World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v18.i40.5771

World J Gastroenterol 2012 October 28; 18(40): 5771-5778
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Correlations between endoscopic and clinical disease activity indices in intestinal Behcet's disease

Hyun Jung Lee, Youn Nam Kim, Hui Won Jang, Han Ho Jeon, Eun Suk Jung, Soo Jung Park, Sung Pil Hong, Tae Il Kim, Won Ho Kim, Chung Mo Nam, Jae Hee Cheon

Hyun Jung Lee, Hui Won Jang, Han Ho Jeon, Eun Suk Jung, Soo Jung Park, Sung Pil Hong, Tae Il Kim, Won Ho Kim, Jae Hee Cheon, Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul 120-752, South Korea
Youn Nam Kim, Department of Biostatistics, Yonsei University College of Medicine, Seoul 120-752, South Korea
Chung Mo Nam, Department of Preventive Medicine, Yonsei University College of Medicine, Seoul 120-752, South Korea
Author contributions: Lee HJ performed the data analysis and wrote the manuscript; Cheon JH had original idea on this subject, performed colonoscopy, performed the data analysis and wrote the manuscript; Jang HW, Jeon HH, Jung ES, Park SJ, Hong SP, Kim TI and Kim WH performed colonoscopy and reviewed the manuscript critically; Kim YN and Nam CM performed the statistical analysis and reviewed the manuscript.
Correspondence to: Jae Hee Cheon, MD, PhD, Division of Gastroenterology, Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, South Korea. geniushee@yuhs.ac
Telephone: +82-2-22281990 Fax: +82-2-3936884
Received: May 11, 2012 Revised: July 4, 2012
Accepted: July 18, 2012
Published online: October 28, 2012

Abstract

AIM: To develop a novel endoscopic severity model of intestinal Behcet's disease (BD) and to evaluate its feasibility by comparing it with the actual disease activity index for intestinal Behcet's disease (DAIBD).

METHODS: We reviewed the medical records of 167 intestinal BD patients between March 1986 and April 2011. We also investigated the endoscopic parameters including ulcer locations, distribution, number, depth, shape, size and margin to identify independent factors associated with DAIBD. An endoscopic severity model was developed using significant colonoscopic variables identified by multivariate regression analysis and its correlation with the DAIBD was evaluated. To determine factors related to the discrepancy between endoscopic severity and clinical activity, clinical characteristics and laboratory markers of the patients were analyzed.

RESULTS: A multivariate regression analysis revealed that the number of intestinal ulcers ($\geqslant$ 2, P = 0.031) and volcanoshaped ulcers (P = 0.001) were predictive factors for the DAIBD. An endoscopic severity model (Y) was developed based on selected endoscopic variables as follows: Y = 47.44 + 9.04 × non-Ileocecal area + 11.85 × $\geqslant$ 2 of intestinal ulcers + 5.03 × shallow ulcers + 12.76 × deep ulcers + 4.47 × geographic-shaped ulcers + 26.93 × volcano-shaped ulcers + 8.65 × $\geqslant$ 20 mm of intestinal ulcers. However, endoscopic parameters used in the multivariate analysis explained only 18.9% of the DAIBD variance. Patients with severe DAIBD scores but with moderately predicted disease activity by the endoscopic severity model had more symptoms of irritable bowel syndrome (21.4% *vs* 4.9%, P = 0.026) and a lower rate of corticosteroid use (50.0% *vs* 75.6%, P = 0.016) than those with severe DAIBD scores and accurately predicted disease by the model.

CONCLUSION: Our study showed that the number of intestinal ulcers and volcano-shaped ulcers were predictive factors for severe DAIBD scores. However, the correlation between endoscopic severity and DAIBD (r = 0.434) was weak.

Key words: Intestinal Behcet's disease; Disease activity index; Colonoscopy; Ulcer; Endoscopic severity

Peer reviewers: Yuji Naito, Professor, Department of Medical Proteomics, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602-8566, Japan; Francis Seow-Choen,

Professor, Seow-Choen Colorectal Centre, Mt Elizabeth Hospital, 290 Orchard Road Paragon Shopping Centre No. 06-06, Singapore 238859, Singapore

Lee HJ, Kim YN, Jang HW, Jeon HH, Jung ES, Park SJ, Hong SP, Kim TI, Kim WH, Nam CM, Cheon JH. Correlations between endoscopic and clinical disease activity indices in intestinal Behcet's disease. *World J Gastroenterol* 2012; 18(40): 5771-5778 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i40/5771.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i40.5771

INTRODUCTION

Behcet's disease (BD) is a chronic, relapsing, multi-systemic inflammatory disorder characterized by recurrent oral and genital ulcers combined with other systemic manifestations. The systemic manifestations are due to involvement of many other organs including the skin, joints, blood vessels, nervous system, epididymis, and gastrointestinal tract[1,2]. In particular, when patients with BD have predominant gastrointestinal symptoms and show intestinal ulcerations according to objective measures, the disease is then diagnosed as "intestinal BD"[3,4].

Intestinal BD is generally accepted as a type of inflammatory bowel disease (IBD), a group of diseases that includes ulcerative colitis (UC) and Crohn's disease (CD). Because IBD has various, fluctuated clinical courses with repeated remission and relapse, the disease activity index is helpful for disease management and therefore has been commonly used in monitoring treatment response. For example, disease activity is usually defined according to the Truelove and Witts' criteria[5] or the Mayo score system[6] as mild, moderate, or severe disease for UC and measured by the Crohn's disease activity index (CDAI)[7] or the Harvey-Bradshaw index[8] for CD.

Endoscopy is by far the best and most widely used modality for assessment of the disease extent and severity of IBD[9]. A study investigating a cohort of CD patients under long-term treatment with infliximab recently reported that mucosal healing was associated with a significantly lower need for abdominal surgery[10]. Furthermore, data from the Active Ulcerative Colitis Trials 1 and 2[11] have suggested that mucosal healing was associated with a better outcome in UC, more specifically, a decreased risk of relapse. Therefore, the macroscopic mucosal appearance is considered a valuable indicator of disease activity. In this regard, colonoscopic activity has been assessed using a modified version of Baron's criteria[12] for UC and the Crohn's disease endoscopic index of severity (CDEIS)[13] for CD.

Although the disease activity index for intestinal Behcet's disease (DAIBD), a relatively simple eight-point system, was recently introduced[14], there are no specific tools for the measurement of endoscopic severity in intestinal BD. There have been several descriptions of clinical outcomes according to colonoscopic findings[15,16], however, endoscopic appearance has never been taken into account in evaluating disease activity in intestinal BD. Therefore, the aim of this study was to identify endoscopic factors associated with the DAIBD, to develop a novel endoscopic severity model of intestinal BD using these factors, and to evaluate the correlations between the actual DAIBD and endoscopic severity.

MATERIALS AND METHODS

Patients

We reviewed the medical records of patients with intestinal BD at Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea, between March 1986 and April 2011. Patients with a history of previous colon operations were excluded from the study and those diagnosed or suspected as having UC, CD, intestinal tuberculosis, infectious colitis, or malignancy were not included in our study.

BD was diagnosed according to the criteria from the 1987 Behcet's Disease Research Committee of Japan[17] and was divided into the following three types: complete, incomplete and suspected BD. Intestinal involvement of BD was evaluated using colonoscopy for the large bowel and terminal ileum involvement and small bowel follow-through or computed tomography enterography for the small bowel involvement in patients with BD who had gastrointestinal symptoms. Diagnosis of intestinal BD was made according to the criteria as previously described using a modified Delphi process[2,18]. Patients were categorized into three groups as definite, probable, and suspected on the basis of colonoscopic findings and extraintestinal systemic manifestations. Clinical activity of intestinal BD was judged by the DAIBD composed of the following eight variables: general well-being, fever, extraintestinal manifestations, abdominal pain, abdominal mass, intestinal complications, and number of liquid stools in one week. The DAIBD was classified into quiescent ($\leqslant$ 19), mild (20-39), moderate (40-74), and severe disease ($\geqslant$ 75)[14].

Methods

We collected demographic data including initial gastrointestinal symptoms and other extraintestinal manifestations related to systemic BD at the time of colonoscopy. We also investigated all colonoscopic findings with respect to location, distribution, number, depth, shape, size, and ulcer margin. Patients with < 5 ulcers that were oval in shape, deep, with discrete borders, and located in the ileocecal area including the terminal ileum, ileocecal valve, and cecum were considered as having typical intestinal BD lesions[19]. When the colon was divided into five segments (ileocecal area, ascending colon, transverse colon, descending colon, and rectosigmoid colon), a localized type was defined when lesions were restricted to only one segment and a diffuse type was defined when lesions were scattered in more than two colonic segments[15]. Furthermore, when two or more ulcers were observed, the largest diameter of the biggest ulcer was

used for the measurement of depth, shape, size and margin for analysis. This study was approved by the Institutional Review Board of Yonsei University College of Medicine and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical analysis

Continuous variables are presented as mean ± SD and categorical variables as frequency and percentage. An endoscopic severity model was constructed using the DAIBD as a dependent variable and the following endoscopic parameters as explanatory variables: ulcer location, distribution, number, depth, shape, size, and margin. To identify independent factors associated with disease activity for intestinal BD, we selected explanatory items using univariate analysis ($P < 0.05$) and also items that were recommended to be included by experts, which were followed by multiple linear regression analysis. The independent variables were evaluated using Student's *t*-test or one-way analysis of variance, with post hoc tests for confirmation of significance (Tukey's test at $\alpha = 0.05$). R^2 in the regression is used for how much the variance of the DAIBD can be explained by the endoscopic parameters. Moreover, relationships between predicted scores and the DAIBD were evaluated using Spearman's correlation coefficients.

Using an endoscopic severity model, we sought to predict actual disease activity for intestinal BD. To evaluate factors associated with any discrepancy between the predicted score using an endoscopy severity model and the actual DAIBD, we divided patients into four groups (quiescent, mild, moderate, and severe groups) according to their actual DAIBD cutoff scores and analyzed clinical characteristics and laboratory markers in each group. They were further classified according to their predicted DAIBD scores using the endoscopic model. Two of the groups of patients with the actual DAIBD scores showed values consistent with the predicted scores by the endoscopic model, while the other two groups of patients showed disagreement between the actual DAIBD and predicted scores; one with lower predicted scores than the actual DAIBD scores and the other with higher predicted scores than the actual DAIBD scores. Student's *t*-test was used to compare continuous variables and chi-squared test was used to compare categorical variables for each group.

$P < 0.05$ was considered statistically significant for all tests. All statistical analyses were performed using SPSS Version 17.0 for Windows (SPSS Inc., Chicago, IL, United States) and/or SAS Version 9.1 (SAS Institute, Gary, NC, United States).

RESULTS

Baseline clinical and colonoscopic characteristics of patients with intestinal BD

A total of 243 patients with intestinal BD were recruited during the study period, and 72 of 243 patients were excluded because they underwent operations such as ileocecectomy, right hemicolectomy, or small bowel resection before undergoing colonoscopy. One patient was excluded after finally being diagnosed with CD after follow-up colonoscopy, and 3 patients were further excluded who were confirmed not to have intestinal BD at the end of the follow-up period. The remaining 167 patients were included in this study. Their clinical and colonoscopic characteristics are summarized in Tables 1 and 2, respectively.

The mean age at diagnosis was 38.5 years (range:15-73 years) for BD and 41.4 years (range: 16-73 years) for intestinal BD. Ninety-six patients (57.5%) were female. According to the diagnostic criteria for BD, 3 patients (1.8%) had the complete type, 78 (46.7%) had the incomplete type, and 53 (31.7%) had the suspected type of disease. Twenty-five patients (15.0%) presented with only typical oral ulcers and 8 (4.8%) had only gastrointestinal lesions without any extraintestinal manifestations. The chief complaints of patients were diarrhea (85.0%), abdominal pain (71.8%), and abdominal tenderness (71.2%). At the time of colonoscopy, 5-aminosalicylic acids or sulfasalazine were prescribed to almost all the patients with intestinal BD (97.6%), azathioprine or 6-mercaptopurine to 24 patients (14.4%), colchicine to 80 (47.9%), and corticosteroids to 72 (43.1%).

On colonoscopy, the ileocecal area was the most common location for intestinal lesions (156 patients, 93.4%), with ileal ulcers present in 4 (2.4%). Localized intestinal involvement was found in 142 patients (85.0%) and 86 (51.5%) had a solitary intestinal ulcer. Regarding the depth and shape of intestinal ulcers, 109 patients (65.3%) had deep ulcers and 79 (47.3%) had oval-shaped ulcers. Patients with intestinal BD had relatively large ulcers; ulcers larger than 20 mm were noted in 82 patients (49.1%). The ulcer margins were usually discrete (75 patients, 44.9%), and 94 patients (56.3%) had typical ulcers. With regard to the intestinal BD diagnostic criteria, 69 (41.3%), 82 (49.1%), and 16 patients (9.6%) were classified as definite, probable, and suspected types, respectively.

Endoscopic factors associated with disease activity for intestinal BD

Univariate analysis revealed that the depth of intestinal ulcers ($F = 5.03$, $P = 0.008$), ulcer shape ($F = 13.33$, $P < 0.001$), and ulcer size ($F = 6.62$, $P < 0.001$) were significantly associated with disease activity for intestinal BD (Table 3). The mean DAIBD score of deep ulcers was significantly greater than that of shallow ulcers as shown by Tukey's multiple comparison test ($P = 0.027$) and the mean DAIBD score of volcano-shaped ulcers was also greater than that of oval-shaped or geographic ulcers ($P < 0.001$ and $P = 0.001$, respectively). The mean DAIBD score of ulcers larger than 20 mm was significantly greater than that of ulcers less than 5 mm or ulcers ranging from 10 mm to 20 mm ($P = 0.014$ and $P = 0.002$, respectively). No difference in the DAIBD

Table 1 Baseline clinical characteristics of patients with intestinal Behcet's disease

Characteristic	No. of patient (%)
Age at diagnosis of BD (yr)	38.5 ± 12.2
Age at diagnosis of intestinal BD (yr)	41.4 ± 12.3
Gender (male:female)	71:96 (42.5:57.5)
Systemic symptoms and signs of BD	
Recurrent oral ulcer	159 (95.2)
Recurrent genital ulcer	78 (46.7)
Ocular lesion	10 (6.0)
Skin lesion	82 (49.1)
Positive pathergy test	4 (2.4)
Arthritis or arthralgia	66 (39.5)
Neurologic lesion	0
Vascular lesion	2 (1.2)
Clinical subtype of BD	
Complete	3 (1.8)
Incomplete	78 (46.7)
Suspected	53 (31.7)
Symptoms and signs of intestinal involvement	
Abdominal pain	120 (71.8)
Diarrhea	142 (85.0)
Abdominal mass	4 (2.4)
Tenderness	119 (71.2)
Nausea/vomiting	4 (2.4)
Melena/hematochezia	31 (18.6)
Fistula	4 (2.4)
Stenosis (intestinal obstruction)	10 (6.0)
Abscess	0
Perforation	0
Current use of medication	
5-ASA or sulfasalazine	163 (97.6)
Azathioprine or 6-mercaptopurine	24 (14.4)
Colchicine	80 (47.9)
Corticosteroid	72 (43.1)
Patient global assessment	
Well	63 (37.7)
Mild	53 (31.7)
Moderate	45 (26.9)
Severe	6 (3.6)
DAIBD	74.9 ± 36.1 (5-155)
Quiescent (≤ 19)	2 (1.2)
Mild (20-39)	32 (19.2)
Moderate (40-74)	50 (29.9)
Severe (≥ 75)	83 (49.7)

BD: Behcet's disease; DAIBD: Disease activity index for intestinal Behcet's disease; 5-ASA: 5-aminosalicylic acid.

Table 2 Baseline colonoscopic characteristics of patients with intestinal Behcet's disease

Characteristic	No. of patient (%)
Location of intestinal lesion	4 (2.4)
Ileal area	156 (93.4)
Ileocecal area	25 (15.0)
Ascending colon	18 (10.8)
Other colonic segment	
Distribution of intestinal lesion	
Localized involvement	142 (85.0)
Diffuse involvement	25 (15.0)
Number of intestinal ulcer	
Solitary	86 (51.5)
2-5	53 (31.7)
≥ 5	28 (16.8)
Depth of intestinal ulcer	
Aphthous	12 (7.2)
Shallow	46 (27.5)
Deep	109 (65.3)
Shape of intestinal ulcer	
Oval	79 (47.3)
Geographic	52 (31.1)
Volcano	36 (21.6)
Size of intestinal ulcer (mm)	
< 5	11 (6.6)
5-10	29 (17.4)
10-20	45 (26.9)
≥ 20	82 (49.1)
Margin of intestinal ulcer	
Discrete	75 (44.9)
Elevation	13 (7.8)
Nodular elevation	32 (19.2)
Marginal erythema	47 (28.1)
Type of intestinal ulcer	
Typical type	94 (56.3)
Atypical type	73 (43.7)
Diagnostic criteria of intestinal BD	
Definite	69 (41.3)
Probable	82 (49.1)
Suspected	16 (9.6)

BD: Behcet's disease.

score was observed with regard to any other endoscopic variables including location, distribution, number, or pattern of ulcer margin.

Significant variables ($P < 0.05$) found on univariate analysis were included in the multivariate analysis to identify independent factors associated with disease activity. Location and number of ulcers that experts have recommended as potentially important predictive factors were also included in the multivariate analysis. Multivariate regression analysis showed that the number of intestinal ulcers (≥ 2, $P = 0.031$) and that of volcano-shaped ulcers ($P = 0.001$) were independent predictive factors for the DAIBD (Table 4).

Using the coefficients from the estimated regression model (Table 4), we generated an endoscopic severity model to predict DAIBD scores (Y) based on five optimal selected endoscopic variables. The final model was as follows: Y = 47.44 + 9.04 × non-ileocecal area + 11.85 × ≥ 2 of intestinal ulcers + 5.03 × shallow ulcers + 12.76 × deep ulcers + 4.47 × geographic-shaped ulcers + 26.93 × volcano-shaped ulcers + 8.65 × ≥ 20 mm of intestinal ulcers.

Predictive factors for discrepancies between predicted endoscopic score and actual DAIBD

However, the five most predictive endoscopic parameters in the multiple linear regression analysis explained only 18.9% of the DAIBD variance. Therefore, we attempted to find out the reasons for this unexpected discrepancy. Using the endoscopic severity model, the predicted DAIBD severity distribution was as follows: 108 patients (64.7%) had moderate disease activity and 59 (35.3%) had severe disease activity (Table 5). Conversely, in this study, the actual DAIBD scores demonstrated that disease activity was quiescent in 2 patients (1.2%), mild in 32 (19.2%), moderate in 50 (29.9%), and severe in 83 (49.7%).

Table 3 Univariate analysis of endoscopic factors associated with the disease activity index for intestinal Behcet's disease

Endoscopic factor	DAIBD (mean ± SD)	*F*/*t* value	*P* value
Location		0.48	0.632
Ileocecal area	74.58 ± 36.74		
Other	80.00 ± 26.08		
Distribution			
Localized	73.98 ± 35.22	-0.82	0.414
Diffuse	80.40 ± 41.10		
Number of intestinal ulcer		0.39	0.679
Solitary	72.67 ± 30.92		
2- 5	76.51 ± 41.75		
≥ 5	78.93 ± 40.08		
Depth of intestinal ulcer		5.03	0.008
Aphthous	57.08 ± 37.02		
Shallow	65.00 ± 30.09		
Deep	81.10 ± 37.01		
Shape of intestinal ulcer		13.33	< 0.001
Oval	65.13 ± 37.79		
Geographic	72.60 ± 28.40		
Volcano	99.86 ± 30.95		
Size of intestinal ulcer (mm)		6.62	< 0.001
< 5	52.73 ± 35.45		
5-10	69.48 ± 36.38		
10-20	63.00 ± 33.02		
≥ 20	86.40 ± 34.29		
Margin of intestinal ulcer		1.95	0.124
Discrete	80.47 ± 37.70		
Elevation	56.54 ± 33.63		
Nodular elevation	75.47 ± 29.93		
Marginal erythema	70.85 ± 36.81		

DAIBD: Disease activity index for intestinal Behcet's disease.

Table 4 Multivariate analysis of endoscopic factors associated with the disease activity index for intestinal Behcet's disease

Endoscopic factor	β coefficient	*P* value
Intercept	47.44	
Location		
Ileocecal area	0	
Other	9.04	0.389
Number of intestinal ulcer		
Solitary	0	
≥ 2	11.85	0.031
Depth of intestinal ulcer		
Aphthous	0	
Shallow	5.03	0.651
Deep	12.76	0.261
Shape of intestinal ulcer		
Oval	0	
Geographic	4.47	0.495
Volcano	26.93	0.001
Size of intestinal ulcer (mm)		
< 20	0	
≥ 20	8.65	0.225

Table 5 Predicted and actual disease activity index for intestinal Behcet's disease scores in intestinal Behcet's disease patients

Actual DAIBD	Predicted DAIBD by an endoscopic model				Total
	Quiescent (≤19)	Mild (20-39)	Moderate (40-74)	Severe (≥ 75)	
Quiescent (≤ 19)	0	0	1	1	2
Mild (20-39)	0	0	28	4	32
Moderate (40-74)	0	0	37	13	50
Severe (≥ 75)	0	0	42	41	83
Total	0	0	108	59	167

DAIBD: Disease activity index for intestinal Behcet's disease.

To find out which predictive factors are causing discrepancies between the predicted endoscopic scores and the actual DAIBD scores, we first analyzed 83 patients with severe actual DAIBD scores. Among the 83 patients, 42 (50.6%) had moderate and 41 (49.4%) had severe predicted disease activity based on the endoscopic severity model. Moderately predicted group had more irritable bowel syndrome symptoms (21.4% *vs* 4.9%, $P = 0.026$) and a lower rate of corticosteroid use (50.0% *vs* 75.6%, $P = 0.016$) than severely predicted group. However, infection rates (16.7% *vs* 12.2%, $P = 0.562$) and rates of systemic BD presentation (57.1% *vs* 46.3%, $P = 0.325$) were not significantly different between the two groups.

Among the remaining 84 patients with mild or moderate DAIBD, 37 patients (44.0%) showed consistent results between the actual DAIBD and their predicted scores, while 47 (56.0%) showed inconsistent results. Clinical or laboratory variables including rate of corticosteroid use (25.5% *vs* 21.6%, $P = 0.676$), erythrocyte sedimentation rate (ESR) (39.15 ± 27.66 mm/h *vs* 33.74 ± 27.98 mm/h, $P = 0.421$), or C-reactive protein (CRP) level (7.11 ± 18.33 mg/L *vs* 2.81 ± 3.99 mg/L, $P = 0.162$) were not significantly different between the two groups.

DISCUSSION

To the best of our knowledge, there have been no studies concerning endoscopic factors associated with disease activity for intestinal BD. Moreover, there is currently no available endoscopic severity model for intestinal BD. To date, the management of intestinal BD and the assessment of its response to treatment depend heavily on expert opinions. Although recently, the DAIBD was proposed to objectively evaluate disease activity, which would be useful to physicians in clinical practice[14], endoscopy has rarely been investigated as a predictor of disease activity in intestinal BD. Accordingly, we aimed to identify endoscopic factors related to disease activity of intestinal BD, to develop a novel scoring model for predicting a severe course of disease, and to clarify the correlation between the DAIBD and endoscopic severity.

In the present study, we first sought to identify the endoscopic factors associated with disease activity for intestinal BD. On univariate analysis, the significant endoscopic predictors of disease activity were depth of intestinal ulcers, ulcer shape and ulcer size. Multivariate analysis revealed that the number of intestinal ulcers and volcano-shaped ulcers were independent predictors of the DAIBD. These results were consistent with those of several prior studies. A Korean study[15] reported that volcano-shaped ulcers responded least to medical treat-

ment, required surgery more frequently, and showed more frequent recurrences than geographic and aphthous-shaped ulcers. Another Korean study[16] revealed that individuals with deep ulcers and ulcers larger than 20 mm had an increased rate of steroid use and more frequent intestinal surgery. Moreover, a recent study by Jung *et al*[20] suggested that those with volcano-shaped ulcers demonstrated a less favorable response to surgical treatment, had more frequent recurrences, and more frequently required reoperation. In addition to volcano-shaped, deep, and larger than 20 mm ulcers, this study showed for the first time that having two or more intestinal ulcers was related to an increased disease severity when compared to solitary ulcers. Although there have been no reports regarding the correlations between the number of ulcers and disease activity in IBD, our results can be explained by the fact that an increase in the extent of mucosal involvement reflects the multiplicity of ulcers because patients with extensive and multiple ulcers are less likely to respond to local or systemic treatments. In systemic BD, the number, frequency, and healing time of oral ulcers and pain have been used to evaluate disease activity in clinical practice and studies[21]. In addition, in our study, ulcers in the ileocecal area showed a lower DAIBD score than ulcers in other location. A recent study on free bowel perforation in intestinal BD patients[22] reported that small bowel perforation was observed in 21.2%. Ileal ulcers might be at higher risk of complications such as perforation, which could be therefore related to severe disease activity. Further studies are required to validate whether the number of intestinal ulcers and ulcer location are truly associated with disease activity in intestinal BD.

Based on the predictive endoscopic factors for disease activity identified on multivariate analysis, we sought to develop an endoscopic severity model for intestinal BD. In multivariate analysis, besides the factors found to be significantly associated with the DAIBD in univariate analysis, potential factors that could achieve the optimized R^2 were also included, reflecting experts' suggestions. Initially, we hypothesized that endoscopic severity would have a highly significant correlation with clinical activity. However, the correlation between endoscopic severity and the DAIBD (r = 0.434) was unexpectedly found to be substantially weak. These results suggest that endoscopic severity might not correlate with clinical disease activity; thus, we cannot precisely judge a patient's condition using only the clinical activity index. Another potential reason for the lack of correlation may be that improvement in endoscopic lesions appeared later than the patient's clinical status. Although there have been no reports on correlations between endoscopic severity and disease activity in intestinal BD, many previous studies have described a poor association between endoscopic severity and clinical activity in IBD. In CD, the Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives have shown that endoscopic severity patterns assessed by the CDEIS correlated poorly (r = 0.32) with clinical activity measured by the CDAI[23]. Daperno *et al*[24] indicated that the correlation of the simple endoscopic score for CD with CDAI (r = 0.39) was better than for the CDEIS, but still far from optimal. In contrast, Allez *et al*[25] observed that patients with CD exhibiting deep and extensive ulcerations on colonoscopy have a more aggressive clinical course with an increased rate of penetrating complications and increased likelihood of surgery. In UC, Carbonnel *et al*[26] demonstrated that extensive and deep ulcerations observed on colonoscopy were associated with an increased risk of colectomy, and another study by Daperno *et al*[27] reported that severe endoscopic lesions were significantly more frequent in non-responders to medical treatment compared with responders. These findings suggest that clinical disease activities might not highly correlate with concrete progress of patients. Endoscopic activity indexes could complement this drawback of clinical indices of IBD including intestinal BD. Further large-scale studies are needed to conclude whether endoscopic severity is superior to clinical disease activity in intestinal BD in terms of reflecting exactly the patient's current condition and predicting prognosis.

Because the correlation between endoscopic severity and the DAIBD was weak, recognizing reasons for the disagreement would be useful for clinicians in practice. To determine possible explanatory factors for the discrepancy between endoscopic severity and clinical activity, we considered laboratory results as well as clinical findings. These unexpected results might be explained that many systemic manifestations of the inflammatory process that result in the appearance of symptoms, but are not necessarily reflected in the mucosal lesions. Patients with systemic BD symptoms including oral and genital ulcers, eye and skin lesions, or arthralgia or concomitant infections may present with higher DAIBD scores than the predicted scores. Moreover, patients with predominant irritable bowel syndrome symptoms might present with higher clinical activity scores because symptoms of irritable bowel syndrome include nonspecific abdominal pain or discomfort and changes in stool frequency and appearance with the onset of symptoms, which might mimic IBD symptoms[28]. In the present study, patients with higher DAIBD scores than predicted scores had more irritable bowel syndrome symptoms and a lower rate of corticosteroid use. It is possible that clinical symptoms improve more quickly with the use of corticosteroids.

Moreover, in a group of patients with a higher endoscopic severity than actual clinical activity, we anticipated that serum biomarkers such as CRP and ESR would explain the discrepancy because the utility of laboratory markers for assessment of IBD activity, risk of complications, prediction of relapse and for monitoring the effect of therapy have been investigated. Consigny *et al*[29] reported that CRP levels (> 20 mg/dL) and ESR (> 15 mm/h) were predictive of relapse in CD, and Travis *et al*[30] revealed that elevated CRP (> 45 mg/L) could predict an

increased risk of colectomy in severe UC. Although many studies in the past few decades have noted that CRP and ESR are associated with systemic BD activity[31,32], the role of CRP and ESR in intestinal BD is still unknown. In the current study, the CRP and ESR levels were numerically higher in the severe predicted DAIBD group without any statistical difference. A recent study by Jung *et al*[33] also demonstrated that CRP or ESR levels were not highly correlated with disease activity in intestinal BD patients. Further studies are needed to evaluate the precise role of laboratory markers in intestinal BD.

The main strength of our study is that this is the first study to consider the use of endoscopy as a measurement tool of disease status in intestinal BD. However, because we retrospectively analyzed clinical and colonoscopic characteristics, our results might have been affected by the limitations of its retrospective design. In addition, the correlations between the predicted endoscopic severity model and the disease activity of intestinal BD were far below the expected values. Further studies to predict the clinical outcomes more accurately by taking into account endoscopic factors and the DAIBD together are required to verify our results.

In conclusion, we evaluated endoscopic factors related to disease activity of intestinal BD and the correlations between clinical activity and endoscopic severity. Our findings indicate that clinicians should closely observe patients with two or more intestinal ulcers and those with volcano-shaped ulcers and that these endoscopic findings could help clinicians make decisions regarding medical strategies for the treatment of intestinal BD. Finally, the understanding of discrepancy between actual and predicted DAIBD by the endoscopic severity model could be helpful in making an appropriate decision regarding medical strategies.

COMMENTS

Background

Because inflammatory bowel disease (IBD) has various, fluctuated clinical courses with repeated remission and relapse, the disease activity index is helpful for disease management. Moreover, recent studies suggested that mucosal healing was associated with a better outcome. Therefore, the macroscopic mucosal appearance is also considered a valuable indicator of disease activity. In this regard, disease activity index including endoscopic severity has been used in ulcerative colitis and Crohn's disease (CD).

Research frontiers

A study investigating a cohort of CD patients under long-term treatment with infliximab recently reported that mucosal healing was associated with a significantly lower need for abdominal surgery and data from the Active Ulcerative Colitis Trials 1 and 2 have suggested that mucosal healing was associated with a decreased risk of relapse. Moreover, because endoscopy could provide a direct assessment of the disease extent and severity, endoscopic severity has been estimated in IBD. However, although the disease activity index for intestinal Behcet's disease (DAIBD) was recently introduced, there are no specific tools for the measurement of endoscopic severity in intestinal Behcet's disease (BD).

Innovations and breakthroughs

This is the first study to consider the use of endoscopy as a measurement tool of disease status in intestinal BD. Their study demonstrated that the number of intestinal ulcers and volcano-shaped ulcers were predictive factors for severe DAIBD scores. However, the correlation between endoscopic severity and DAIBD (r = 0.434) was weak. Patients with severe DAIBD scores but with moderately predicted disease activity by the endoscopic severity model had more symptoms of irritable bowel syndrome and a lower rate of corticosteroid use than those with severe DAIBD scores and accurately predicted disease by the model.

Applications

This study suggests that clinicians should closely observe patients with two or more intestinal ulcers and those with volcano-shaped ulcers and that these endoscopic findings could help clinicians make decisions regarding medical strategies for the treatment of intestinal BD. Furthermore, the understanding of discrepancy between actual and predicted DAIBD by the endoscopic severity model could be helpful in making an appropriate decision regarding medical strategies.

Terminology

BD is a chronic, relapsing, multi-systemic inflammatory disorder and intestinal BD is diagnosed when patients with BD have predominant gastrointestinal symptoms and show intestinal ulcerations according to objective measures.

Peer review

In the present study, the authors showed that the number of intestinal ulcers and volcano-shaped ulcers were predictive factors for severe DAIBD scores, and that the correlation between endoscopic severity and DAIBD (r = 0.434) was weak. This study was well-investigated and will give us interesting information about the clinical indices of intestinal Behcet's disease.

REFERENCES

1 **Sakane T**, Takeno M, Suzuki N, Inaba G. Behçet's disease. *N Engl J Med* 1999; **341**: 1284-1291

2 **Kobayashi K**, Ueno F, Bito S, Iwao Y, Fukushima T, Hiwatashi N, Igarashi M, Iizuka BE, Matsuda T, Matsui T, Matsumoto T, Sugita A, Takeno M, Hibi T. Development of consensus statements for the diagnosis and management of intestinal Behçet's disease using a modified Delphi approach. *J Gastroenterol* 2007; **42**: 737-745

3 **Kasahara Y**, Tanaka S, Nishino M, Umemura H, Shiraha S, Kuyama T. Intestinal involvement in Behçet's disease: review of 136 surgical cases in the Japanese literature. *Dis Colon Rectum* 1981; **24**: 103-106

4 **Baba S**, Maruta M, Ando K, Teramoto T, Endo I. Intestinal Behçet's disease: report of five cases. *Dis Colon Rectum* 1976; **19**: 428-440

5 **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041-1048

6 **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317**: 1625-1629

7 **Best WR**, Becktel JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology* 1979; **77**: 843-846

8 **Harvey RF**, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980; **1**: 514

9 **Cheon JH**, Kim WH. Recent advances of endoscopy in inflammatory bowel diseases. *Gut Liver* 2007; **1**: 118-125

10 **Schnitzler F**, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1295-1301

11 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476

12 **Baron JH**, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Br Med J* 1964; **1**: 89-92

13 **Mary JY**, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a

prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989; **30**: 983-989
14 **Cheon JH**, Han DS, Park JY, Ye BD, Jung SA, Park YS, Kim YS, Kim JS, Nam CM, Kim YN, Yang SK, Kim WH. Development, validation, and responsiveness of a novel disease activity index for intestinal Behçet's disease. *Inflamm Bowel Dis* 2011; **17**: 605-613
15 **Kim JS**, Lim SH, Choi IJ, Moon H, Jung HC, Song IS, Kim CY. Prediction of the clinical course of Behçet's colitis according to macroscopic classification by colonoscopy. *Endoscopy* 2000; **32**: 635-640
16 **Kim MC,** Shin SJ, Lim SG, Lee KR, Woo H, Choi SJ, Jo JS, Eum JH, Cha DY, Hwang JC, Lee KM, Lee KJ, Kim JH. Clinical Course of Intestinal Behcet's Disease according to the Characteristics of Ulcer in Colonoscopy. *Intest Res* 2010; **8:** 40-47
17 **Mizushima Y**. [Revised diagnostic criteria for Behçet's disease in 1987]. *Ryumachi* 1988; **28**: 66-70
18 **Cheon JH**, Kim ES, Shin SJ, Kim TI, Lee KM, Kim SW, Kim JS, Kim YS, Choi CH, Ye BD, Yang SK, Choi EH, Kim WH. Development and validation of novel diagnostic criteria for intestinal Behçet's disease in Korean patients with ileocolonic ulcers. *Am J Gastroenterol* 2009; **104**: 2492-2499
19 **Lee CR**, Kim WH, Cho YS, Kim MH, Kim JH, Park IS, Bang D. Colonoscopic findings in intestinal Behçet's disease. *Inflamm Bowel Dis* 2001; **7**: 243-249
20 **Jung YS**, Yoon JY, Lee JH, Jeon SM, Hong SP, Kim TI, Kim WH, Cheon JH. Prognostic factors and long-term clinical outcomes for surgical patients with intestinal Behcet's disease. *Inflamm Bowel Dis* 2011; **17**: 1594-1602
21 **Mumcu G**, Sur H, Inanc N, Karacayli U, Cimilli H, Sisman N, Ergun T, Direskeneli H. A composite index for determining the impact of oral ulcer activity in Behcet's disease and recurrent aphthous stomatitis. *J Oral Pathol Med* 2009; **38**: 785-791
22 **Moon CM**, Cheon JH, Shin JK, Jeon SM, Bok HJ, Lee JH, Park JJ, Hong SP, Kim TI, Kim NK, Kim WH. Prediction of free bowel perforation in patients with intestinal Behçet's disease using clinical and colonoscopic findings. *Dig Dis Sci* 2010; **55**: 2904-2911
23 **Cellier C**, Sahmoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, Florent C, Bouvry M, Mary JY, Modigliani R. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. *Gut* 1994; **35**: 231-235
24 **Daperno M**, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JY, Colombel JF, Rutgeerts P. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; **60**: 505-512
25 **Allez M**, Lemann M, Bonnet J, Cattan P, Jian R, Modigliani R. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. *Am J Gastroenterol* 2002; **97**: 947-953
26 **Carbonnel F**, Lavergne A, Lémann M, Bitoun A, Valleur P, Hautefeuille P, Galian A, Modigliani R, Rambaud JC. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. *Dig Dis Sci* 1994; **39**: 1550-1557
27 **Daperno M**, Sostegni R, Scaglione N, Ercole E, Rigazio C, Rocca R, Pera A. Outcome of a conservative approach in severe ulcerative colitis. *Dig Liver Dis* 2004; **36**: 21-28
28 **Grundmann O**, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment: an update for health-care practitioners. *J Gastroenterol Hepatol* 2010; **25**: 691-699
29 **Consigny Y**, Modigliani R, Colombel JF, Dupas JL, Lémann M, Mary JY. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. *Inflamm Bowel Dis* 2006; **12**: 551-557
30 **Travis SP**, Farrant JM, Ricketts C, Nolan DJ, Mortensen NM, Kettlewell MG, Jewell DP. Predicting outcome in severe ulcerative colitis. *Gut* 1996; **38**: 905-910
31 **Coskun B**, Saral Y, Gödekmerdan A, Erden I, Coskun N. Activation markers in Behçet's disease. *Skinmed* 2005; **4**: 282-286
32 **Müftüoğlu AU**, Yazici H, Yurdakul S, Tüzün Y, Pazarli H, Güngen G, Deniz S. Behçet's disease. Relation of serum C-reactive protein and erythrocyte sedimentation rates to disease activity. *Int J Dermatol* 1986; **25**: 235-239
33 **Jung YS**, Kim SW, Yoon JY, Lee JH, Jeon SM, Hong SP, Kim TI, Kim WH, Cheon JH. Expression of a soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) correlates with clinical disease activity in intestinal Behcet's disease. *Inflamm Bowel Dis* 2011; **17**: 2130-2137

S- Editor Gou SX **L- Editor** A **E- Editor** Xiong L