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Long-term Outcomes and Risk Factors for Reoperation After Surgical Treatment for Gastrointestinal Crohn Disease According to Anti-tumor Necrosis Factor-α Antibody Use: 35 Years of Experience at a Single Institute in Korea

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Purpose: Crohn disease is characterized by high rates of recurrence and reoperations. However, few studies have investigated long-term surgical outcomes in Asian populations. We investigated risk factors for reoperation, particularly those associated with anti-tumor necrosis factor-α (anti-TNF-α) antibody use, and long-term follow-up results.
Methods: We reviewed the records of 148 patients (100 males and 48 females) who underwent surgery for gastrointestinal Crohn disease and retrospectively analyzed long-term outcomes and risk factors.
Results: The mean age at diagnosis was 28.8 years. Thirty-eight patients (25.7%) received monoclonal antibody treatment before reoperation. A small bowel and colon resection was most commonly performed (83 patients, 56.1%). The median follow-up was 149 months, during which 47 patients underwent reoperation. The median interval between the primary and the secondary surgeries was 65 months, with accumulated reoperation rates of 16.5%, 31.8%, and 57.2% after 5, 10, and 15 years, respectively. Obstruction was the most common indication for reoperation (37 patients, 25.0%). In a multivariable analysis, age <17 years at diagnosis (A1) (odds ratio [OR], 2.20; P = 0.023), penetrating behavior (B3) (OR, 4.39; P < 0.001), and no azathioprine use (OR, 2.87; P = 0.003) were associated with reoperation. Anti-TNF-α antibody use did not affect the reoperation rate (P = 0.767).
Conclusion: We showed a high reoperation rate regardless of treatment with anti-TNF-α antibody, which indicates that recurrent surgery is still needed to cure patients with gastrointestinal Crohn diseases. Younger age at primary operation, penetrating behavior, and no azathioprine use were significant factors associated with reoperation for gastrointestinal Crohn disease.

Keywords: *Crohn disease; Reoperation; Azathioprine; Infliximab*

INTRODUCTION

Gastrointestinal Crohn disease (CD) is a chronic inflammatory bowel disease with an unpredictable clinical course. Although long-term management of CD can be achieved with anti-inflammatory or immunosuppressive drugs, most CD patients experience repeated relapses and remission of inflammation. Surgical treatment becomes necessary when an intestinal obstruction or perforation occurs, with or without an abscess or fistula. Currently, there is no cure for CD; approximately 80% of patients un-

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dergo surgery during their lifetimes, and more than half of these patients require reoperation for recurrent CD after surgical treatment [1-5]. Recent reports indicate that infliximab, a tumor necrosis factor-α (TNF-α)-specific antibody, is significantly prophylactic against recurrent CD [6]. A human monoclonal antibody, adalimumab, has also been introduced with encouraging results [7, 8]. However, a complete cure for CD is not yet available, despite these new treatment modalities.

Many studies in Western countries have investigated the risk factors for reoperation in patients with CD and have identified the extent of disease at diagnosis, the presence of a perianal fistula, family history, smoking history, and perforating disease as risk factors. Accordingly, these risk factors are important for the postsurgical management of patients with CD [5, 9-12]. However, the risk factors for reoperation in Asian patients may differ from those in Western patients because Asian populations exhibit clinical characteristics (e.g., serologic and genetic types) different from those of Western populations [13, 14]. Although we previously reported the surgical outcomes and high rate of reoperation for our patients with CD, which were similar to those of Western patients, no studies have investigated the long-term surgical outcomes related to reoperation according to anti-TNF-α antibody use in Korean patients with CD. This study, therefore, aimed to evaluate the long-term outcomes of surgical treatment for gastrointestinal CD according to anti-TNF-α antibody use and to analyze the risk factors for reoperation in Korean patients with CD.

METHODS

This study was approved by the Institutional Review Board of the Seoul National University Hospital (H-1503-088-657). We identified 148 patients who had undergone surgery for gastrointestinal CD at our institute from 1978 to 2013. Most patients were diagnosed according to preoperative clinical impressions, endoscopic findings, and pathologic results. Patients who had previously undergone surgery for anal CD alone were excluded from this study. We retrospectively reviewed the patient's medical records to investigate sex, ages at diagnosis and primary operation, smoking habits, body mass index (BMI), medication history, indications of primary operation and reoperation, types of primary operation and reoperation, location of disease, length of bowel resection, and postoperative complications.

We used the Montreal classification to classify patients with CD; this is a 2005 revision of the Vienna classification (Table 1) [15]. We also compared patients with BMIs above and below a BMI threshold of 18.5 kg/m^2 to determine the effects of being underweight (BMI <18.5 kg/m^2) and nonunderweight (BMI ≥18.5 kg/m^2) [16]. We defined a primary operation as the first operation for a patient with gastrointestinal CD; a subsequent operation because of disease recurrence and relapse was defined as a reoperation. The long-term cumulative reoperation rates before and after 2002, the first year of anti TNF-α antibody (infliximab) use, were evaluated and compared. We further verified the risk factors for reoperation, including the use of anti-TNF-α antibody, in our study population.

Table 1. The Montreal classification of Crohn disease

Class	Criteria
Age at diagnosis	
A1	<17 yr
A2	17–40 yr
A3	>40 yr
Location	
L1	Ileal
L1	Colonic
L3	Ileocolonic
L4 modifier	Isolated upper disease
Behavior	
B1	Nonstricturing, nonpenetrating
B2	Stricturing
B3	Penetrating
Bp modifier	Perineal disease modifier

The statistical analysis was performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). In a univariate analysis of the risk factors for reoperation, the chi-square test was used to compare categorical variables, and the Student t-test was used to compare continuous variables. The cumulative reoperation rate was derived from a Kaplan-Meyer analysis. In the multivariate analysis, a Cox regression analysis was used to compare the cumulative reoperation rates. Statistical significance was indicated at a P-value <0.05.

RESULTS

Clinical characteristics and primary operation

The patients' clinical characteristics are shown in Table 2. One hundred patients were male, and 48 were female. The mean ages at diagnosis and primary operation were 28.8 and 31.9 years, respectively, and the mean interval from diagnosis to primary operation was 57.7 months (range, 0–209 months). Eighty (54.1%) and 60 patients (40.5%) had taken medication for CD before and after the primary operation, respectively. Thirty-eight patients (25.7%) used anti-TNF-α antibodies. An additional 16 patients used infliximab before the primary operation, and 22 began to use infliximab after the primary operation. Three patients used adalimumab and two patients used both infliximab and adalimumab after primary operation.

The rate of primary surgery for CD has recently increased at our institute (Fig. 1). Obstruction (n = 37, 25.0%) was the most common indication for primary surgery, and small bowel and colon

Table 2. Clinical characteristics of patients with Crohn disease

Characteristic	Value
Sex	
Male	100 (67.6)
Female	48 (32.4)
Age at diagnosis (yr)	28.8 ± 14.4
Age at primary operation (yr)	31.9 ± 13.6
Period from diagnosis to primary operation (mo)[a]	57.7 ± 61.1
Body mass index (kg/m^2)	
≥18.5	69 (54.8)
<18.5	57 (45.2)
Smoking	
Yes	23 (16.3)
No	118 (83.7)
Montreal classification	
Age at diagnosis	
A1	27 (18.2)
A2	92 (62.2)
A3	29 (19.6)
Location	
L1	80 (55.6)
L2	19 (13.2)
L3	45 (31.3)
L4	30 (20.3)
Behavior	
B1	14 (9.5)
B2	56 (38.1)
B3	77 (52.4)
Bp	36 (24.7)
Preoperative medication for CD	
Yes	80 (54.1)
No	60 (40.5)
Medication	
5-ASA	119 (80.4)
Azathioprine	111 (75.0)
Steroid	110 (74.3)
Infliximab/adalimumab	38 (25.7)
TB medication before diagnosis	
Yes	53 (35.8)
No	94 (63.5)
Indication of primary operation	
Obstruction	37 (25.0)
Abdominal abscess or mass	24 (16.2)
Diagnostic laparotomy	22 (14.9)
Medical intractability	21 (14.2)
Perforation	19 (12.8)
Enterocutaneous fistula	18 (12.2)
Internal fistula	7 (4.7)
Type of primary operation	
Small bowel and colon resection	83 (56.1)
Small bowel resection	53 (35.8)
Colon resection	10 (6.8)
Stricturoplasty only	1 (0.7)
Drainage of abdominal abscess	1 (0.7)
Stricturoplasty	
Yes	22 (14.9)
No	127 (85.1)
Stoma formation	
Yes	5 (3.4)
No	143 (96.6)
Bypass	
Yes	2 (1.4)
No	146 (98.6)
Resected bowel length (cm)	47.8 ± 37.2
>40 (median)	69 (49.3)
≤40 (median)	71 (50.7)
Postoperative complications	
Yes	39 (29.8)
No	92 (70.2)

(Continued to the next)
(Continued)

Values are presented as number (%) or mean ± standard deviation.
CD, Crohn disease; ASA, Aminosalicylic acid; TB, tubercle bacillus.
[a]Patients who were diagnosed after surgery had been excluded.

resection (n = 83, 56.1%) was the most common surgical procedure. Twenty-two patients (14.9%) underwent a stricturoplasty, and 5 patients (3.4%) underwent stoma formation. Bowel resection was performed in 147 patients, with a median bowel resection length of 40 cm (range, 8–325 cm). Thirty-nine patients (29.8%) experienced postoperative complications (Table 3). The most common complication was wound seroma (n = 16, 41.0%).

Follow-up and reoperation for recurrence

The median follow-up period was 149 months (range, 5–395 months), and 47 patients (31.8%) underwent reoperation after a median interval of 198 months (range, 14–330 months). Bowel obstruction (n = 14, 29.8%) was the most common indication for reoperation, and small bowel resection (n = 27, 27.4%) was the most common reoperation procedure (Table 4). Six patients (4.1%)

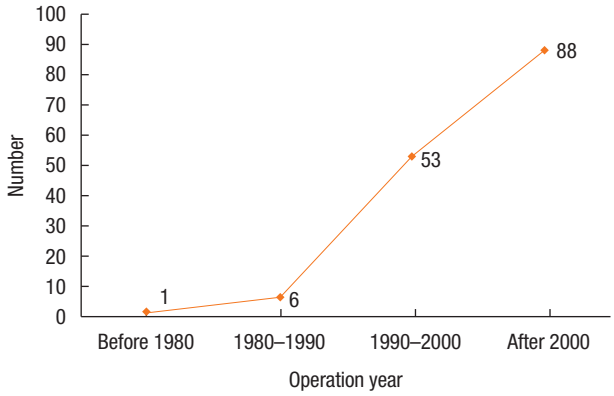

Fig. 1. Changes in the numbers of surgeries for intestinal Crohn disease (every 10 years).

Table 3. Postoperative complications after primary operation (n = 39)

Complication	No. of patients (%)
Wound seroma	16 (41.0)
Enterocutaneous fistula	6 (15.4)
Ileus	5 (12.8)
Intra-abdominal abscess	5 (12.8)
Anastomosis site leakage	3 (7.7)
Urinary tract infection	2 (5.1)
Fever of unknown origin	1 (2.6)
Cerebrovascular accident	1 (2.6)
Total	39

required a third operation, 4 (2.7%) a fourth operation, and 1 patient (0.7%) a fifth operation (Fig. 2), and they all had undergone a small bowel and colon resection (Table 5). After the primary operation, the 5-, 10-, 15-, and 20-year cumulative reoperation rates were 17.4%, 31.5%, 57.0%, and 68.7%, respectively (Fig. 3).

In the reoperation group, 29 patients underwent a primary operation for penetrating disease, among whom 22 (75.9%) required reoperation for recurrent penetrating disease. Seventeen patients underwent a primary operation for nonpenetrating disease, among whom 10 (58.8%) required reoperation for recurrent nonpenetrating disease. A significant difference in sustained disease behavior was observed between the groups (P = 0.029).

Analysis of risk factors for reoperation

In a univariate analysis of the risk factors for reoperation, according to the Montreal classification, the behavior (B) significantly affected the reoperation rate (P = 0.010), as did the interval from diagnosis to primary operation (P = 0.027). However, medication use, including anti-TNF-α antibodies (infliximab or adalimumab), did not significantly affect the reoperation rate (Table 6). In a multivariate analysis via a logistic regression, an age <17 years at diagnosis (A1) (odds ratio [OR], 2.20; 95% confidence interval

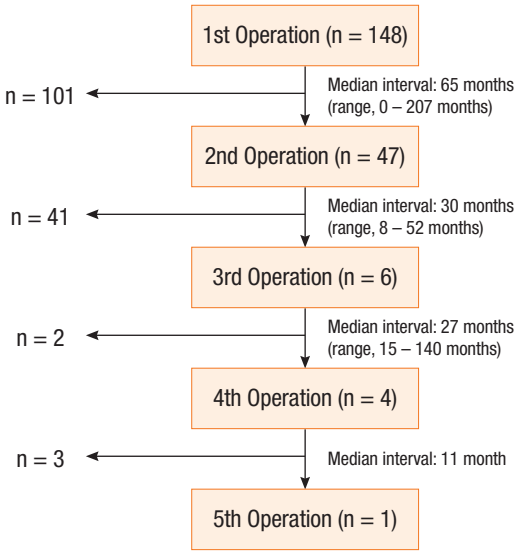

Fig. 2. Reoperation during the follow-up period.

Table 4. Reoperation for gastrointestinal Crohn disease

Reoperation	No. of patients (%)
Indication of reoperation	
Obstruction	15 (31.9)
Enterocutaneous fistula	11 (23.4)
Perforation	8 (17.0)
Internal fistula	5 (10.6)
Abdominal abscess or mass	5 (10.6)
Medical intractability	2 (4.3)
Diagnostic laparotomy	1 (2.1)
Type of reoperation	
Small bowel resection	27 (57.4)
Small bowel and colon resection	15 (31.9)
Colon resection	4 (8.5)
Proximal gastrectomy	1 (2.1)
Stoma formation	
Yes	4 (8.5)
No	43 (91.5)
Stricturoplasty	
Yes	5 (10.6)
No	42 (89.4)

[CI], 1.12–4.31; P = 0.023), penetrating behavior (B3) (OR, 4.39; 95% CI, 2.19–8.80; P < 0.001), and no azathioprine use (OR, 2.87; 95% CI, 1.43–5.76; P = 0.003) were associated with a significantly higher reoperation rate (Table 7). In contrast, no significant difference in the cumulative reoperation rate was observed according to the year of primary operation (before and after 2002) rela-

Table 5. Operations performed after reoperation for gastrointestinal Crohn disease

Reoperation	No. of patients (%)
Indication of reoperation	
Enterocutaneous fistula	4 (36.4)
Obstruction	4 (36.4)
Perforation	2 (18.2)
Abdominal abscess or mass	1 (9.1)
Type of reoperation	
Small bowel and colon resection	11 (100)
Stoma formation	
Yes	0 (0)
No	11 (100)
Stricturoplasty	
Yes	1 (9.1)
No	10 (90.9)

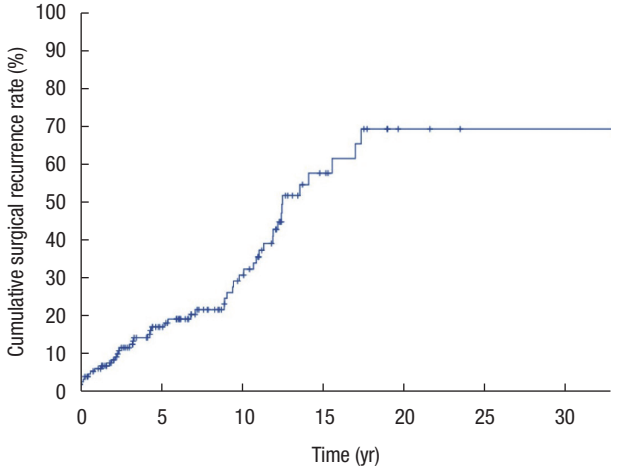

Fig. 3. Cumulative reoperation rate for intestinal Crohn disease.

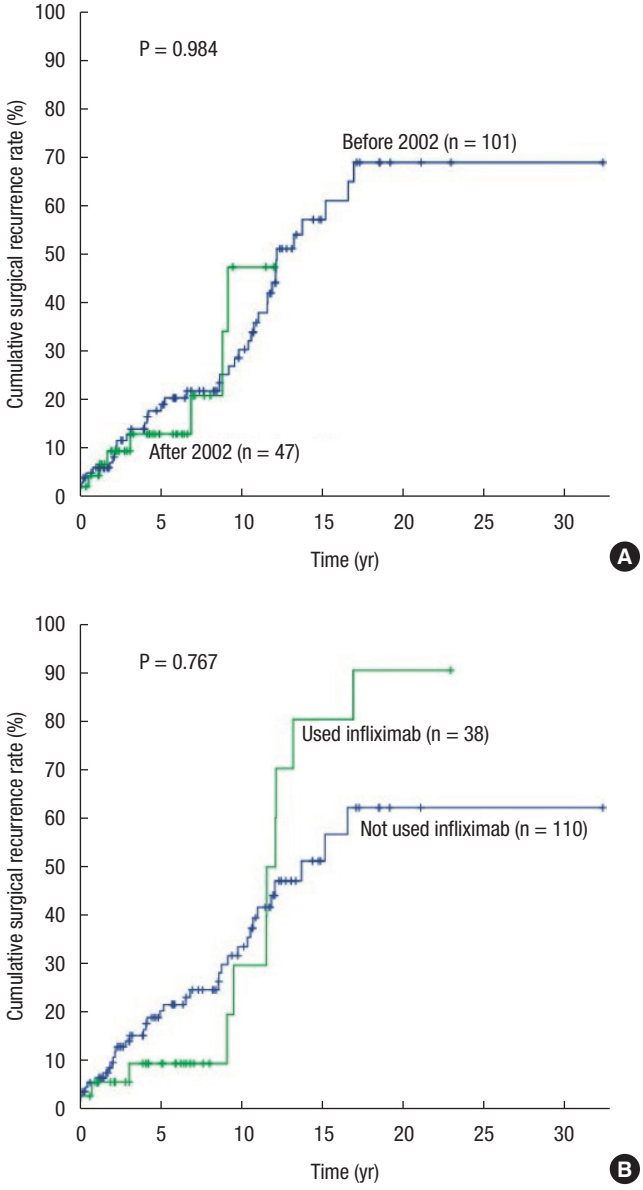

Fig. 4. Comparisons of infliximab use (A) between groups treated and not treated with infliximab and (B) between groups diagnosed before and after 2002 (the year infliximab became available as a treatment option).

tive to anti-TNF-α antibody availability (P = 0.984 and P = 0.767, respectively) (Fig. 4).

DISCUSSION

In this study of a Korean population, the cumulative reoperation rates for gastrointestinal CD were found to be 31.8% and 68.9% at 10 and 20 years after the primary operation, respectively. An age <17 years at diagnosis (A1), penetrating disease (B3), and no azathioprine use were found to be significant risk factors for reoperation in patients with CD. However, anti-TNF-α antibody use was not a significant risk factor. In eastern Asian countries (e.g., Korea, China, and Japan), the incidence of CD has recently increased, despite the traditional categorization of these areas as countries with low CD incidence. In Korea, the reported annual incidence rate has increased from 1.34 per 100,000 inhabitants in 1986 to 11.24 per 100,000 inhabitants in 2005 [17, 18]. Our data similarly showed an increase in the number of patients with CD who had undergone surgery (Fig. 1), and our observed reoperation rates were as high as those in Western studies of CD (38% and 52% at 10 and 20 years, respectively) [9, 19]. Similar reports of the long-term outcomes (<35 years) of patients with CD in Asian countries are very rare. Given the dramatic changes in CD

Table 6. Comparison of the reoperation and the no reoperation groups

Variable	Reoperation (+) (n = 47)	Reoperation (–) (n = 101)	P-value
Sex			0.260
Male	35 (35.0)	65 (65.0)	
Female	12 (25.0)	36 (75.0)	
Age at diagnosis (yr)			0.601
>27[a]	21 (29.6)	50 (70.4)	
≤27	26 (33.8)	51 (66.2)	
Age at primary operation (yr)			0.078
>31[a]	17 (24.3)	53 (75.7)	
≤31	30 (38.5)	48 (61.5)	
Period from diagnosis to primary operation (mo)			0.027*
>34[a]	9 (20.5)	35 (79.5)	
≤34	21 (42.9)	28 (57.1)	
Body mass index (kg/m^2)			0.676
≥18.5	17 (24.6)	52 (75.4)	
<18.5	12 (21.1)	45 (78.9)	
Smoking			0.143
Yes	4 (17.4)	19 (82.6)	
No	42 (35.6)	76 (64.4)	
Montreal classification			
Age at diagnosis			0.124
A1	13 (48.1)	14 (51.9)	
A2	27 (29.3)	65 (70.7)	
A3	7 (24.1)	22 (75.9)	
Location			0.068
L1	28 (35.0)	52 (65.0)	
L2	9 (47.4)	10 (52.6)	
L3	9 (20.0)	36 (80.0)	
L4[b]	8 (26.7)	22 (73.3)	0.661
Behavior			0.010*
B1	0 (0)	14 (100)	
B2	17 (30.4)	39 (69.6)	
B3	29 (37.7)	48 (62.3)	
Bp[b]	16 (44.4)	20 (55.6)	0.064
Preoperative medication for CD			0.285
Yes	22 (27.5)	58 (72.5)	
No	24 (36.4)	42 (63.6)	
Medication			
5-ASA	36 (30.5)	82 (69.5)	0.518
Azathioprine	31 (27.9)	80 (72.1)	0.103
Steroid	34 (30.9)	76 (69.1)	0.692
Infliximab/adalimumab	11 (28.9)	27 (71.1)	0.840
TB medication before diagnosis			0.361
Yes	14 (30.4)	39 (38.6)	
No	32 (69.6)	62 (61.4)	
Indication of primary operation			0.017*
Obstruction	10 (27.0)	27 (73.0)	
Abdominal abscess or mass	2 (8.3)	22 (61.9)	
Diagnostic laparotomy	8 (38.1)	13 (12.9)	
Medical intractability	8 (40.0)	12 (60.0)	
Perforation	6 (31.6)	13 (68.4)	
Enterocutaneous fistula	8 (44.4)	10 (55.6)	
Internal fistula	3 (42.9)	4 (57.1)	
Type of primary operation			0.461
Small bowel and colon resection	23 (27.7)	60 (72.3)	
Small bowel resection	19 (35.8)	34 (64.2)	
Colon resection	5 (50.0)	5 (50.0)	
Stricturoplasty only	0 (0)	1 (100)	
Drainage of abdominal abscess	0 (0)	1 (100)	
Stoma formation			0.327
Yes	3 (60.0)	2 (40.0)	
No	44 (30.8)	99 (69.2)	
Stricturoplasty			0.626
Yes	8 (36.4)	14 (63.6)	
No	39 (31.0)	87 (69.0)	
Bypass			0.536
Yes	1 (50.0)	1 (50.0)	
No	46 (31.5)	100 (68.5)	
Resected bowel length (cm)			0.101
>40 (median)	16 (23.2)	53 (76.8)	
≤40 (median)	26 (36.1)	46 (63.9)	
Postoperative complications			0.272
Yes	12 (30.8)	27 (69.2)	
No	27 (21.5)	73 (78.5)	

Values are presented as number (%). P-values were also calculated separately.
CD, Crohn disease; ASA, Aminosalicylic acid; TB, tubercle bacillus.
*P < 0.05. [a]Median values. [b]These variables are independent of the other variables belonging to the same class.

Table 7. Multivariate analysis of risk factors for reoperation

Variable	Univariate P-value	Multivariate analysis	
		OR (95% CI)	P-value
Smoking	0.050*	–	0.605
Age at diagnosis			
<17 yr (A1)	0.001*	2.20 (1.12–4.31)	0.023*
Behavior			
Penetrating (B3)	<0.001*	4.39 (2.19–8.80)	<0.001*
No azathioprine use	0.009*	2.87 (1.43–5.76)	0.003*
Indication of primary operation			
Abdominal abscess or mass	0.035*	–	0.070
Stoma formation	<0.001*	–	0.077

OR, odds ratio; CI, confidence interval.
*P < 0.05.

treatment, such long-term follow-up studies of Eastern Asian patients at a single center are valuable.

The introduction of anti-TNF-α antibodies represented a revolutionary improvement in the treatment and management of CD. Initially, two trials, ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients With Fistulizing Crohn's Disease) I and ACCENT II, evaluated the best infliximab dosing methods in patients with CD [20, 21]. More recently, adalimumab, another anti-TNF antibody, has been investigated as a second-line anti-TNF-α therapy for patients who have developed an intolerance to infliximab [7]. Despite some reports of infliximab-induced reductions in the recurrence rate after primary surgery [22, 23], no previous studies have evaluated whether anti-TNF-α antibody use would improve the reoperation rate among patients with CD who had undergone a previous operation [24, 25]. In our study, no significant differences were observed between patients who had and had not used anti-TNF-α antibody therapies. Similarly, we found no significant differences between patients who underwent surgery before or after 2002, the first year during which anti-TNF-α antibodies were used at our institute. In Korea, anti-TNF-α antibodies are used to treat severe CD because of a strict insurance system that limits the use of infliximab for treating CD to patients who have already tried two other types of medications and have CDAI scores >220 or to those with a fistulizing CD who have already used two other kinds of treatments; accordingly, our patients who had used these drugs had more severe and more complex disease. As a result, it is difficult for Korean patients in an earlier phase of CD to obtain infliximab, a factor that might interfere with the ability to demonstrate an association between infliximab use and better treatment results. In fact, another study failed to demonstrate a reduction in the reoperation rate following the use of anti-TNF-α antibodies and indicated a need for earlier infliximab treatment [26]. Additional studies have suggested that top-down therapy might be more effective than conventional management for patients in remission [27, 28], although the effect of top-down therapy on the CD reoperation rate is not yet well established. Although anti-TNF-α antibodies are currently expected to provide effective treatment for CD, recurrent surgery still remains necessary for patients with CD.

In our study, patients younger than 17 years at diagnosis (A1) had a higher reoperation rate. However, the influence of age on the reoperation rate among patients with CD remains controversial [2]. In our study, younger patients did not have a significantly longer period of disease relative to older patients (167.5 months in A1 vs. 144.8 months in others, P = 0.170). As a result, other disease factors might affect the reoperation rate. One study showed that patients diagnosed at a younger age tended to have a positive family history of CD and more complicated disease [29]. Another recent study reported that the phenotypes of younger patients with CD differed from those of older patients [30]. Although that study did not report a higher risk of reoperation, it suggested the existence of different intrinsic disease components in younger patients. Similarly, our study also demonstrated differences in the composition and location of CD. Approximately 59% of A1 patients had ileocolic disease (L3) whereas approximately 62% of A2 and A3 patients had ileal disease (L1) (P = 0.001). Finally, some studies reported an association between *NOD2/CARD15* genotypic mutations and the age at CD diagnosis [31-33]; however, this mutation has not been detected in Eastern Asian patients with CD [13, 34].

We also observed a higher reoperation rate among patients with penetrating disease (B3). Many studies have shown an increased risk of earlier reoperation with perforating disease [10, 35, 36], and some of these studies have suggested a trend toward recurrent perforation in patients previously treated for perforating disease. Because complicated disease behaviors such as penetrating or stricturing disease require surgical treatment [37], the reoperation rate may be higher among such patients. In the present study, more than half of the patients had penetrating disease at the primary operation, and these patients exhibited a significant likelihood of reoperation for penetrating disease (n = 23, 74.2%, P = 0.038). We might consider that these disease behaviors originate from a more aggressive intrinsic disease property that leads to a higher reoperation rate among affected patients.

Only azathioprine treatment effectively prevented reoperation in this study. Azathioprine is an effective medication for the postoperative management of CD, and some studies have reported reduced rates of surgical relapse of CD after long-term postsurgical thiopurine use [38, 39]. A prospective study previously demonstrated a lower rate of clinical recurrence with azathioprine use than with mesalazine use, despite also reporting a higher azathioprine discontinuation rate because of adverse drug reactions [40]. Another study reported the preventive effect of 6-mercaptopurine, with a 27% reduction in clinical recurrence and a 16% reduction in radiological recurrence relative to a placebo group [41]. Yet another study reported reduced risks of clinical recurrence

(relative risk [RR], 0.59) and severe endoscopic recurrence (RR, 0.64) among patients treated with azathioprine/6-mercaptopurine [42]. Additionally, a study reported that long-term (>36 months) maintenance treatment with thiopurine decreased the risk of surgical recurrence (hazard ratio, 0.41; P = 0.004) [38]. In our patients, the effect of azathioprine was also superior to that of 5-aminosalicylate acid alone (P = 0.033).

This study had some limitations. First, the study was designed retrospectively, leading to a possible failure to evaluate many factors associated with the CD status because of missing data. Selection bias resulting from the operator's inclination is also possible. The small study size relative to those in Western studies also hindered the evaluation of other variables that had been identified as potential risk factors. Nevertheless, our study is unique among Asian populations, in which the incidence of CD is increasing, as we have included long-term (>35 years) surgical outcomes and an analysis of anti-TNF-α antibody use.

In summary, our long-term follow-up results confirmed a high rate of reoperation for gastrointestinal CD in the Korean population. An age <17 years at diagnosis, penetrating disease behavior, and no azathioprine use were verified risk factors for reoperation. However, we were unable to demonstrate a prophylactic effect of anti-TNF-α antibody therapy against reoperation.

CONFLICT OF INTEREST

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

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