrating)	
p ^b (perianal disease modifier)	

^aL4 is a modifier that can be added to L1-L3 when concomitant upper gastrointestinal disease is present. ^bp is added to B1-B3 when concomitant perianal disease is present.

(Table 3). Medical intractability (21.5%), intestinal obstruction (24.2%), intra-abdominal abscess (23.4%), and enterocutaneous fistula (18.5%) were common causes of primary abdominal surgery. Intestinal obstruction (31.5%) and intra-abdominal abscess (33.1%) were also common causes of repeated abdominal surgery (Table 4). Small bowel segmental resection (28.2%) was the most common procedure performed in the first abdominal surgery. Of the total number of first abdominal surgeries for CD patients, a right colectomy and an ileocectomy were performed in 26.7% and 25.0% of the patients, respectively (Table 5).

Table 6 summarizes the results of the univariate and the multivariate analyses. The risk of repeated abdominal surgery was approximately three times higher in young patients (under the age of 16 years) than in older patients (odds ratio [OR], 3.056; 95% confidence interval [CI], 1.021 to 9.150; P = 0.046). Stricturing behavior was a greater risk factor for repeated abdominal surgery (OR, 2.438; 95% CI, 1.144 to 5.196; P = 0.021) than was penetrating behavior or non-stricturing and non-penetrating behavior. However, the number of surgeries was not influenced by the location of the disease at diagnosis. Intractability, obstruction, abscess and fistula were the main causes of surgery, and only abscess was associated with repeat surgery (OR, 2.393; 95% CI, 1.098 to 5.216; P = 0.028). Concerning the type of surgery, an ileostomy may be a risk factor for repeat abdominal surgery (OR, 11.437; 95% CI,

Table 3. Allocation of patients to the 36 subgroups of the Montreal classification

	A1			A2			A3			Total
	B1	B2	B3	B1	B2	B3	B1	B2	B3	
L1	1.4	1.2	0.3	5.2	14.7	11.1	1.7	2.8	2.8	41.2
L2	0.6	0.6	0.2	4.8	5.1	3.1	1.4	0.8	0.5	16.9
L3	1.5	2.3	0.6	6.5	11.8	10.9	1.5	1.8	0.6	37.6
L4	0.0	0.2	0.3	0.6	1.5	0.9	0.2	0.2	0.5	4.3
Total	3.5	4.3	1.4	17.1	33.2	26.0	4.8	5.5	4.3	100.0

Values are presented as percentage.

A, age at diagnosis; A1, ≤16 yr; A2, 17-40 yr; A3, ≥41 yr; B, behavior; B1, non-stricturing, non-penetrating; B2, structuring; B3, penetrating; L, location; L1, ileal; L2, colonic; L3, ileocolonic; L4, isolated upper disease.

Table 4. Causes of abdominal surgery in Crohn's disease patients

Cause	No. of abdominal surgeries			Total
	1	2	≥3	
Intractability	113 (21.5)	6 (4.8)	4 (10.3)	123 (17.9)
Intestinal obstruction	127 (24.2)	39 (31.5)	11 (28.2)	177 (25.7)
Intra-abdominal abscess	123 (23.4)	41 (33.1)	10 (25.6)	174 (25.3)
Enterocutaneous fistula	97 (18.5)	14 (11.3)	4 (10.3)	115 (16.7)
Fulminant colitis	5 (1.0)	0 (0)	0 (0)	5 (0.7)
Massive bleeding	7 (1.3)	6 (4.8)	0 (0)	13 (1.9)
Others	53 (10.1)	18 (14.5)	10 (25.6)	81 (11.8)

Values are presented as number (%).

Table 5. Types of abdominal surgery in Crohn's disease patients

Type of surgery	No. of abdominal surgeries			Total
	1	2	≥3	
Strictureplasty only	3 (0.6)	0 (0)	2 (4.8)	5 (0.7)
Small bowel resection	147 (28.2)	54 (41.9)	15 (35.7)	216 (31.2)
Ileocecectomy	130 (25.0)	28 (21.7)	8 (19.0)	166 (24.0)
Right colectomy	139 (26.7)	23 (17.8)	3 (7.1)	165 (23.8)
Left colectomy	7 (1.3)	0 (0)	2 (4.8)	9 (1.3)
Total colectomy	33 (6.3)	2 (1.6)	2 (4.8)	37 (5.3)
Total proctocolectomy with ileal pouch anal anastomosis	0 (0)	2 (1.6)	1 (2.4)	3 (0.4)
Total proctocolectomy with permanent ileostomy	23 (4.4)	2 (1.6)	0 (0)	25 (3.6)
Ileostomy only	3 (0.6)	9 (7.0)	0 (0)	12 (1.7)
Others	36 (6.9)	9 (7.0)	9 (21.4)	54 (7.8)

Values are presented as number (%).

1.451 to 90.124; $P = 0.021$). Emergency surgery (OR, 4.994; 95% CI, 2.123 to 11.745; $P < 0.001$) and delayed diagnosis after surgery (OR, 2.339; 95% CI, 1.147 to 4.771; $P = 0.019$) increased the risk for repeat abdominal surgery.

DISCUSSION

According to the European consensus on definitions and diagnosis of CD, recurrence is primarily used to define the reappearance of lesions after surgical resection while relapse refers to the reappearance of symptoms [9]. Recurrence is the main problem during the treatment of CD. Knowing the risk factors for recurrence would be helpful in managing CD not only for physicians but also for patients. However, due to the heterogeneous nature of CD, the reported risk factors for recurrence after abdominal surgery for CD patients have been inconsistent, so clarifying the risk factors for repeated abdominal surgery in CD patients is difficult. The recurrence rate varies according to the diagnostic method, follow-up duration and ethnicity.

Despite the obvious limitation of using age at diagnosis as a surrogate marker of disease onset, it is nevertheless an attractive, readily available, and stable criterion for distinguishing different disease patterns at diagnosis [10]. With respect to age of onset, the Montreal classification allows for early onset of disease to be categorized separately as a new A1 category for patients with a diagnosis age of 16 years or younger whereas A2 and A3 account for diagnosis ages of 17 to 40 years and of over 40 years, respectively [11]. This change reflects many studies that have reported that specific serotypes or genotypes are more frequently found in early onset CD [12-15]. Early onset CD is usually more severe than A2 or A3 onset. Thia et al. [10] observed that young patients had a tendency toward recurrent clinical flares, indicating a more active disease, and were more likely to receive immunosuppressive therapy than older patients. Polito et al. [16] observed that compared

to an older age at diagnosis, defined as individuals older than 40 years of age, a younger age at diagnosis, defined as individuals under 20 years of age, was associated with greater small bowel involvement, more severe stricturing disease, and a higher surgical rate. These results are consistent with the results from the present study. A young age, less than 16 years, was a risk factor for repeated abdominal surgery in CD patients.

Several studies have reviewed early disease onset or diagnosis among CD patients with a family history [16, 17]. Polito et al. [16] postulated that the role of genetic anticipation with greater contribution of maladaptive genes led to an earlier onset of disease manifestation and greater severity in patients with a positive family history. Given that only 2% of the patients in the present study had a positive family history, other reasons may account for young patients experiencing a more severe clinical course than older patients in the present study cohort [10].

Non-stricturing, non-penetrating, stricturing, and penetrating disease behaviors are the main categories in the classification of CD patients. The present study revealed that stricturing disease behavior was associated with repeated abdominal surgery in CD patients. This result is significantly different from other reports. In other studies, penetrating behavior was a risk factor for postsurgical recurrence [8, 18-20]. However, Khoury et al. [21] reported that stricturing behavior was a risk factor for early reoperation. Concerning disease location, several studies demonstrated that the risk of recurrence was highest in ileocolonic CD and lowest in colonic CD [22-24]. In the present study, disease location was not a risk factor for repeat abdominal surgery in CD patients. The influences of disease location and disease behavior on the postoperative recurrence of CD are unclear because these clinical characteristics have been observed to change over time [25].

Among the surgical procedures performed in the first abdominal surgery, only the ileostomy increased the risk for repeated abdominal surgery in CD patients. Because the diseased bowel was

Table 6. Univariate and multivariate analyses of risk factors for repeat abdominal surgery in Crohn's disease patients

	No.	1 time vs. ≥ 2 times					
		Univariate analysis			Multivariate analysis		
		β	P-value	OR (95% CI)	β	P-value	OR (95% CI)
Gender							
Male	492	0.014	0.948	1.014 (0.671-1.532)	0.041	0.889	1.042 (0.585-1.858)
Female	216	0	-		0	-	
Family history							
Yes	11	-0.205	0.795	0.815 (0.174-3.820)	0.587	0.519	1.798 (0.302-10.694)
No	574	0	-		0	-	
Age at diagnosis (yr)							
≤16	57	0.321	0.450	1.379 (0.599-3.171)	1.117	0.046	3.056 (1.021-9.150)
17-40	483	0.354	0.244	1.425 (0.785-2.587)	0.540	0.167	1.717 (0.797-3.696)
≥41	85	0	-		0	-	
Location							
Ileal	239	0.147	0.759	1.159 (0.451-2.974)	-0.273	0.652	0.761 (0.232-2.495)
Colonic	90	0.299	0.563	1.348 (0.490-3.710)	0.312	0.669	1.366 (0.328-5.688)
Ileocolonic	230	0.221	0.645	1.248 (0.486-3.202)	0.354	0.582	1.425 (0.404-5.028)
Isolated upper disease	31	0	-		0	-	
Behavior							
Non-stricturing, non-penetrating	140	0.035	0.902	1.035 (0.595-1.803)	0.058	0.885	1.060 (0.483-2.324)
Stricturing	251	0.496	0.033	1.643 (1.041-2.593)	0.891	0.021	2.438 (1.144-5.196)
Penetrating	192	0	-		0	-	
Type of surgery							
Strictureplasty	5	1.083	0.248	2.952 (0.471-18.508)	1.025	0.383	2.788 (0.278-27.949)
Small bowel resection	199	0.648	0.013	1.912 (1.148-3.183)	0.333	0.352	1.395 (0.692-2.811)
Right colectomy	156	-0.267	0.386	0.766 (0.419-1.400)	-0.807	0.050	0.446 (0.199-1.000)
Left colectomy	8	-0.458	0.674	0.633 (0.075-5.351)	-1.125	0.357	0.325 (0.030-3.558)
Total colectomy	35	-0.879	0.169	0.415 (0.119-1.453)	-0.725	0.438	0.485 (0.078-3.028)
Total proctocolectomy with IPAA	20	-0.709	0.360	0.492 (0.108-2.244)	-1.191	0.284	0.304 (0.304-2.682)
Ileostomy only	10	2.874	<0.001	17.714 (3.566-87.989)	2.437	0.021	11.437 (1.451-90.124)
Others	43	0.760	0.050	2.138 (1.002-4.564)	0.533	0.309	1.705 (0.609-4.768)
Ileocectomy	152	0	-		0	-	
Indication of surgery							
Medical intractability	117	-1.834	<0.001	0.160 (0.069-0.368)	-0.864	0.086	0.421 (0.157-1.130)
Intra-abdominal abscess	162	-0.004	0.986	0.996 (0.616-1.610)	0.873	0.028	2.393 (1.098-5.216)
Enterocutaneous fistula	102	-1.003	0.003	0.367 (0.187-0.719)	-0.304	0.543	0.738 (0.277-1.965)
Massive bleeding	8	0.410	0.585	1.506 (0.346-6.556)	1.112	0.285	3.041 (0.395-23.386)
Others	74	0.248	0.410	1.281 (0.711-2.307)	1.206	0.011	3.342 (1.317-8.480)
Intestinal obstruction	165	0	-		0	-	
Time interval							
Diagnosis after surgery	55	1.359	0.000	3.893 (2.157-7.024)	1.608	<0.001	4.994 (2.123-11.745)
Within 7 days	144	0.480	0.039	1.615 (1.026-2.544)	0.850	0.019	2.339 (1.147-4.771)
Between 7 and 30 days	32	0.603	0.146	1.828 (0.811-4.120)	0.321	0.655	1.378 (0.337-5.636)
Over 30 days	397	0	-		0	-	

OR, odds ratio; CI, confidence interval; IPAA, ileal pouch anal anastomosis.

not resected in that procedure, an increased reoperation rate was inevitable. However, contrary to other reports, the stricturoplasty was not associated with repeated abdominal surgery reports [26-29]. Unlike other reports [30-32], in the present study, the segmental colon resection was not a risk factor for repeated abdominal surgery in CD patients.

Emergency surgery and delayed diagnosis of CD after surgery could increase the risk for repeated abdominal surgery in CD patients. Hellberg et al. [33] demonstrated that no difference in recurrence existed between emergency and elective surgery. A limited resection could not be performed under an emergency situation because determining the extent of resection during emergency surgery was difficult. Understandably, a repeated abdominal surgery could be necessary. Similarly, in the presence of an intra-abdominal abscess, surgeons usually tend to perform fewer surgeries. Therefore, the probability of recurrence might be higher after the first abdominal surgery if the indication for the first operation had been an intra-abdominal abscess.

The present study had several limitations. First, some data were missing because of the retrospective collection technique, which could affect the results. Second, the efficacy of the medical treatment after surgery was not analyzed. Medical treatment, such as the use of immunomodulators or anti-tumor necrosis factor- α , after abdominal surgery for CD could decrease the recurrence rate and affect the results of the present study.

In conclusion, young age (under 16 years of age), stricturing behavior, intra-abdominal abscess, emergency surgery, and delayed diagnosis after surgery may be risk factors for repeated abdominal surgery in Korean patients with CD.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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