

Risk Factors for Postoperative Recurrence in Korean Patients with Crohn's Disease

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Background/Aims: A considerable number of patients with Crohn's disease still need intestinal resection surgery. Postoperative recurrence is an important issue in Crohn's disease management, including the selection of high-risk patients. Eastern Asian patients showed several differences from Caucasian patients. Therefore, we investigated the postoperative surgical recurrence outcome and identified risk factors in Korean patients. **Methods:** Clinical data of 372 patients with Crohn's disease who underwent first intestinal resection between January 2004 and August 2014 at 14 hospitals in Korea were retrospectively reviewed. **Results:** Over the follow-up period, 50 patients (17.1%) showed surgical recurrence. The cumulative surgical recurrence rate was 6.5% at 1 year and 15.4% at 7 years. Age under 16 ($p=0.011$; hazard ratio [HR], 5.136; 95% confidence interval [CI], 1.576 to 16.731), colonic involvement ($p=0.023$; HR, 2.011; 95% CI, 1.102 to 3.670), and the presence of perianal disease at surgery ($p=0.008$; HR, 2.239; 95% CI, 1.236 to 4.059) were independent risk factors associated with surgical recurrence. Postoperative thiopurine treatment ($p=0.002$; HR, 0.393; 95% CI, 0.218 to 0.710) was a protective factor for surgical recurrence. **Conclusions:** Among the disease characteristics at surgery, younger age, colonic location, and perianal le-

sions were independent risk factors for surgical recurrence. Postoperative thiopurine treatment significantly reduced the incidence of surgical recurrence. (**Gut Liver 2020;14:331-337**)

Key Words: Crohn disease; Recurrence; Surgery; Risk factors; Thiopurine

INTRODUCTION

Crohn's disease (CD) is a chronic, progressive, and disabling inflammatory bowel disease with uncertain etiology and pathogenesis. CD can affect any part of the gastrointestinal tract with systemic manifestations.¹ The natural course of the CD is characterized by relapse and remissions. Advancement in medical treatment, such as immunomodulators and anti-tumor necrosis factor (anti-TNF)- α antibody, has changed the treatment strategy for CD.² Using anti-TNF- α antibody and immunomodulator has achieved mucosal healing that led to long-term maintenance of remission and lowering surgery rate. In a Danish cohort study, 5-year cumulative probability of first major surgery decreased from 44.7% in a cohort (1979 to 1986) to 19.6% in a cohort (2003 to 2011) for CD.³

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Nevertheless, considerable patients with CD need surgical intervention including a requirement for intestinal resection even in the biologic agent treatment era.⁴ Intestinal resection for CD is limited to maintain the complete remission status due to high recurrence rate. More than half of the patients experience a clinical recurrence within 5 years and surgical recurrence within 10 years.⁵ Therefore, the prevention of postoperative recurrence, especially the need for repeated intestinal resection after the first surgery is a crucial issue.

Selecting high-risk patients for CD recurrence is an important problem. Smoking, perforating disease phenotype, and previous intestinal resection have been suggested from previous studies as factors that predict earlier postoperative recurrence.^{6,7} A prior randomized clinical trial showed that treatment according to clinical risk factors of recurrence, early colonoscopy and treatment step-up for recurrence is better for prevention of CD recurrence.⁸

However, most of the previous studies regarding postoperative recurrence in CD were performed in Western nations and mainly Caucasians because of relatively lower incidence CD in Eastern Asia. Clinical characteristics such as age at diagnosis, cigarette smoking, disease location, behavior, and treatment strategy showed differences between the East and the West in studies.^{9,10} Indeed, factors that predict postoperative recurrence are still unclear and the data are lacking, especially in Eastern Asian countries. Previous studies were limited in terms of small patient number, single hospital patients or lack of clinical and medication data.¹¹⁻¹³ Consequently, research of postoperative recurrence is needed to target Eastern Asian patients with CD.

Therefore, we investigated postoperative surgical recurrence outcomes and identified the risk factors associated with postoperative recurrence after intestinal resection surgery in Korean patients with CD through a multicenter setting study.

MATERIALS AND METHODS

1. Patients

Clinical data of 372 patients with CD who underwent first intestinal resection due to CD from January 2004 to August 2014 at 14 hospitals in Korea were retrospectively reviewed. Surgical intervention without intestinal resection such as operation limited in appendectomy, perianal procedure, and strictureplasty was not included as intestinal resection surgery. Surgical recurrence was defined as additional intestinal resection owing to CD, except surgery-related complications.

Patients with the following were excluded: follow-up period less than 1 year after intestinal resection (n=43), and patients with insufficient clinical, surgical information (n=37). After excluding 80 patients based on our exclusion criteria, a total of 292 patients were finally selected.

This study was approved by the Institutional Review Board of Wonkwang University Hospital in Iksan, Korea (IRB number:

WKUH 201401-HRE-007).

2. Primary and secondary outcomes

The primary outcome was to investigate the risk factors of postoperative surgical recurrences in Korean patients with CD. The secondary outcome was to evaluate surgical recurrence rates according to risk factors.

3. Statistical analysis

Data are expressed as the median (interquartile range), number, or number (%), as appropriate. Factors associated with surgical recurrence were investigated using the Kaplan-Meier analysis and Cox regression. Any variables identified as significant ($p < 0.05$) in the univariate analysis were included in the multivariate analysis.

For comparison of the cumulative probability of surgical recurrences, Kaplan-Meier estimator survival analysis was used. For comparing outcomes, the chi-square test or Fisher exact test was used for categorical data, and the Student t-test was used for continuous variables. Data analysis was performed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). A two-sided p -value < 0.05 was considered statistically significant.

RESULTS

1. Baseline characteristics

Baseline characteristics of the patients are summarized in Table 1. The median age at diagnosis was 25.6 years and at surgery was 29.6 years, respectively. Based on Montreal classification, the majority of the patients presented with ileocolonic location (L3, 46.2%) and non-stricturing, non-penetrating behavior (B1, 53.1%) at diagnosis. At the time of surgery, the patients' disease phenotype changed, resulting in the most common location to terminal ileum (L1, 53.1%) and behavior to penetrating type (B3, 66.4%). Most of the patients were diagnosed between ages of 17 and 40 (n=196, 67.1%). Patients with age under 16 years at diagnosis and at surgery were 63 (21.6%) and 34 (11.6%). At diagnosis, 51 patients (17.5%) were current smokers and 11 patients (21.6%) stopped smoking before their first intestinal resection surgery. Perianal diseases were presented in 135 patients (46.2%) before their first intestinal resection surgery.

2. Medical management

Patients' medical therapy histories before and after surgery is described in Table 2. The median duration from diagnosis to surgery was 29.0 months and median follow-up periods after intestinal resection was 46.0 months. Thiopurine (azathioprine or 6-mercaptopurine) was used in 161 patients (55.1%) before surgery and 207 patients (70.9%) after first intestinal resection surgery. The number of patients using anti-TNF agents (infliximab or adalimumab) before and after intestinal resection sur-

gery was 58 (19.9%) and 93 (31.8%). In preoperative anti-TNF users, 35 patients (60.3%) reused anti-TNF agents after bowel resection.

3. Postoperative surgical recurrence

Postoperative surgical recurrence outcome is showed in Table 3. Fifty patients (17.1%) received second intestinal resection surgery due to CD. The cumulative surgical recurrence rate increased from 6.5% at 1 year to 15.4% at 7 years.

Table 1. Baseline Characteristics at Diagnosis and Surgery

Variable	Diagnosis (n=292)	Surgery (n=292)
Sex		
Male	198 (67.8)	198 (67.8)
Female	94 (32.2)	94 (32.2)
Age, yr	25.6 (17.0–32.0)	29.6 (21.0–35.8)
A1 (16)	63 (21.6)	34 (11.6)
A2 (17–40)	196 (67.1)	207 (70.9)
A3 (>40)	33 (11.3)	51 (17.5)
Location		
L1 (ileal)	116 (39.7)	155 (53.1)
L2 (colonic)	37 (12.7)	41 (14.0)
L3 (ileocolonic)	135 (46.2)	92 (31.5)
L4 (isolated upper disease)	4 (1.4)	4 (1.4)
Behavior		
B1 (non-stricturing, non-penetrating)	130 (44.5)	42 (14.4)
B2 (stricturing)*	102 (34.9)	86 (29.5)
B3 (penetrating) [†]	70 (24.0)	194 (66.4)
P (perianal disease)	115 (39.4)	135 (46.2)
Current smoking		
Current smoker	51 (17.5)	40 (13.7)
Ex-smoker + non-smoker	241 (82.5)	252 (86.3)
CD diagnosed after surgery	49 (16.8)	-
Family history of IBD	8 (2.7)	-

Data are presented as number (%) or median (range).

CD, Crohn's disease; IBD, inflammatory bowel disease.

*Stricturing behavior, including the B2 (stricturing) and B2+B3 (stricturing and penetrating) phenotypes; [†]Penetrating behavior, including the B3 (penetrating) and B2+B3 (stricturing and penetrating) phenotypes.

4. Factors associated with surgical recurrence

To determine independent factors associated with surgical recurrence, variables including baseline characteristics and type of medication were analyzed. Among the variables, age at surgery ($p=0.003$), colonic involvement ($p=0.009$), penetrating phenotype ($p=0.042$), perianal disease ($p=0.014$), and postoperative thiopurine use ($p=0.014$) were associated with surgical recurrence in univariate analysis. In multivariate analysis, age under 16 at surgery ($p=0.011$; hazard ratio [HR], 5.136; 95% confidence intervals [CI], 1.576 to 16.731), colonic involvement at surgery ($p=0.023$; HR, 2.011; 95% CI, 1.102 to 3.670), and presence of perianal disease before surgery ($p=0.008$; HR, 2.239; 95% CI, 1.236 to 4.059) were independent risk factors associated with surgical recurrence. Using postoperative thiopurine medication ($p=0.002$; HR, 0.393; 95% CI, 0.218 to 0.710) was a protective factor from surgical recurrence (Table 4).

5. Surgical recurrence outcome according to risk factors

High-risk group patients and low-risk group patients were stratified according to the number of risk factors that showed significant in multivariate analysis. Patients who had one risk factor were not different from those without risk factors. However, patients who had two or three risk factors showed higher rate of surgical recurrence (Table 5). There was no difference in follow-up duration between the two groups. Time to surgical recurrence was 84.3 months in patients with the high-risk group and 103.4 months in the low-risk group (Table 6).

Table 2. Crohn's Disease Medical Therapy (n=292)

Variable	Before surgery	After surgery
Follow-up duration, mo	29.0 (1.0–74.8)	46.0 (24.0–72.0)
Surgical recurrence	-	50 (17.1)
Medication		
5-ASA	225 (77.1)	260 (89.0)
Corticosteroid	169 (57.9)	99 (33.9)
Thiopurine	161 (55.1)	207 (70.9)
Anti-TNF	58 (19.9)	93 (31.8)
Infliximab	52 (17.8)	78 (26.7)
Adalimumab	10 (3.4)	21 (7.2)
Infliximab and adalimumab	4 (1.4)	8 (2.7)

Data are presented as median (range) or number (%).

ASA, aminosalicylic acid; TNF, tumor necrosis factor.

Table 3. Surgical Recurrence Outcome

Variable	Time after first bowel resection surgery (yr)						
	1	2	3	4	5	6	7
Surgical recurrence	19/292 (6.5)	23/221 (10.4)	30/175 (17.1)	30/135 (22.2)	21/105 (20.0)	16/74 (21.6)	14/55 (25.5)
Cumulative surgical recurrence	19/292 (6.5)	25/292 (8.5)	34/292 (11.6)	40/292 (13.7)	41/292 (14.0)	43/292 (14.7)	45/292 (15.4)

Data are presented as number/number (%).

Table 4. Independent Factors Associated with Postoperative Surgical Recurrence

Variables	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age at Surgery			0.003			0.011
≤16	5.933	1.8492–19.108		5.136	1.576–16.731	
17–40	2.483	0.876–7.058		2.169	0.759–6.204	
≥41	Reference			Reference		
Sex	1.317	0.744–2.334	0.342			
Family history	0.653	0.090–4.740	0.850			
Previous appendectomy	1.068	0.500–2.280	0.864			
Diagnosis by initial surgery	1.716	0.723–4.074	0.215			
Disease location at surgery			0.009			0.023
Ileum	Reference			Reference		
Colon*	2.173	1.196–3.951		2.011	1.102–3.670	
Disease behavior at surgery						
Non-stricturing, non-penetrating	0.381	0.118–1.225	0.092			
Stricturing [†]	0.793	0.419–1.501	0.475			
Penetrating [‡]	2.019	1.009–4.041	0.042			0.131
Perianal disease at surgery	2.017	1.137–3.576	0.014	2.239	1.236–4.059	0.008
Current smoking at surgery	1.290	0.509–3.268	0.589			
Emergent surgery	0.954	0.501–1.817	0.885			
Preoperative Medication						
5-ASA	1.015	0.528–1.953	0.964			
Corticosteroid	0.785	0.450–1.371	0.393			
Thiopurine	1.191	0.674–2.105	0.546			
Anti-TNF	0.852	0.399–1.820	0.679			
Postoperative Medication						
5-ASA	0.497	0.221–1.116	0.083			
Corticosteroid	1.092	0.613–1.943	0.765			
Thiopurine	0.496	0.280–0.878	0.014	0.393	0.218–0.710	0.002
Anti-TNF	0.698	0.378–1.290	0.025			

HR, hazard ratio; CI, confidence interval; ASA, aminosalicylic acid; TNF, tumor necrosis factor.

*Colonic involvement, including L2 (colonic) and L3 (ileocolonic); [†]Stricturing behavior, including the B2 (stricturing) and B2+B3 (stricturing and penetrating) phenotypes; [‡]Penetrating behavior, including the B3 (penetrating) and B2+B3 (stricturing and penetrating) phenotypes.

Table 5. Surgical Recurrence Outcome According to Nonmodifiable Risk Factors

No. of risk factors*	No. (%)	HR	95% CI	p-value
0	90 (30.8)			
1	113 (38.7)	2.536	0.945–6.803	0.065
2	78 (26.7)	4.110	1.532–11.027	0.005
3	11 (3.8)	12.550	3.818–41.258	0.001

HR, hazard ratio; CI, confidence interval.

*The risk factors are defined as an age at surgery of less than 16, the presence of perianal disease at surgery, and colonic or ileocolonic location at surgery.

Table 6. Surgical Recurrence Outcome According to Risk Factors

Variable	Low risk group (0 or 1 risk factor*)	High risk group (2 or 3 risk factors)	p-value
No.	203 (69.5)	89 (30.5)	
Follow-up duration, mo	44.0 (23.0–71.0)	50.0 (26.0–77.5)	0.267
Surgical recurrence	25 (12.3)	25 (28.1)	0.001
Time to surgical recurrence, mo	103.4 (96.7–111.3)	84.3 (73.3–95.3)	0.001

Data are presented as number (%) or median (interquartile range).

*The risk factors are defined as an age at surgery of less than 16, the presence of perianal disease at surgery, and colonic or ileocolonic location at surgery.

DISCUSSION

The rapidly increasing tendency with complicated disease behavior over the past few decades and postoperative recurrence are crucial issues of CD management in Korea.¹¹ Eastern Asian patients, including Koreans, have shown different clinical characteristics and disease courses from Caucasian CD patients.⁹ In this study, we identified the clinical characteristics and long-term outcomes in a large number of Korean patients from multiple referral centers.

The differences between our study patients from Western CD patients were male predominance (67.8%), a small number of patients who were diagnosed CD after age 40 (11.3%), smaller proportion of smokers and less frequent colonic involvement at surgery, and more common presence of perianal disease before surgery.^{9,14} The reason for these differences is mostly unknown. However, it is suggested that altered gut microbiota and genetic differences, such as no association with NOD2 and more strong association with TNFSF 15 compared with Caucasian, may be related.¹⁵ Higher exposure to social life or Westernized life style in Asian males compared to females might contribute to male predominance. Also, age-specific environmental factors or different sensitivities to certain infectious factors might cause a second small peak onset of CD.^{16,17}

Previously, the surgical recurrence rate in Western CD patients was 20%–50% compared to 14%–25% in Korean CD patients including present study within 5 years.^{5,18} Lower recurrence rate in Korean patients is might be due to the lower smoking rate and the genetic difference making less aggressive natural course compared to Western CD patients.¹³ However, the surgical recurrence rate in Western CD patients showed a wide range depending on the time period. Moreover, some recent studies conducted in the West showed only 8.6% within 8 years and 19.1% in 10 years.^{19,20} Therefore, it is still unclear to consider the ethnic difference as a risk factor for surgical recurrence.

Regarding medical treatment, 55.1% of patients used thiopurine and only 19.9% of patients used anti-TNF medication before their first intestinal resection surgery. These results were similar to a recent single-center retrospective study.¹¹ A tendency towards the lower proportion of anti-TNF agents in Asian

countries compared to the West was well described in several studies. Although the efficacy of anti-TNF agents did not differ between the West and Asian countries, the lower proportion of usage may be originated from limited and strict indications under national insurance coverage in our study period in Korea.⁹ In this study, independent risk factors for postoperative surgical recurrence were younger age, colonic involvement, and the presence of perianal lesion at the surgery. Especially, patients who had more than 2 risk factors showed higher surgical recurrence. Thiopurine medication after surgery reduced surgical recurrence significantly. Patients with age under 16 at surgery showed much higher surgical recurrence than those with age over 16, especially compared to those with age over 40. Recent American Gastroenterological Association review also suggested younger age at onset as one of the risk factors for postoperative recurrence.⁷ It was indicated that patients with younger age at onset have more extensive disease involvement and aggressive clinical course characteristics distinct from adult-onset patients.^{21–23} Indeed, our study population revealed more frequent colonic involvement and penetrating behavior compared to adult-onset patients. A different pathogenic mechanism such as the presence of a specific mutation in genes encoding the IL10R between the age groups may be related.²⁴

There were conflicting results regarding disease location and surgical recurrence. In our study, a total of 34 patients (25.6%) with colonic involvement showed surgical recurrence with a shorter median duration of 111.0 months compared to 119.0 months in patients with ileal location. It may be originated from involved bowel length, but our study was limited due to lack of surgical data. Some Western studies suggested that ileal location of CD is a predictive factor.²⁵ But other studies showed colonic or ileocolonic location is related to higher recurrence rates compared the ileal disease.^{26,27} Also, in previous studies conducted in Korea, the relationship between location and surgical recurrence has not been clear.¹¹

Patients with perianal disease are related to complicated disease phenotype, higher risk of surgery, hospitalization, and severe disease courses.²⁸ Also, presence of perianal disease is a well-known risk factor for postoperative recurrence.⁶ A recent study conducted in Korea demonstrated that patients with peri-

anal disease had increased risks of abdominal reoperation (HR, 1.978; 95% CI, 1.034 to 3.784), and postoperative 5-ASA (HR, 0.388; 95% CI, 0.175 to 0.858) and thiopurine medication (HR, 0.499; 95% CI, 0.249 to 0.999) reduced risks of abdominal reoperation.²⁹ The present study showed similar results in regard of perianal disease and benefit of postoperative thiopurine use. Also, patients with younger age at onset showed a higher rate of perianal disease in both studies. However, unlike the previous study, this study showed younger age was one of the risk factors and postoperative 5-ASA medication was not effective to prevent a recurrence.

Many studies from Western countries have shown that smoking is a strong risk factor for the postoperative recurrence of CD.^{4,6,7} Smoking rate in general population in Korea (19.9% to 25.9%) is comparable or higher than that of Western countries (18.4% to 20.7%).³⁰ However, a relatively small number of patients were current smokers at the time of diagnosis (n=51, 17.5%) and surgery (n=40, 13.7%) in the present study. This result was consistent with population-based cohort studies in Asian patients with CD that showed lower smoking rate (11.8% to 28.0%) than Western (57.0%) and Eastern European patients (62.0%).³¹

Another important finding was that thiopurine medication after surgery significantly reduced surgical recurrence. However, other medications including anti-TNF agents were not associated with surgical recurrence in our study. The top-down strategy of using an anti-TNF agent early in the postoperative period, as well as early in the disease course, has been proposed.² Recently, several studies conducted in Asia showed contrary results from the present study.^{11,32} During our follow-up periods, the use of anti-TNF agents, both infliximab and adalimumab, were covered by national insurance whenever fulfilling following criteria of unresponsive effect with more than 2 drugs or moderate CD with contraindication to corticosteroid or immunomodulator. Therefore, a considerable number of patients could use anti-TNF medications after marked endoscopic and clinical recurrence. As a result, using anti-TNF medication still could not prevent a surgical recurrence.

There are several limitations in the present study. First, we could not evaluate endoscopic recurrence and clinical recurrence. Because of the study design which was multicenter and retrospective, there was no universal follow-up protocol. Therefore, we acquired only small number of endoscopic follow-up results and clinical data such as Crohn's Disease Activity Index, admission or medication step-up due to CD exacerbation. Second, we had limited data collection for histological and surgical-related factors that may be associated with surgical recurrence. Nevertheless, this study has the significance that it is the first study involving most of the referral centers nationwide, thus reflecting the overall results of Korean patients.

In conclusion, patients with younger age at onset, colonic location, and the presence of perianal disease need careful

monitoring and intensive management strategies. Thiopurine medication in postoperative patients might be effective methods for the prevention of surgical recurrence.

CONFLICTS OF INTEREST

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

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AUTHOR CONTRIBUTIONS

Conceptualization: J.H.C., G.S.S., B.I.J. Data curation: S.B.K., J.H.C., G.S.S., B.I.J. Formal analysis: J.M.L., S.B.K., G.S.S. Investigation: S.B.K., J.H.C., G.S.S., B.I.J. Methodology and project administration: J.H.C., G.S.S., B.I.J. Resources: J.H.C., J.J.P., E.S.K., S.W.J., S.A.J., D.I.P., C.K.L., J.P.I., Y.S.K., H.S.K., J.L., C.S.E., B.I.J., G.S.S. Writing - original draft: S.B.K. Writing - review & editing: G.S.S., B.I.J.

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