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Outcome Predictors for Intestinal Behçet's Disease

Jae Jun Park,[1] Won Ho Kim,[2] and Jae Hee Cheon[2]

[1]Department of Internal Medicine and Institute of Gastroenterology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul;
[2]Department of Internal Medicine and Institute of Gastroenterology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea.

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Corresponding author: Dr. Jae Hee Cheon, Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
Tel: 82-2-2228-1990, Fax: 82-2-393-6884
E-mail: geniushee@yuhs.ac

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Behçet's disease (BD) is a multisystem inflammatory disorder that presents as recurrent oral and genital ulcers in conjunction with other dermatological and ocular manifestations. The prevalence of BD is higher in Middle and East Asia than in Western countries. Intestinal BD is a specific subtype of BD, characterized by intestinal ulcers and associated gastrointestinal symptoms. Similar to inflammatory bowel disease, intestinal BD exhibits a fluctuating disease course with repeated episodes of relapse and remission that necessitate adequate maintenance therapy after achievement of clinical remission. Medical treatment of intestinal BD is largely empirical since well-controlled studies have been difficult to perform due to the heterogeneity and rarity of the disease. To date, 5-aminosalicylic acid, systemic corticosteroids, and immunosuppressants have been used anecdotally to treat intestinal BD. The clinical course of intestinal BD shows considerable variability, and the exact point at which more potent agents such as immunosuppressants should be used has not yet been elucidated. Given the difficulty in predicting which patients will experience complicated disease courses and the fact that these drugs are related with certain risk resulting from immunosuppression, proper identification of prognostic factors in intestinal BD may allow physicians to implement tailored medical therapy and individualized patient monitoring based on risk stratification. In this review, the impact of baseline characteristics on the long-term course of intestinal BD, prognostic factors during various medical therapies, and outcome predictors related to surgery will be discussed.

Key Words: Intestinal Behçet's disease, prognostic factors, medical treatment, surgical treatment

INTRODUCTION

Behçet's disease (BD) is a chronic relapsing multisystemic vasculitic disorder characterized by recurrent oral and genital ulcers, ocular lesions, skin manifestations, arthritis, as well as vascular, neurologic, and intestinal involvement.[1,2] The disease prevalence is relatively high in East Asia, including Korea and Japan, as well as in Mediterranean countries with approximately 1-10 cases per 10000 people. In Europe and North America, however, the prevalence is considerably lower at a rate of only 1-2 patients per 1000000 people.[3,4] While the prognosis for BD varies, involvement of the central nervous system and large blood vessels often re-

sults in a fatal prognosis.[5]

Because gastrointestinal (GI) involvement can also lead to severe morbidity and mortality, BD is particularly designated "intestinal BD" if GI symptoms predominate, and typical ulcerative GI lesions are objectively documented.[6] The frequency of GI involvement varies depending on geographic location, ranging from 3% to 50%.[7-10] Symptomatic or documented intestinal involvement is rare in Mediterranean patients with BD, whereas it is common in East Asian countries including Korea and Japan. The most frequently affected site is the ileocecal region, and common clinical symptoms include abdominal pain, diarrhea, and bleeding.[11] Although the diagnosis of systemic BD is usually made according to criteria suggested by the Behçet's Disease Research Committee of Japan[12] or the International Study Group for Behçet's Disease,[13] adequate diagnosis of intestinal BD using these criteria is limited due to various extraintestinal manifestations that emerge at different time points throughout the disease course.[14] Therefore, novel diagnostic criteria for intestinal BD were recently proposed, which may be particularly useful in patients with ileocolonic ulcers that do not fully satisfy the diagnostic criteria for systemic BD.[15]

Similar to inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, intestinal BD runs a chronic, fluctuating, and unpredictable course characterized by repeated episodes of relapse and remission.[16] As a result, the primary goals of intestinal BD management are induction and maintenance of symptom remission to minimize recurrences, surgical procedures, and irreversible bowel damage.[7] However, optimal medical treatment for intestinal BD has not been firmly established due to the rarity of the disease, which has limited the ability to conduct well-controlled clinical studies. Currently, treatment of intestinal BD is largely accomplished using IBD medications including 5-aminosalicylic acid (5-ASA), corticosteroids, and immunosuppressants.[1]

The clinical course of intestinal BD varies considerably from patient to patient, and the exact time point at which more potent agents such as immunosuppressants should be introduced has not yet been elucidated. Given the difficulty in predicting which individuals will experience complicated courses or inevitable surgery and the fact that these therapeutic agents are associated with certain risks resulting from immunosuppression, proper identification of prognostic factors for intestinal BD may help facilitate risk stratification at an earlier stage of the disease, and thus, allow for implementation of tailored treatment and individualized monitoring strategies. Although clinical data for specific outcomes of intestinal BD are not yet sufficient, multiple studies regarding these issues have been published over the last decade. In this review, the impact of baseline characteristics on the long-term course of intestinal BD, prognostic factors for various medical treatments, and outcome predictors related to surgery will be discussed.

LONG-TERM OUTCOME PREDICTORS FOR INTESTINAL BEHÇET'S DISEASE

There are very scant data on clinical predictors of the long term evolution of intestinal BD. In one retrospective study carried out by Jung, et al.[17] including 130 patients who were regularly followed for more than 5 years at a single tertiary academic medical center, a large proportion of patients (71.5%) experienced a mild clinical course, whereas the remaining 28.5% of patients had a severe clinical course with multiple relapses or chronic symptoms. Therein, initial presentation with higher disease activity [disease activity index for intestinal Behçet's disease (DAIBD) ≥40] was independently associated with a more severe clinical course [odds ratio (OR), 6.2; 95% confidential interval (CI), 1.1-33.5].

It has been reported that the cumulative rates of surgical intervention are 20% at 1 year, 27-33% at 5 years, and 31-46% 10 years after diagnosis.[18,19] Regarding predictors for requiring an operation, younger age (<40 years) at the time of diagnosis [hazard ratio (HR), 2.41; 95% CI, 1.28-4.54], higher initial disease activity (DAIBD ≥70) (HR, 5.43; 95% CI, 2.65-11.1) and the presence of volcano-shaped intestinal ulcers (HR, 6.99; 95% CI, 2.75-17.73) (Fig. 1) were independent predictive factors.[18]

OUTCOME PREDICTORS DURING VARIOUS MEDICAL TREATMENTS

Overall outcomes during medical treatment

Remission rates 8 weeks after the initiation of medical treatment have been reported to be 38-67% in cases of intestinal BD.[20,21] Kim, et al.[22] reported that patients with volcano-type ulcers showed a significantly lower complete remission rate in response to initial medical therapy than those with non-volcano type ulcers (24% versus 68%, respectively, $p<0.05$). Despite an initial response to medical treatment, a substan-

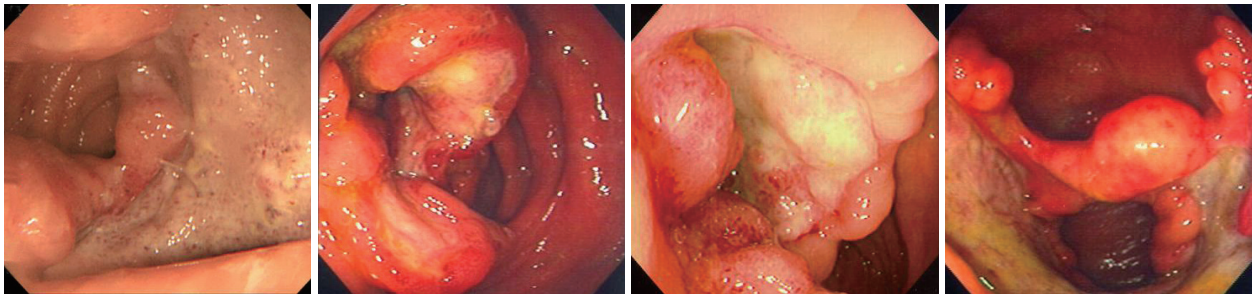

Fig. 1. Volcano-type ulcers in patients with intestinal Behçet's disease. The ileocolonoscopic findings show large, well-demarcated, deeply penetrating ulcers with nodular margins.

tial number of patients experienced relapse during the follow-up period. Several studies have reported cumulative recurrence rates of 25% at 2 years and 43-49% at 5 years after medically induced remission with single or combined drug therapies including 5-ASA/sulfasalazine, corticosteroids, and immunosuppressants.[20,21] Regarding outcome predictors after medically induced remission, Chung, et al.[21] identified several predictive factors for relapse including a lack of complete remission after 8 weeks of medical treatment (HR, 4.599; 95% CI, 2.005-10.547), the presence of volcano-type ulcers (HR, 3.247; 95% CI, 1.666-6.328) or deep ulcers (HR, 4.051; 95% CI, 1.777-9.235), and the presence of apparent GI symptoms at the time of diagnosis (HR, 3.650; 95% CI, 1.853-7.191). Additionally, in a 2 year follow-up study of 80 intestinal BD patients that had achieved clinical remission, Yim, et al.[23] found that lack of mucosal healing at the time of clinical remission was an independent predictor of relapse (HR, 3.891; 95% CI, 1.616-9.346). This result was in agreement with previous IBD data that showed that mucosal healing was associated with sustained clinical remission and reduced rates of hospitalization and surgical resection.[24]

In medically treated patients, Choi, et al.[20] showed that patients who achieved complete remission of intestinal lesions after 8 weeks of medical treatment had a lower probability of receiving an operation than those who had not (13% and 36% at 2 years, and 13% and 43% at 5 years, respectively, p=0.028). This finding implies that mucosal healing is an important prognosticator for future surgery. In the same context, Chung, et al.[21] showed that characteristics of baseline endoscopic lesions could predict future surgery in medically treated intestinal BD patients [volcano-shaped ulcer (HR, 3.830; 95% CI, 1.179-12.447), deep ulcers (HR, 9.723; 95% CI, 1.262-74.933)]. These results corroborate data reported by Kim, et al.[22] which also showed a higher surgical rate in patients with volcano-type ulcers than in non-volcano type ulcers (52% versus 12%, respectively, p<0.05).

To date, there is limited data regarding specific serologic markers for intestinal BD. Based on a cohort of 106 medically treated intestinal BD patients, Choi, et al.[25] found that the cumulative probability of a first operation was significantly higher in patients with anti-*Saccharomyces cerevisiae* antibody (ASCA)-positive intestinal BD than in those that were ASCA-negative (44.8% and 17.2% at 1 year, and 53% and 24.3% 2 years after diagnosis, respectively, p=0.006). This finding implies that ASCA positivity could predict a more aggressive disease course in patients with intestinal BD. Additionally, Naganuma, et al.[26] reported that the baseline percentage of peripheral $CD8^+DR^+$lymphocytes in peripheral blood in intestinal BD patients during remission was significantly higher in patients with recurrence than in those without recurrence (10.4±2.5% versus 4.3±1.2%, respectively, p=0.037), suggesting that peripheral $CD8^+DR^+$ lymphocytes are a potential marker for relapse. Another recent study examining anti-α-enolase antibody (AAEA) showed that the cumulative rate of steroid use in patients that were positive for IgM AAEA was significantly higher than those that were negative (38% and 31% at 1 year, 46% and 43% at 3 years, and 60% and 48% at 5 years, respectively, p=0.022).[27] Early documentation of these serologic markers, if the clinical setting is available, might be useful for prognostic identification of intestinal BD patients.

Predictors during 5-ASA therapy

Although there is a lack of high level evidence regarding the efficacy of 5-ASA, the use thereof is indicated in all cases of intestinal BD due to its relatively high safety profile and limited alternative therapeutic options.[1,7] The optimal doses of mesalazine and sulfasalazine for adult patients are 2.25-3 g/day and 3-4 g/day, respectively. In a retrospective cohort study of 143 patients with intestinal BD who received 5-ASA/sulfasalazine alone for maintenance of remission, Jung, et al.[28] found that the cumulative relapse rates at 1, 3, 5, and 10 years after remission were 8.1%, 22.6%,

31.2%, and 46.7%, respectively. Independent factors associated with relapse were younger age (<35 years) at the time of diagnosis (HR, 18.17; 95% CI, 1.30-254.75), higher C-reactive protein (CRP) level (≥1.5 mg/dL) (HR, 2.08; 95% CI, 1.01-4.29), and greater disease activity (DAIBD ≥60) at the time of 5-ASA/sulfasalazine initiation (HR, 2.30; 95% CI, 1.10-4.83).[28]

Predictors during corticosteroid therapy

Corticosteroids are indicated for patients with disease that is refractory to 5-ASA, severe systemic symptoms, recurrent GI bleeding, or moderate to severe disease activity.[1] The initial dose of corticosteroids for these patients is 0.5-1 mg/kg per day of prednisolone for 1-2 weeks. When clinical improvement is observed, prednisolone should be tapered by 5 mg each week. Greater than 10 mg of prednisolone per day is not advised for long periods of time.[1] In a retrospective cohort study of 54 patients with moderate to severe intestinal BD that were treated with a first course of systemic corticosteroids (mean starting dosage, 0.58 mg/kg; range, 0.39-1.20 mg/kg), there were 25 (46.3%) patients with complete remission, 23 (42.6%) patients with partial remission, and 6 (11.1%) patients who showed no response at 1 month post-treatment.[29] After 1 year, 26 (48.1%) patients remained in prolonged response status, 19 (35.2%) patients showed corticosteroid dependency, and the remaining 4 (7.4%) patients had undergone surgery. The cumulative probabilities of surgery for this cohort were 17.5% and 49.1% at 1 and 3 years, respectively. In this cohort, prolonged response at 3 months was the only factor that was independently associated with a decreased risk of surgery in the long-term (HR, 0.176; 95% CI, 0.048-0.649).[29]

Predictors during immunosuppressant therapy

Immunosuppressants are indicated when patients are corticosteroid-dependent or corticosteroid-resistant.[1] Currently, thiopurines including 6-mercaptopurine and its pro-drug, azathioprine, are the main empiric therapeutic agents used for maintenance in patients with intestinal BD. The standard dose of azathioprine used in this population is 50-100 mg/day.[1] In a single center cohort study performed by Jung, et al.,[30] the cumulative rates of thiopurine requirement in patients with intestinal BD at 1 year, 5 years, and 10 years after diagnosis were 10.5%, 22.1%, and 32.3%, respectively. Among 39 patients who underwent thiopurine therapy for maintaining medically or surgically induced remission, the cumulative relapse rates at 1 year, 3 years, and 5 years after remission were 5.8%, 43.7%, and 51.7%, respectively.[30] Younger age (<25 years) at the time of diagnosis (HR, 7.20; 95% CI, 1.64-31.53) and a lower hemoglobin level (<11 g/dL) (HR, 14.77; 95% CI, 2.94-74.19) at the time of remission were independent predictive factors for relapse in this population.[30]

Predictors during biologic agent therapy

Although corticosteroids and immunosuppressants are effective treatments for intestinal BD, patients who are refractory to these conventional therapies will eventually require ileocecal resection. However, these surgical patients have a higher risk of recurrent disease than patients receiving medical therapy alone.[26] Since it is known that tumor necrosis factor-α (TNF-α) contributes to the pathogenesis of BD,[31] agents which block TNF-α may have therapeutic potential. Several case series have reported that infliximab, a chimeric monoclonal antibody against TNF-α, is effective for inducing and maintaining remission in cases of intestinal BD.[32-39] In a recent multicenter retrospective study of 28 cases of corticosteroid or immunosuppressant non-responsive intestinal BD,[40] 18 (64.3%) showed a clinical response [including 8 patients (28.6%) with clinical remission] 4 weeks after the initiation of infliximab therapy. Moreover, at 30 weeks, 13 (50.0%) showed a clinical response [including 12 patients (46.2%) with clinical remission]. Independent predictors of a sustained response to infliximab were older age (>40 years) at the time of diagnosis (OR, 8.7; 95% CI, 1.173-64.581), female gender (OR, 13.72; 95% CI, 1.574-119.617), longer disease duration (≥5 years) (OR, 9.19; 95% CI, 1.234-68.394), concomitant immunosuppressant use (OR, 33.96; 95% CI, 1.480-779.212), and clinical remission at 4 weeks after the initiation of treatment (OR, 8.93; 95% CI, 1.457-55.556).[40]

OUTCOME PREDICTORS RELATED TO SURGICAL TREATMENT

Surgical resection is indicated for patients who are unresponsive to medical treatments or those with bowel complications including stricture, fistula, severe bleeding, or perforation. Of these complications, bowel perforation is the most serious and necessitates emergent operative management. Moon, et al.[41] previously conducted a study in 129 patients with symptomatic intestinal BD, showing that 33 (25.6%) patients were diagnosed with intestinal perforation and underwent subse-

Table 1. Outcome Predictors for Intestinal Behçet's Disease

Long-term outcome predictors for intestinal BD
1. Predictors of a severe disease course:
Higher disease activity (DAIBD ≥40) at the time of diagnosis[17]
2. Predictors for operation:
Younger age (<40 yrs) at the time of diagnosis[18]
Higher initial disease activity (DAIBD ≥70)[18]
Volcano-type ulcers[18]
Outcome predictors under various medical therapies
1. Predictors after overall medical treatment
1) Predictors of lack of complete remission after initial medical therapy: Volcano-type ulcers*[22]
2) Predictors of relapse:
Absence of initial remission at 8 wks[21]
Volcano-type ulcers[21]
Apparent GI symptoms at the time of diagnosis[21]
Lack of mucosal healing at the time of clinical remission[23]
Higher percentage of peripheral $CD8^+DR^+$lymphocytes at the time of remission*[26]
3) Predictors of surgery:
Lack of complete remission of intestinal lesions at 8 wks*[20]
Volcano-type ulcers*[21,22]
Deep ulcers[21]
ASCA positivity*[25]
4) Predictors of steroid use: AAEA positivity*[27]
2. Predictors during 5-ASA therapy
1) Predictors of relapse:
Younger age (<35 yrs) at the time of diagnosis[28]
Higher CRP level (≥1.5 mg/dL) at initiation of 5-ASA[28]
Higher disease activity (DAIBD ≥60) at initiation of 5-ASA[28]
3. Predictors during corticosteroid therapy
1) Predictors of surgery:
Lack of prolonged response 3 months after corticosteroid initiation[29]
4. Predictors during immunosuppressant (thiopurine) therapy
1) Predictors of relapse:
Younger age (<25 yrs) at the time of diagnosis[30]
Lower hemoglobin (<11g/dL) level at the time of remission[30]
5. Predictors during infliximab therapy
1) Predictors of sustained response:
Older age (≥40 yrs) at the time of diagnosis[40]
Female gender[40]
Longer (≥5 yrs) disease duration[40]
Concomitant immunomodulator use[40]
Achievement of remission at 4 wks[40]
Outcome predictors related to surgical treatment
1. Predictors of free bowel perforation:
Younger age (≤25 yrs) at the time of diagnosis[41]
History of prior laparotomy[41]
Volcano-type ulcers[41]
2. Predictors of postoperative endoscopic recurrence:
Previous surgical indication with perforation or fistula*[20]
3. Predictors of relapse after first surgery:
Volcano-type ulcers[42]
Higher CRP level (>4.4 mg/dL)[42]
Intestinal perforation on surgical pathology[42]
4. Predictors of a second operation:
Absence of postoperative azathioprine use*[20]
Volcano-type ulcers[42]
Higher CRP level (>4.4 mg/dL)[42]
History of postoperative steroid therapy[42]

BD, Behçet's disease; DAIBD, disease activity index for intestinal Behçet's disease; GI, gastrointestinal; ASCA, anti-Saccharomyces cerevisiae antibody; AAEA, anti-α-enolase antibody; 5-ASA, 5-aminosalysilic acid; CRP, C-reactive protein.
*Unadjusted results.

quent surgery during follow-up. Younger age (≤25 years) at the time of diagnosis (HR, 3.25; 95% CI, 1.41-7.48), a history of prior laparotomy (HR, 5.53; 95% CI, 2.25-13.56), and volcano-shaped intestinal ulcers (HR, 2.84; 95% CI, 1.14-7.08) were identified as independent risk factors for bowel perforation in patients with intestinal BD.[41]

Regarding post-operative outcomes in intestinal BD, Choi, et al.[20] showed that the cumulative recurrence rates of intestinal lesions were 28% at 1 year, 49% at 2 years, and 75% at 5 years. Most recurrences occurred at the anastomotic site or within the vicinity of the site (81%, 25/31) as determined by endoscopy.[20] Among the clinical variables studied, previous surgery for perforation or fistula was the only significant factor associated with post-operative endoscopic recurrence (p=0.020).[20] More recently, Jung, et al.[42] showed that the cumulative clinical recurrence rates after surgical treatment in 72 patients with intestinal BD were 29.2% at 2 years and 47.2% at 5 years. In that study, they identified volcano-shaped ulcers (HR, 14.34; 95% CI, 3.52-58.41), higher CRP level (>4.4 mg/dL) (HR, 4.13; 95% CI, 1.23-13.88), and intestinal perforation on surgical pathology (HR, 4.77; 95% CI, 1.12-20.33) as independent predictors of recurrence.[42]

Cumulative reoperation rates have been reported as 13-18% at 2 years and 22-38% five years after initial surgery.[19,20,42] Regarding outcome predictors for a second surgery, Choi, et al.[20] reported that patients who received postoperative azathioprine had lower reoperation rates than those that did not (7% versus 25% at 2 years, 25% versus 47% at 5 years, respectively, p=0.035). Beyond that, Jung, et al.[42] found that volcano-shaped ulcers (HR, 47.98; 95% CI, 4.21-547.35), higher CRP levels (>4.4 mg/dL) (HR, 46.85; 95% CI, 1.88-1170.25), and a history of postopera-

tive steroid therapy (HR, 26.02; 95% CI, 1.99-339.37) were independent predictive factors for reoperation.

CONCLUSIONS

In this review, several clinical variables including younger age, higher disease activity at the time of diagnosis, volcano-type ulcers, absence of mucosal healing, higher CRP level, history of surgery, and lack of initial response to medical therapy were repeatedly shown to be poor prognostic factors in patients with intestinal BD (Table 1). These clinical predictors may help physicians in guiding adequate patient monitoring and individually optimized treatment based on risk stratification. Nevertheless, application of these diverse predictors into daily practice seems somewhat limited, and the true predictive power of these parameters has not yet been evaluated in an independent population. Therefore, studies with the aim of developing a validated prediction model for clinical outcomes in intestinal BD are warranted. Moreover, the clinical efficacy of tailored management strategies based on risk stratification such as early use of immunosuppressants and intensive patient monitoring in patients that are at higher risk for unfavorable outcomes should also be confirmed. Given the growing body of research in genetics and pharmacogenomics, more accurate predictions of clinical courses for patients with intestinal BD may be possible in the near future.

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