

Prevalence and risk factors of bowel symptoms in Korean patients with ulcerative colitis in endoscopic remission: a retrospective study

Kwangwoo Nam

Dankook University Hospital

Sang Hyoung Park (✉ umdalpin@hanmail.net)

Asan Medical Center <https://orcid.org/0000-0002-5366-5749>

Jun Ho Oh

University of Ulsan College of Medicine

Ho-Su Lee

University of Ulsan College of Medicine

Soomin Noh

Asan Medical Center

Jae Cheol Park

Asan Medical Center

Jin Yong Kim

Asan Medical Center

Eun Hye Oh

Asan Medical Center

Jeongseok Kim

Asan Medical Center

Nam Seok Ham

Asan Medical Center

Sung Wook Hwang

Asan Medical Center

Dong-Hoon Yang

Asan Medical Center

Byong Duk Ye

Asan Medical Center

Jeong-Sik Byeon

Asan Medical Center

Seung-Jae Myung

Asan Medical Center

Suk-Kyun Yang

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Abstract

Background

Many patients with ulcerative colitis (UC) in clinical remission frequently complain of bowel symptoms such as increased stool frequency (SF) and rectal bleeding (RB). However, studies on these patient-reported outcomes in patients with inactive UC are limited, especially in Korea. We investigated the prevalence and risk factors of bowel symptoms in Korean patients with inactive UC.

Methods

We investigated the prevalence of bowel symptoms in patients with endoscopically quiescent UC between June 1989 and December 2016 using a well-characterized referral center-based cohort. The Mayo clinic score (MCS) was used to evaluate bowel symptoms at the most recent visit near the date of endoscopy. Clinical characteristics of the patients were compared based on the presence or absence of bowel symptoms.

Results

Overall, 741 patients with endoscopically quiescent UC were identified, of whom 222 (30%) and 48 (6.5%) had an SF and RB subscore of ≥ 1 , respectively. Patients with bowel symptoms (SF + RB ≥ 1 ; n = 244 [32.9%]) had higher rates of left-sided colitis (E2) or extensive colitis (E3) than patients without bowel symptoms (SF + RB = 0; n = 497 [67.1%]; $P = 0.002$). Multivariate analysis revealed that female sex (odds ratio [OR]: 1.568; 95% confidence interval [CI]: 1.023–2.402; $P = 0.039$) and E2 or E3 (OR 1.411; 95% CI 1.020–1.951; $P = 0.038$) were the significant risk factors for increased SF.

Conclusions

This study revealed that one-third of patients with endoscopically quiescent UC reported increased SF. Female sex and disease extent may be associated with bowel symptoms.

Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory disease involving colonic mucosa and submucosa. The incidence and prevalence of UC have significantly increased in Europe and North America [1], and a similar trend has been observed in Asia, especially Korea [2]. Patients with UC typically experience periodic clinical remission and relapse [3]. However, many patients with UC who receive appropriate medical treatment can stay in remission with mild disease activity, and recent studies have reported that colectomy rates have significantly decreased among these patients [4–6].

Although the prime therapeutic target in patients with UC is endoscopic mucosal healing [7], a growing interest has been noted in evaluating patient-reported outcomes (PROs) regarding the disease activity. Stool frequency (SF) and rectal bleeding (RB) are commonly evaluated PROs. Mayo clinic score (MCS) and Truelove and Witt's score, the most commonly used disease activity and severity indexes for UC, both include SF and RB. An increase in SF and presence of RB are considered composite indexes that suggest disease relapse before endoscopic confirmation [8]. In addition, PROs that include SF and RB have presented good correlation with disease activity of UC [9].

Many patients with UC in the clinical remission frequently complain of bowel symptoms such as increased SF and RB. In previous studies, irritable bowel-like symptoms were more commonly reported in patients with inflammatory bowel disease (IBD) with low disease activity (33–46%) than in healthy controls (7%) or patients with irritable bowel syndrome (IBS; 8%) [10–12]. Previously, IBS was considered completely different from IBD; however, recent studies have suggested that some overlap may exist between these two disease entities [13]. Although the degree of inflammation and visceral hypersensitivity between IBD and IBS are different, they have similarities regarding the brain-gut axis, some genetic factors, dysbiosis, and impaired epithelial barrier function [14].

To date, there have been few studies on symptom-based PROs in patients with inactive UC, especially among Korean patients [15]. Therefore, this study investigated the prevalence and risk factors of bowel symptoms in Korean patients with inactive UC.

Materials And Methods

Patients and study design

This study was based on a well-characterized referral center-based large cohort of Korean patients with UC. Medical records of patients enrolled in the Asan IBD registry between June 1989 and December 2016 were reviewed [4]. This registry includes all patients diagnosed with UC and treated at the Asan Medical Center. The diagnosis of UC were based on the conventional clinical, radiologic, endoscopic, and histopathologic criteria, as described previously [16]. Demographic and clinical features of the enrolled patients were evaluated. Immunosuppressive drugs ever used were classified as follows: corticosteroids (orally or intravenously administered prednisolone or methylprednisolone; a daily dose equivalent to ≥ 20 mg of prednisolone for ≥ 4 weeks), immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, or tacrolimus), and biologics (infliximab, adalimumab, golimumab, or vedolizumab).

Endoscopic and clinical evaluation

Endoscopic evaluation was performed for the surveillance of UC after clinical remission. In case of multiple endoscopic evaluation, most recent examination was selected for the evaluation. Endoscopic remission was defined as no evidence of active disease in colonoscopy or sigmoidoscopy (Mayo endoscopic subscore [MES] = 0). The maximum extent of UC was evaluated and classified as proctitis

(E1), left-sided colitis (E2), and extensive colitis (E3). MCS was obtained at each visit to evaluate clinical status [4, 17]. In our center, partial MCS (MCS without MES) of each patient was routinely determined at their every visit. The presence of bowel symptoms was evaluated using SF and RB from MCS at the visit near the date of endoscopy. Patients were classified based on the presence or absence of bowel symptoms ($SF + RB \geq 1$ vs. $SF + RB = 0$), and the clinical characteristics of each group were compared. These findings were used to evaluate the risk factors of bowel symptoms in patients with inactive UC.

Statistical analysis

Continuous variables were expressed as medians with interquartile range (IQR) and were compared using the Mann–Whitney U–test. Categorical variables were expressed as numbers with percentages and were compared using the chi-square test or Fisher’s exact test. Logistic regression analysis was performed to evaluate the risk factors of bowel symptoms in patients with inactive UC. Variables with $P < 0.1$ in univariate analyses were further evaluated using multivariate analysis. All statistical analyses were performed using SPSS software version 25.0 (SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

Results

Demographics and baseline characteristics of the patients

A total of 741 patients were confirmed with at least one or more endoscopically quiescent UC (MES = 0) between June 1989 and December 2016. These patients were followed up until March 2019 (Fig. 1). The total patient-years of follow-up was 8875.3 years, and the median patient-years of follow-up per patient was 11.3 years (IQR: 7.4–16.3). The median age at the time of UC diagnosis was 41 years (IQR: 32–51). In total, 343 (46.3%) patients were women. The analysis of maximum extent of UC revealed that E3 was the most common (39.1%), followed by E2 (32.4%) and E1 (26.6%). Patients’ exposure to immunosuppressive drugs was found to be as follows: corticosteroids, 57.1%; immunosuppressants, 25.8%; and biologics, 10.7% (Table 1).

Table 1
Demographic and clinical features of the studied patients

	Total (N = 741)
Total patient-years of follow-up (years)	8875.3
Median (IQR) (years)	11.3 (7.4–16.3)
Demographic features	
Age at diagnosis of UC, median (IQR) (years)	41.0 (32–51)
Sex, female, n (%)	343 (46.3)
Family history of IBD, n (%)	68 (9.2)
History of appendectomy	20 (2.7)
Current or ex-smoker	299 (40.4)
Extraintestinal manifestation, n (%)	21 (2.8)
PSC, n (%)	9 (1.2)
Maximum extent of UC	
Proctitis (E1), n (%)	197 (26.6)
Left-sided colitis (E2), n (%)	240 (32.4)
Extensive colitis (E3), n (%)	290 (39.1)
Not enough data, n (%)	4 (0.5)
Exposure to immunosuppressive drugs of IBD	
CS (prednisolone or methylprednisolone), n (%)	423 (57.1)
IS (azathiopurine/6-mercaptopurine, methotrexate, cyclosporine, or tacrolimus), n (%)	191 (25.8)
Biologics (infliximab, adalimumab, golimumab, or vedolizumab), n (%)	79 (10.7)
<i>CS, corticosteroid; IBD, inflammatory bowel disease; IQR, interquartile range; IS, immunosuppressant; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.</i>	

Characteristics of patients with bowel symptoms and comparison with patients without bowel symptoms

Medical records of the enrolled patients were reviewed and patients with bowel symptoms (SF + RB \geq 1; n = 244 [32.9%]) and without bowel symptoms (SF + RB = 0; n = 497 [67.1%]) were identified (Fig. 1). Interval between the date of endoscopy and the nearest visit at evaluation was a median of 8 days (IQR: 6.5–15). No significant differences were noted between the two groups regarding demographic features and

patient-years of follow-up. The analysis of maximum extent of UC revealed that E2 or E3 were more common among patients with bowel symptoms than among those without bowel symptoms ($P= 0.002$). With regard to the exposure of immunosuppressive drugs, patients with bowel symptoms had significantly higher exposure to corticosteroids ($P < 0.001$) and immunosuppressants ($P = 0.030$) than those without bowel symptoms (Table 2).

Table 2

Comparison of demographic and clinical characteristics of the patients with endoscopically quiescent ulcerative colitis with bowel symptoms with those without bowel symptoms

	UC patients with bowel symptoms (n = 244)	UC patients without bowel symptoms (n = 497)	P value
Total patient-years of follow-up (years)	2970.6	5904.7	0.489*
Median (IQR) (years)	11.6 (6.3–15.4)	10.8 (6.3–15.4)	
Demographic features			
Age at diagnosis of UC, median (IQR) (years)	41 (31–52)	41 (32–51)	0.680*
Sex, female, n (%)	101 (41.4)	242 (48.7)	0.061**
Family history of IBD, n (%)	22 (9.0)	46 (9.3)	0.916**
History of appendectomy, n (%)	6 (2.5)	14 (2.8)	0.778**
Current or ex-smoker, n (%)	90 (36.9)	209 (42.1)	0.178**
Extraintestinal manifestation, n (%)	4 (1.6)	17 (3.4)	0.170**
PSC, n (%)	3 (1.2)	6 (1.2)	1.000***
Maximum extent of UC			0.002***
Proctitis (E1), n (%)	44 (18.0)	153 (30.8)	
Left-sided colitis (E2), n (%)`	86 (35.2)	154 (31.0)	
Extensive colitis (E3), n (%)	108 (44.3)	182 (36.6)	
Not enough data, n (%)	6 (2.5)	8 (1.6)	
Exposure to immunosuppressive drugs of UC, n (%)			
CS (prednisolone or methylprednisolone), n (%)	160 (65.6)	263 (52.9)	< 0.001**

Bold font indicates statistical significance.

CS, corticosteroid; IBD, inflammatory bowel disease; IQR, interquartile range; IS, immunosuppressant; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

* Mann-Whitney test

** chi-square test

***Fisher's exact test

	UC patients with bowel symptoms (n = 244)	UC patients without bowel symptoms (n = 497)	P value
IS (azathiopurine/6-mercaptopurine, methotrexate, cyclosporine, or tacrolimus), n (%)	75 (30.7)	116 (23.3)	0.030**
Biologics (infliximab, adalimumab, golimumab, or vedolizumab), n (%)	23 (9.4)	56 (11.3)	0.445**
Bold font indicates statistical significance.			
<i>CS, corticosteroid; IBD, inflammatory bowel disease; IQR, interquartile range; IS, immunosuppressant; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.</i>			
<i>* Mann-Whitney test</i>			
<i>** chi-square test</i>			
<i>***Fisher's exact test</i>			

Among the patients with bowel symptoms (n = 244), 222 (91.0%) patients had SF \geq 1, whereas 196 (80.3%) patients had RB = 0. The distribution of SF + RB was as follows; SF + RB = 1, 191 (78.3%) patients; SF + RB = 2, 36 (14.8%) patients; SF + RB = 3, 14 (5.7%) patients; SF + RB = 4, 2 (0.8%) patients; and SF + RB = 5, 1 (0.4%) patient (Table 3).

Table 3

Distribution of partial Mayo clinic score in patients with bowel symptoms and in those without bowel symptoms

	UC patients with bowel symptoms (n = 244)	UC patients without bowel symptoms (n = 497)
Stool frequency subscore at evaluation, n (%)		
0	22 (9.0)	497 (100)
1	192 (78.7)	0 (0)
2	25 (10.2)	0 (0)
3	5 (2.0)	0 (0)
Rectal bleeding subscore at evaluation, n (%)		
0	196 (80.3)	497 (100)
1	39 (16.0)	0 (0)
2	5 (2.0)	0 (0)
3	4 (1.6)	0 (0)
Stool frequency + rectal bleeding subscore at evaluation, n (%)		
0	0 (0)	497 (100)
1	191 (78.3)	0 (0)
2	36 (14.8)	0 (0)
3	14 (5.7)	0 (0)
4	2 (0.8)	0 (0)
5	1 (0.4)	0 (0)
<i>UC, ulcerative colitis.</i>		

Risk factors of bowel symptoms in patients with endoscopically quiescent UC

To identify the risk factors of bowel symptoms in patients with endoscopically quiescent UC, we performed logistic regression analysis. In the univariate analysis, female sex, E2 or E3 in maximum extent, exposure to corticosteroid, and exposure to immunosuppressant showed $P < 0.1$ for both increased SF and SF + RB. In the multivariate analysis, female sex (odds ratio [OR]: 1.568; 95% confidence interval [CI]: 1.023–2.402; $P = 0.039$) and E2 or E3 in maximum extent (OR: 1.411; 95% CI: 1.020–1.951; P

= 0.038) were found to be the significant risk factors of increased SF. In addition, E2 or E3 in maximum extent (OR: 1.508; 95% CI: 1.002–2.268; $P= 0.049$) was the significant risk factor of SF + RB (Table 4).

Table 4
Factors associated with bowel symptoms in patients with endoscopically quiescent ulcerative colitis. (A) stool frequency, (B) stool frequency + rectal bleeding

(A) Stool frequency	OR	95% CI	P value
Sex, female	1.568	1.023–2.402	0.039
Maximum extent of UC, left-sided colitis or extensive colitis	1.411	1.020–1.951	0.038
Exposure to CS	1.348	0.906–2.006	0.140
Exposure to IS	1.243	0.834–1.850	0.186
(B) Stool frequency + rectal bleeding	OR	95% CI	P value
Sex, female	1.315	0.960–1.800	0.088
Maximum extent of UC, left-sided colitis or extensive colitis	1.508	1.002–2.268	0.049
Exposure to CS	1.366	0.930–2.007	0.062
Exposure to IS	1.117	0.756–1.652	0.578
Bold font indicates statistical significance.			
<i>CI, confidence interval; CS, corticosteroid; IS, immunosuppressant; OR, odds ratio.</i>			

Discussion/conclusion

We evaluated bowel symptoms in patients with endoscopically quiescent UC by using PROs based on SF and RB derived from MCS and found that approximately one-third of patients complained of bowel symptoms mainly due to increased SF. The multivariate analysis revealed that female sex and greater extent of bowel damage (E2 or E3) were significant risk factors for increased SF and greater extent of bowel damage for SF + RB.

Monitoring disease activity in patients with UC is essential. MCS that includes SF, RB, MES, and PGA is most commonly used as the disease activity index. Because frequent endoscopic evaluation in patients with inactive UC is not usually performed, partial MCS is more commonly used during follow-up visits in the real-world setting. In general, PGA reflects patients' impaired quality of life which is affected by abdominal pain, discomfort; however, due to the subjective aspects of PGA, it is difficult to consider MCS as an objective index of PRO. In contrast, SF and RB are symptom-based PROs that are usually considered clinical targets of remission [18] and are associated with endoscopic remission. Studies have reported that in some patients, these PROs did not exactly correlate with endoscopic findings, and up to one third of the patients with endoscopically and histologically inactive UC may experience increased SF

[19]. In the present study, we defined strict endoscopic remission as MES = 0, and 33% of the patients still complained of increased SF and/or RB, mostly due to increased SF (30%).

There have been some suggestions regarding PROs in patients with UC. Walmsley et al. suggested a simple clinical colitis activity index including bowel frequency (day and night), urgency, bloody stool, general well-being, and extracolonic features had good correlation with other complex indexes [20]. Bewtra et al. indicated that SF, RB, and patient-reported general well-being accurately determined clinical disease activity [9]. SF and RB can be used in routine clinical practice because they can easily be derived from MCS. However, SF and RB in patients with endoscopically quiescent UC may present different patterns. Jharap et al. investigated the relationship between mucosal healing and PROs (SF + RB) in patients with UC who were treated with adalimumab or placebo, and reported that among the patients with MES = 0, the proportion of patients with SF ≥ 1 (71.2%) was higher than that of patients with RB ≥ 1 (12.8%) [21], which is consistent with our results (SF ≥ 1 vs. RB ≥ 1 ; 30% vs. 6.5%). This suggests that RB is more influenced by mucosal healing than SF, and other factors might be associated with increased SF in these patients. In addition, although 20% of patients with bowel symptoms showed RB ≥ 1 in this study, their rectal bleeding symptoms were not severe to occur anemia or require red blood cell transfusion.

One possible explanation is that these patients might still have low-grade inflammation in the bowel wall, which was insufficient to generate definite erythema, erosion or ulcers, but could provoke IBS-like symptoms. Low-grade inflammation may be associated with altered enteric nervous system and microbiota, similar to IBS. However, some discrepancies were reported between IBS-like symptoms and fecal calprotectin levels in patients with UC [13]. In the present study, female sex was a significant risk factor of increased SF, which appears similar to IBS. In general, functional gastrointestinal disorders, including IBS, are more common in women than men [22, 23]. This gender difference is considered to be associated with the difference of visceral pain perception, autonomic function, and sex hormonal effect. Thus, patients with endoscopically quiescent UC but presenting bowel symptoms may share common features with IBS more than expected, and same management of IBS such as low FODMAP diet and usage of bowel movement drugs may be also helpful in these patients.

Previous disease extent can be another explanation. In the present study, the maximum extent of UC was analyzed, and it was found that E2 and E3 were more common in patients with bowel symptoms than in those without bowel symptoms (Table 2). Proximal disease extension of UC not only indicates the progression of UC but also a more damaged bowel. Long-term disease involvement of UC could lead to anatomical changes in the diseased bowel, which may be associated with impaired motility and absorptive function, similar to IBS [24]. In multivariate analysis, previous E2 or E3 suggesting greater bowel damage was a significant risk factor of increased SF and SF + RB. Henriksen et al. conducted a long-term follow-up study for 20 years on the prevalence of IBS-like symptoms in patients with UC and reported that the overall prevalence of IBS-like symptoms was 27%, which was not significantly different than those among patients with ongoing inflammation and those without signs of inflammation (25–

35%) [25]. These IBS-like symptoms might be affected by previous long-term bowel damage during 20 years.

This study has some limitations. First, the retrospective nature of this study cannot eliminate selection bias. Our study was based on a tertiary center-based registry, and hence, we could not avoid referral bias. Our results may not reflect the general aspect of bowel symptoms in patients with inactive UC. In addition, some patients' drug histories were incomplete, thus we could not provide concomitant medication for UC treatment or bowel movement (e.g., anti-diarrheal drugs, laxatives). Second, we did not assess histological findings of endoscopically quiescent UC. The presence of histologic bowel inflammation in the absence of endoscopic activity may be the cause of bowel symptoms [13]. Fecal calprotectin levels, which correlate with mucosal activity, were not assessed in the majority of the enrolled patients. To overcome these limitations, we applied more strict criteria of endoscopic remission (MES = 0) than those applied in previous studies (MES = 0 or 1) [19, 25]. Third, we did not evaluate the relapse rate according to the patients' bowel symptoms because we focused on temporal findings of bowel symptoms. In addition, MCS records bowel symptoms during previous 3 days by definition, thus it may not correctly reflect persistent bowel symptom. To minimize the overlap of temporal worsening of symptoms such as infectious enteritis, we minimize the interval between the day of endoscopy and the nearest visit (median 8 days). Fourth, some patients (2.2%) underwent sigmoidoscopy only after endoscopic remission thus it is impossible to reveal possible residual inflammation in the proximal colon. However, these patients were in clinically stable state without evidence of disease aggravation, thus we included these patients.

In conclusion, even in patients with endoscopically quiescent UC, approximately one-third of the patients reported bowel symptoms, especially increased SF. These results might be associated with female sex and previous significant bowel damage. Physicians who treat IBD patients must know these phenomena and could suggest proper management of bowel symptoms in patients with long-standing UC.

Abbreviations

CI, confidence interval; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IQR, interquartile range; MCS, Mayo clinic score; MES, Mayo endoscopic subscore; OR, odds ratio; PRO, patient-reported outcome; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis

Declarations

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Authors' contributions:

Study concept and design: KN and SHP

Acquisition of data: SHP, SN, JCP, JYK, EHO, JK, NSH, SWH, DHY, BDY, JSB, SJM and SKY

Statistical analysis and interpretation of data: KN, SHP, JHO and HSL

Drafting of the manuscript: KN and SHP

Critical revision of the manuscript for important intellectual content: SHP, BDY and SKY

All authors approved the final version of the article.

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Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author or request.

Ethics approval and consent to participate:

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Asan Medical Center (IRB no. 2019-0664). The requirement of written informed consent was waived owing to the retrospective nature of this study.

Consent for publication:

Not applicable. The requirement for informed consent from patients was waived by the IRB.

Competing interests:

The authors declare no competing interests.

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Figures

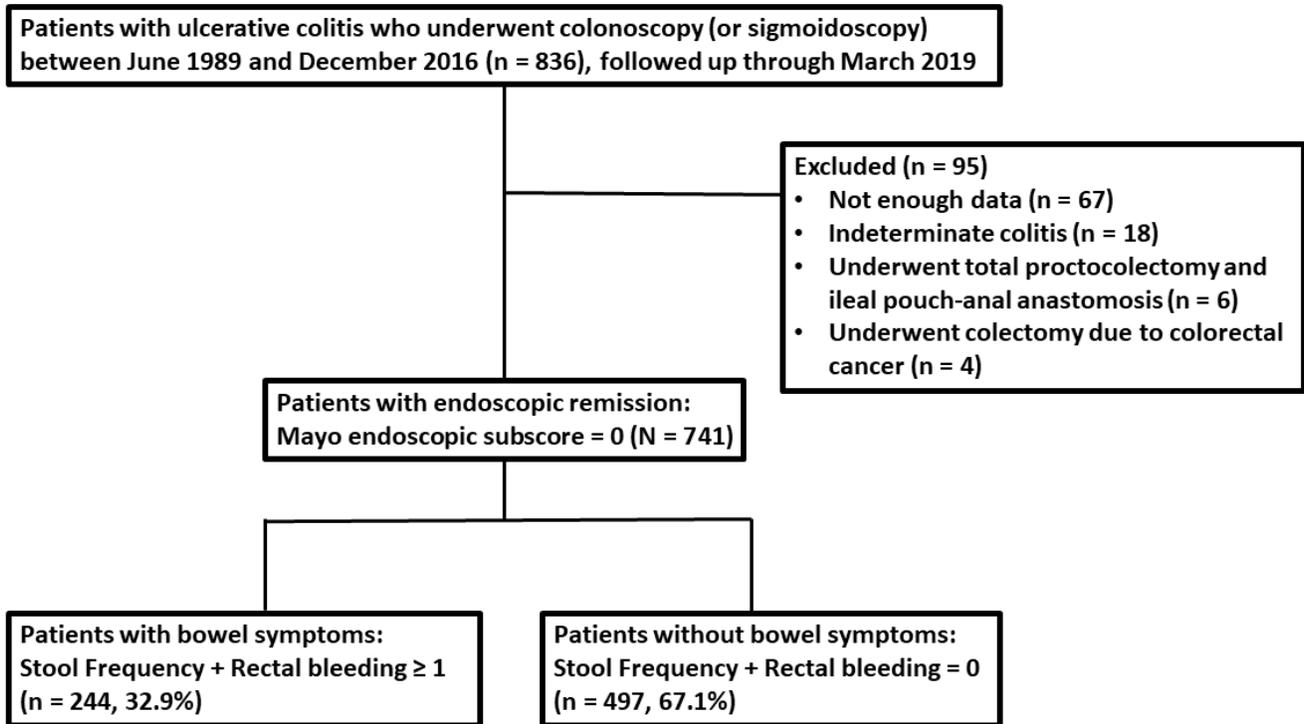


Figure 1

Study flowchart