



Risk Factors for Surgery in Patients with Intestinal Behçet's Disease During Anti-Tumor Necrosis Factor-Alpha Therapy

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Purpose: Behçet's disease (BD) is a chronic inflammatory immune-mediated disease involving multiorgan systems. Gastrointestinal (GI) manifestations of BD include abdominal pain, vomiting, GI bleeding, fistula formation, obstruction, and perforation that might require surgery. Recently, anti-tumor necrosis factor-alpha (anti-TNF- α) therapy has been shown to have favorable outcomes in patients with intestinal BD who are refractory to conventional therapy. This study sought to figure out the risk factors for undergoing surgery during anti-TNF- α therapy in patients with intestinal BD.

Materials and Methods: In this retrospective analysis of intestinal BD patients who were treated with anti-TNF- α , we collected the baseline patient data including comorbidities, clinical, endoscopic, and radiologic characteristics, and the Disease Activity Index for Intestinal Behçet's Disease at the time of anti-TNF- α initiation. Each potential risk factor was compared. For multivariate analysis, Cox regression was used.

Results: A total of 62 patients were considered eligible for analysis, and 15 of them (24.1%) underwent surgery. In univariate analysis, the presence of extraintestinal manifestation, such as joint symptoms and erythrocyte sedimentation rate (ESR), were significantly associated with surgery during therapy. In multivariate analysis, drug response within 4 weeks [hazard ratio (HR), 64.59], skin and joint manifestation (HR, 10.23 and HR, 6.22), geographic ulcer (HR, 743.97), and ESR >42.5 mm/h (HR, 9.16) were found to be factors predictive of undergoing surgery during anti-TNF- α therapy.

Conclusion: We found five risk factors predictive of surgery in patients with intestinal BD receiving anti-TNF- α therapy, which can guide physicians in selecting appropriate patients between anti-TNF- α therapy and early surgery.

Key Words: Intestinal Behçet's disease, risk factors, tumor necrosis factor-alpha, surgery

INTRODUCTION

Behçet's disease (BD) is a chronic relapsing multisystemic inflammatory disease characterized by repeated oral and geni-

tal ulcerations, ocular lesions, skin manifestations, arthritis, vasculitis, and gastrointestinal (GI) involvement. Its etiology remains unknown, but many consider it a systemic vasculitis.¹ Approximately 3%–16% of patients with BD have GI tract involvement.² Intestinal lesions may precede the extraintestinal manifestations.³ Although the clinical manifestations of intestinal BD vary from mild abdominal pain to perforation and excessive bleeding, GI involvement in BD often suggests a poor prognosis despite treatment.^{1,4}

Intestinal BD shares treatment strategies with inflammatory bowel diseases, such as Crohn's disease.⁴ Although conventional therapies, such as 5-aminosalicylic acids, corticosteroids, and immunomodulators, are available, a considerable number of patients eventually become unresponsive to these pharmaceutical treatments. Biologic agents, such as anti-tumor ne-

Received: July 8, 2022 **Revised:** December 12, 2022

Accepted: December 13, 2022 **Published online:** January 16, 2023

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•The authors have no potential conflicts of interest to disclose.

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crisis factor- α (TNF- α) agents, have been approved for the treatment of intestinal BD and used as standard therapy, and they appear to be promising for more severe and/or refractory intestinal BD cases.^{1,5-8} Infliximab, a chimeric monoclonal anti-TNF- α antibody, and adalimumab, a completely humanized Immunoglobulin G1 monoclonal anti-TNF- α antibody, are the two most studied biologic agents.¹

Despite the evident benefits of medical therapy, patients with intestinal BD often require surgery and may experience complications, such as intestinal perforation, bleeding, and abscess. Perforation and massive GI bleeding are absolute indications for surgery, while abdominal abscess, fistula, and stricture are possible indications. In addition, patients who are refractory to medical treatments, including corticosteroids and anti-TNF- α agents, require surgical intervention.^{9,10} Factors that can predict which patients will show a poor response to anti-TNF- α therapy have not been well studied to date. These predictive factors could aid physicians in determining the appropriate therapeutic options. Surgery should be considered early for patients who are expected to have poor anti-TNF responsiveness.

Cumulative rates of surgical interventions for intestinal BD are reportedly 20% at 1 year, 27%–33% at 5 years, and 31%–46% at 10 years after diagnosis.¹¹⁻¹³ The surgery rate is expected to decrease after the initiation of anti-TNF- α therapy. However, it is not yet known which patients will require surgery despite the use of anti-TNF- α . Therefore, this study aimed to determine the risk factors for surgery in patients with intestinal BD receiving anti-TNF- α agents.

MATERIALS AND METHODS

Study population

Hospitalized or ambulatory patients with intestinal BD who were 18–80 years of age were eligible for enrollment in this study. We reviewed the medical records of patients with intestinal BD who underwent anti-TNF- α treatment at Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea, between February 2014 and June 2020. The diagnosis of intestinal BD was confirmed in all patients using the established Korean and Japanese criteria.^{14,15} Patients with definite, probable, or suspected intestinal BD were included. The analysis included all patients whose records were available at the time of anti-TNF- α treatment initiation, even if the treatment was first started at another hospital.

In patients with uncontrolled moderate or severe symptoms despite conventional medical therapy, two anti-TNF- α agents were typically considered.^{8,11} Infliximab 5 mg/kg was administered at 0, 2, and 6 weeks and every 8 weeks thereafter. Adalimumab 160 mg was administered at week 0, 80 mg at week 2, and 40 mg at week 4, followed by 40 mg for maintenance every other week.¹⁶ Patients who were taking anti-TNF- α for causes

other than intestinal BD (e.g., rheumatic diseases, such as ankylosing spondylitis) were excluded from the analysis.

Surgery was defined as resection of the small bowel, colon, or rectum after the initiation of anti-TNF- α therapy. Surgery was considered for patients whose symptoms were intractable to medical therapy or for those with complications, such as perforation, abscess, fistula, stricture, or GI bleeding.^{8,17,18}

Assessments

The medical records included baseline demographics (sex, age, age at diagnosis, alcohol intake, smoking status, and hematologic comorbidities), clinical information at the start of anti-TNF- α therapy (fever, oral ulcers, genital ulcers, eye symptoms, skin symptoms, joint symptoms, vascular symptoms, and neurologic symptoms), and the Disease Activity Index for Intestinal Behçet's Disease (DAIBD) score. The DAIBD score includes general well-being for 1 week, extraintestinal manifestations, abdominal pain in 1 week, abdominal mass, abdominal tenderness, intestinal complications, and the number of liquid stools in 1 week.^{1,19} DAIBD was classified as moderate for a score of 40 or higher and severe for a score of 75 or higher; all patients in this study were classified into the moderate or severe group. All clinical manifestations (fever and extraintestinal symptoms) were reviewed at the time of anti-TNF- α administration. Blood tests included hemoglobin level (mg/dL), erythrocyte sedimentation rate (mm/h), C-reactive protein level (CRP) (mg/L), and recent imaging or endoscopic studies.

Typical ulcers in intestinal BD are single or few, large, deep, discrete, and round or oval-shaped.^{20,21} The most common intestinal BD invasion site is the ileocecal area⁴; therefore, a case involving only one bowel segment was considered localized distribution. The macroscopic findings of the ulcers were categorized into the volcano-like, geographic, and aphthous types,²² and the depth of each was reviewed. These were collected using the most recent colonoscopy results from the first anti-TNF- α dose.

Remission rates 8 weeks after the initiation of medical treatment for intestinal BD are reportedly 38%–67%.^{21,23} Four weeks after the first anti-TNF- α administration, the drug response was evaluated by an expert in an outpatient or in-hospital setting and the DAIBD score determined. We defined anti-TNF response as global GI symptom scores and endoscopic assessments. Complete remission, marked improvement, improvement, and no change were included regardless of confirmation of mucosal healing.²⁴ The causes of surgery (refractory abdominal pain, perforation, abscess, or obstruction) were evaluated on the basis of clinical symptoms and computed tomography findings.

Information on drugs (aminosalicylic acids, corticosteroids, azathioprine/6-mercaptopurine, methotrexate, colchicine, or cyclosporine A) concomitantly used with anti-TNF- α was collected. Corticosteroid use included both oral and intravenous routes. Regarding surgical history, only bowel resection asso-

ciated with intestinal BD was documented. Surgery only after the administration of the most recently administered anti-TNF- α was considered the main clinical outcome. This study complied with the Declaration of Helsinki and was approved by our Institutional Ethics Committee (IRB number : 2022-1254-001).

Statistical analysis

Descriptive data are expressed as the mean \pm standard deviation when normally distributed, and as the median \pm interquartile range (25th to 75th percentiles) when non-normally distributed. The primary objective of the present study was to identify the risk factors for surgery in patients undergoing anti-TNF- α therapy. Continuous data were analyzed using the Student's *t* test (or Mann-Whitney test when data were not normally distributed), and categorical data were compared with Pearson's χ^2 test. Items with a *p* value <0.2 and clinically significant endoscopic characteristics were included as variables in the multivariate analysis to correct for each effect. Not all of the patients with intestinal BD reached endoscopic healing with medical treatment only. Since the event of surgery itself suggests that the severity has increased over time, we assumed that Cox regression would be more appropriate than logistic regression. A multivariate analysis using the Cox proportional hazards regression model including significant univariate factors (*p*<0.05) determined the independent risk factors. Hazard ratio (HRs) and 95% confidence interval (CIs) for each risk factor were calculated. Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

Comparisons of baseline clinical characteristics and endoscopic findings

Overall, among the 753 patients with intestinal BD registered at our clinic, 79 underwent anti-TNF- α therapy. After excluding those who underwent anti-TNF- α therapy for diseases other than intestinal BD and those whose records were not available at the time of the first anti-TNF- α dose, 62 patients were finally included. Among them, 56 (90.3%) were treated with adalimumab, and 5 (8.0%) were treated with infliximab. The patients' demographic and clinical characteristics are presented in Table 1.

Twenty-five patients (40.3%) were male. There was no significant difference in the age at diagnosis between the surgery and non-surgery groups. The presence of hematologic comorbidities (e.g., myelodysplastic syndrome) did not differ significantly between groups (*p*=0.587). The DAIBD score, which indicates intestinal BD severity, did not differ significantly between groups. The most common associated symptom was oral ulcer (25.85%). There were no significant differences in the associated extraintestinal manifestations between groups, except for a

Table 1. Baseline Patient Characteristics

	n=62	Surgery (n=15)	Non-surgery (n=47)	<i>p</i> value
Age at diagnosis, yr	40.37	39.93 \pm 12.2	40.51 \pm 14.6	0.891
Sex, male	25	6 (40)	19 (40.4)	0.977
Smoking history				0.237
Never smoker	52	11 (73.3)	41 (87.2)	
Alcohol drinking history				0.478
Never drinker	45	11 (73.3)	34 (72.3)	
Hematologic diseases	5	2 (13.3)	3 (6.4)	0.587
Anti-TNF- α therapy				>0.999
Adalimumab	56	14 (93.3)	42 (89.4)	
Infliximab	5	1 (6.7)	4 (8.5)	
History of previous anti-TNF- α	15	4 (26.7)	11 (23.4)	>0.999
DAIBD		140.0 \pm 13.8	130.4 \pm 7.25	0.527
Moderate	3	0 (0)	3 (6.4)	
Severe	59	15 (100)	44 (93.6)	
Response within 4 weeks	55	11 (73.3)	44 (93.6)	0.052
Associated symptoms				
Fever	6	3 (20)	3 (6.4)	0.146
Oral ulcer	16	4 (26.7)	12 (25.5)	>0.999
Genital ulcer	3	0 (0)	3 (6.4)	>0.999
Eye symptom	3	1 (6.7)	2 (4.3)	>0.999
Skin symptom	6	3 (20)	3 (6.4)	0.146
Joint symptom	6	5 (33.3)	1 (2.1)	0.002
Vascular symptom	1	0 (0)	1 (2.1)	>0.999
Neurologic symptom	0	0 (0)	0 (0)	
Hemoglobin (g/dL)		11.1 \pm 1.59	11.3 \pm 1.77	0.766
Anemia	44	12 (80)	32 (68.1)	0.519
ESR (mm/hr)		63.4 \pm 38.4	50.3 \pm 31.6	0.190
CRP (mg/L)		39.2 (6.72–55.10)	27.12 (3.20–38.3)	0.303
Medications				
Aminosalicylic acid	60	14 (93.3)	46 (97.9)	0.428
Corticosteroids	36	9 (8.7)	27 (57.4)	0.861
Azathioprine/6-mercaptopurine	30	7 (46.7)	23 (48.9)	0.878
Methotrexate	7	0 (0)	7 (14.9)	0.180
Colchicine	5	0 (0)	5 (10.6)	0.323
Cyclosporine A	1	1 (6.7)	0 (0)	0.242

Anti-TNF- α , anti-tumor necrosis factor alpha; DAIBD, Disease Activity Index for Intestinal Behçet's Disease; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Data are presented as mean \pm standard deviation or n (%).

significant difference in the presence of joint symptoms (33.3% vs. 2.1%; *p*=0.002).

Sixty patients (96.7%) received aminosalicylic acids, and 37 (59.6%) received immunomodulators (methotrexate or azathioprine/6-mercaptopurine). A total of 36 patients (58.0%) received corticosteroid therapy at varying doses. Twenty-four percent (n=15) had previously used other anti-TNF- α agents. There were no significant intergroup differences in medica-

tion use.

Next, we compared the most recent endoscopy results performed before the start of the anti-TNF- α agent (Table 2). Since a radiologic imaging study (e.g., computed tomography) is preferred to endoscopy to determine the treatment plan in patients with the acute exacerbation of intestinal BD, the interval between endoscopic assessment and drug administration varied in our study (average 392 days, median 168.5, Q1 52.25 days–Q3 637 days). Forty-eight patients (77.4%) had deep ulcers; of them, 44 (70.9%) were localized in the short intestinal segment. Fifty-one patients (82.5%) had a typical intestinal BD ulcer shape on the most recent endoscopy. There were no significant intergroup differences in ulcer number, depth, type, or distribution.

Four weeks after the start of anti-TNF- α treatment, the response, including the DAIBD, was checked at the outpatient or in-hospital level. Of the 55 patients who showed a favorable response at 4 weeks, 11 underwent surgery after treatment. Patients who experienced a 4-week improvement were not significantly different between the surgery group and non-surgery group (73.3% vs. 93.6%, $p=0.052$).

Surgery after anti-TNF- α therapy

Fifteen patients (24%) underwent bowel resection during the follow-up period. The mean patient age at the time of surgery was 47.1 years. The shortest mean time from the first drug administration to surgery was 602 days (range, 51–1627 days). The reasons for surgery were refractory abdominal pain [7 patients

(46.6%)], intractability with medical treatment [5 patients (33.3%)], abscess (with or without perforation) [1 patient (6.6%)], bowel perforation [2 patients (13.3%)], and bleeding [3 patients (20%)], considering multiple choices. In cases of surgery due to medical intractability, intestinal perforation was confirmed postoperatively.

Identification of risk factors for surgery

Multivariate analysis using Cox regression was performed for the most significant ($p<0.2$) factors and clinically significant endoscopic factors (ulcer shape, ulcer depth) to determine which were independent. The multivariate analysis identified five independent risk factors associated with surgical intervention: skin symptoms (HR, 10.23; 95% CI, 1.66–62.99), joint symptoms (HR, 6.22; 95% CI, 1.49–26.01), volcano type or geographic ulcer (HR, 743.97; 95% CI, 20.09–27550.25), erythrocyte sedimentation rate (ESR) >42.5 mm/h (HR, 9.16; 95% CI, 1.33–62.78), and poor response in 4 weeks (HR, 64.59; 95% CI, 6.02–693.31) (Table 3).

DISCUSSION

Intestinal BD often presents with concurrent symptoms of recurrent oral and genital aphthous ulcerations, arthritis, and skin manifestations with ocular, vascular, and neurological involvement. It shows a fluctuating clinical course with repeated episodes of relapse and remission. The symptoms can range from mild abdominal discomfort to massive bleeding, fistula, or bowel perforation. Since patients with intestinal BD require lifelong treatment, clinicians should be aware of predictive factors for drug response. In particular, identifying the risk factors for surgery after or during treatment with anti-TNF agents are of clinical importance, since it remains unclear whether anti-TNF agents or surgery is more appropriate for patients for whom conventional therapy fails.

In this study, 15 of 62 patients were treated surgically for intestinal BD during the follow-up period. Surgery was mainly performed in response to medical therapy intractability. Patients who did not show a favorable response in a month, who had skin or joint symptoms at the initiation of anti-TNF- α therapy, who had volcano-like or geographic ulcers, or whose ESR was higher than 42.5 mm/h were at a higher risk of surgery.^{11,12,17,25} In a retrospective review, younger age (≤ 25 years) at diagnosis, a history of prior laparotomy, and volcano-shaped

Table 2. Baseline Endoscopic Characteristics

	n=62	Surgery (n=15)	Non-surgery (n=47)	p value
Ulcer shape				0.407
Geographic or volcano	2	1 (7.7)	1 (2.3)	
Oval, round, aphthous	55	12 (92.3)	43 (97.7)	
Number of ulcers				0.757
Multiple (≥ 2)	24	6 (40)	18 (38.3)	
Ulcer depth				0.370
Deep	48	10 (76.9)	38 (88.4)	
Ulcer type				0.580
Typical	51	13 (100)	38 (88.4)	
Ulcer distribution				0.711
Localized	44	11 (84.6)	33 (76.7)	

Data are presented as n (%).

Table 3. Five Predictive Factors for Surgery in Intestinal BD Patients after Anti-TNF- α Treatment

	HR	95% CI	p value
Skin symptoms (with vs. without)	10.23	1.66–62.99	<0.05
Joint symptoms (with vs. without)	6.22	1.49–26.01	<0.05
Ulcer shape (geographic or volcano type ulcer vs. oral, round, and so on)	743.97	20.09–27550.25	<0.05
Erythrocyte sedimentation rate (>42.5 vs. ≤ 42.5)	9.16	1.33–62.78	<0.05
Response within 4 weeks (no vs. yes)	64.59	6.02–693.31	<0.05

HR, hazard ratio; CI, confidence interval.

intestinal ulcers were identified as independent risk factors for free bowel perforation.²⁶ Patients with volcano-type ulcers reportedly show a significantly lower complete remission rate in response to initial medical therapy compared to those with non-volcano-type ulcers.²² Therefore, the risk of surgery could be higher in patients with geographic or volcano-type ulcers, as shown in this study. In medically treated intestinal BD patients, a volcano-shaped ulcer was predictive of the likelihood of surgery.^{22,23} The difference between our results and those of previous studies was that ulcer depth was not significantly associated with surgery. The reason is assumed to be that most of patients' ulcerations were deep.

Another study showed that patients who achieved complete remission of their intestinal lesions after 8 weeks of medical treatment had a lower probability of requiring surgery compared to those who did not.²¹ In a multicenter retrospective study, which investigated the effectiveness of infliximab, the achievement of remission at week 4 were found to be one of the predictive factors of sustained response in intestinal BD.²⁷ In this paper, response evaluations of 0, 2, 4, 30, and 54 weeks were included. This is most likely due to the finding that anti-TNF- α is a rapidly acting drug and a patient who fails to respond early has a low possibility of developing a good response later in the treatment process. This finding was consistent with our analysis showing a poor response at 4 weeks as an independent risk factor for subsequent surgery. This implies that the early assessment of treatment response after anti-TNF- α initiation is valuable for predicting future prognosis.

In a previous study, the younger group of patients diagnosed at 40 years of age or younger showed a higher cumulative probability of requiring surgery,¹² but we found no significant difference between surgery and age at diagnosis in this study. A Korean multicenter retrospective study of 28 patients who were treated with infliximab demonstrated that older age (>40 years), female sex, longer disease duration (>5 years), concomitant immunomodulator use, and achievement of remission within 4 weeks were predictive of a sustained response.²⁷ To date, consistent results are lacking on this issue; therefore, further studies are warranted.

In this study, a higher CRP level did not significantly increase the risk of surgery at any cut-off value; but in the case of ESR, ESR >42.5 mm/h significantly increased the odds of surgery. According to previous studies, ESR and CRP were correlated with disease activity; therefore, it can be inferred that disease activity with a higher inflammatory burden at the time of administration also affects subsequent surgery.¹

These results are consistent with those of previous studies, which showed that extraintestinal symptoms in intestinal BD predict a poor prognosis. Each extraintestinal symptom count has a score of 5 in the DAIBD, and initial higher disease activity is an independent predictor of surgery and a severe disease course in intestinal BD.^{12,25} In addition, extraintestinal symptoms are often accompanied by pain, which can lower the pa-

tient's quality of life. Previous reports demonstrated that patients with extraintestinal symptoms show a poor prognosis for inflammatory bowel disease.^{28,29}

Our study had several limitations. First, it was a single-center retrospective study with a relatively small sample size. Since one study has reported the postoperative recurrence of intestinal ulcers in more than half of patients³⁰ and that volcano-shaped ulcers and higher CRP levels increase the risk of reoperation,¹⁰ a prospective observation is needed to confirm the risk factors. Also, the number of patients who had surgery was not large enough to make statistically significant result in our univariate analysis. Second, the doses of anti-TNF- α and other drugs (e.g., steroids) could not be analyzed or adjusted. Further multicenter, longitudinal, long-term follow-up studies should consider the drug dose.

In conclusion, our study is the first to reveal the predictive factors for surgery in patients with intestinal BD using anti-TNF- α . Surgery should be considered in a timely manner when an intestinal BD patient is suspected of having severe complications or does not respond properly to medical treatment.^{6,19} We identified five risk factors predictive of surgery in patients with intestinal BD receiving anti-TNF- α therapy, which can guide physicians in selecting appropriate patients for anti-TNF- α therapy versus early surgery.

AUTHOR CONTRIBUTIONS

Conceptualization: Jae Hee Cheon. **Data curation:** all authors. **Formal analysis:** all authors. **Investigation:** all authors. **Methodology:** So Jung Han, Jihye Park, and Jae Hee Cheon. **Project administration:** So Jung Han and Jae Hee Cheon. **Resources:** Eun Ae Kang, Jihye Park, Soo Jung Park, Jae Jun Park, Tae Il Kim, Won Ho Kim, and Jae Hee Cheon. **Software:** So Jung Han. **Supervision:** Jae Hee Cheon. **Validation:** So Jung Han and Jae Hee Cheon. **Visualization:** So Jung Han and Jae Hee Cheon. **Writing—original draft:** So Jung Han. **Writing—review & editing:** So Jung Han and Jae Hee Cheon. **Approval of final manuscript:** all authors.

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