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TITLE PAGE

Title: Natural History and Impact of Irritable Bowel Syndrome-type Symptoms in Inflammatory Bowel Disease During 6 Years of Longitudinal Follow-up.

Short Title: Longitudinal Impact of IBS-type Symptoms in IBD.

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Abbreviations:

CD	Crohn's disease
CI	confidence interval
FC	faecal calprotectin
HADS	hospital anxiety and depression scale
HR	hazard ratio

IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
PHQ-15	patient health questionnaire-15
SD	standard deviation
SF-36	36-item short-form
TNF	tumor necrosis factor
UC	ulcerative colitis

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SUMMARY

Background & Aims: The long-term natural history and impact of irritable bowel syndrome (IBS)-type symptoms on outcomes in inflammatory bowel disease (IBD) are uncertain. We assessed this in a longitudinal follow-up study of secondary care patients.

Methods: We assessed natural history of IBS-type symptoms in IBD via Rome III criteria applied at baseline, 2 years, and 6 years. We defined longitudinal disease activity as need for glucocorticosteroids or flare, escalation, hospitalisation, or intestinal resection. To assess healthcare utilisation, we recorded number of outpatient clinic attendances and investigations. We also collected anxiety, depression, and somatoform symptom scores, as well as quality of life scores during follow-up.

Results: Among 125 individuals with Rome III data at all three time points, only 41 (32.8%) never reported IBS-type symptoms. Fifteen patients (12.0%) had IBS-type symptoms at baseline that resolved, 19 (15.2%) had fluctuating symptoms, 35 (28.0%) had new onset symptoms, and 15 (12.0%) had persistent symptoms. Among more than 300 patients with IBD activity data, IBS-type symptoms were not associated with an increased likelihood of need for glucocorticosteroids or flare, escalation, hospitalisation, or intestinal resection. However, mean number of outpatient appointments and endoscopic investigations were significantly higher among those with IBS-type symptoms. Anxiety, depression, and somatoform symptom scores were significantly higher and quality of life scores significantly lower in those reporting IBS-type symptoms at least once during the study.

Conclusions: IBS-type symptoms affected more than two-thirds of patients with IBD during >6 years of follow-up and were associated with increased healthcare utilisation, and worse anxiety,

depression, and somatoform symptom, and quality of life scores, but not adverse disease activity outcomes.

Keywords: inflammatory bowel disease; irritable bowel syndrome; quality of life; mood

INTRODUCTION

Inflammatory bowel disease (IBD), which encompasses Crohn's disease (CD) and ulcerative colitis (UC), is a chronic gastrointestinal disorder with an increasing prevalence globally.(1) It is estimated that by 2028, due to the fact that incidence exceeds mortality, 1% of the population in some Western countries will have IBD.(2) There is no cure for either CD or UC, and patients experience recurrent flares of disease activity with diarrhoea, rectal bleeding, and abdominal pain. Symptoms during flares of activity may overlap with those of irritable bowel syndrome (IBS), a disorder of gut-brain interaction characterised by abdominal pain and altered stool frequency or form. IBS is more common than IBD, affecting between 5% and 10% of the general population.(3) However, the prevalence of symptoms compatible with IBS in patients with IBD is up to three times higher than in the general population,(4, 5) and such symptoms impact negatively on psychological health and quality of life.(6)

Although some investigators have suggested that IBS-type symptoms are a manifestation of disease activity,(7) their presence does not necessarily correlate with inflammation.(8) Even among patients with IBD in deep endoscopic and/or histological remission up to 25% report symptoms consistent with IBS.(9) The aetiology of both IBS and IBD is uncertain. However, abnormal intestinal permeability, perturbations of the intestinal microbiota, immune activation, and mucosal inflammation are common to both.(10-12) Given that IBS is highly prevalent the co-existence of IBS-type symptoms in IBD may occur by chance, but IBS can also be precipitated by acute gastrointestinal inflammation, the best known examples being after acute enteric infection or diverticulitis.(13, 14) Given this, IBD may itself be a risk factor for developing IBS.

Confusion between IBS-type symptoms and ongoing IBD activity can lead to difficulties in making clinical decisions about treatment based on symptoms alone.(15) In addition, there are concerns that such symptoms are a manifestation of disease activity and may, therefore, impact adversely on prognosis. Despite this, there have been few studies examining this issue. One relatively small Swedish study of 94 patients with UC in endoscopic remission reported that the presence of these symptoms at baseline was not associated with subsequent disease activity.(16) A previous study from our group did not demonstrate any adverse impact of IBS-type symptoms on objective measures of subsequent disease activity in patients with IBD in biochemical remission at baseline.(17) However, follow-up in these two studies was limited to 1 year,(16) and 2 years,(17) respectively, and there may have been insufficient time for some of the rarer endpoints, such as hospitalisation or intestinal resection, to occur.

A recent expert review has highlighted the need for a better understanding of the course of IBS-type symptoms in IBD, as well as their impact on prognosis.(18) We, therefore, conducted a further follow-up of individuals in our previous study 6 years after recruitment.(17) We hypothesised that these symptoms would not be associated with adverse disease outcomes, but would lead to increased healthcare utilisation and, if persistent, have a greater impact on psychological health and quality of life.

METHODS

Participants and Setting

We recruited patients aged ≥16 years with an established radiological, endoscopic, or histological diagnosis of CD or UC into a cross-sectional survey between November 2012 and June 2015.(8, 19) All participants were recruited from the IBD clinic at St. James's University Hospital, Leeds, United Kingdom, which is the sole provider of IBD care to these patients. We excluded patients with IBD-unclassified, end ileostomy, or colostomy, due to the difficulties in assessing disease activity indices in these patients, as well as individuals who did not understand written English. We followed these individuals up with a first follow-up postal questionnaire after a minimum period of 2 years had elapsed from recruitment, with a further mailout to non-responders, and have published these data previously.(17, 20) We obtained ethical approval to conduct further prospective longitudinal follow up (REC ref: 12/YH/0443/AM03), with a second follow-up postal questionnaire sent in November 2019, again with a further mailout to non-responders, and a review of participants medical records up to November 2021. We reported study findings in accordance with the STROBE guidelines.(21)

Data Collection and Synthesis

We recorded date of recruitment into the original cross-sectional survey, demographic data, type of IBD, current medication use for IBD, Rome III IBS symptom data, anxiety and depression symptom data, somatoform symptom data, quality of life data, and faecal calprotectin (FC) (Immundiagnostik, Bensheim, Germany) at baseline, as described previously.(8, 19)

Definition of Disease Activity and Presence of IBS-type Symptoms

Using a combination of disease activity indices (Harvey-Bradshaw index for CD,(22) and simple clinical colitis activity index for UC,(23) with a score ≥5 used to define clinical disease activity for both as previously recommended (24, 25)), presence or absence of symptoms compatible with Rome III-defined IBS,(26) and an FC level of ≥250mcg/g to define active inflammation,(27) we categorised patients into four groups, as described elsewhere.(8) Briefly, those with IBS-type symptoms with an FC <250mcg/g were defined as having IBD with IBS-type symptoms, regardless of disease activity indices. Those without IBS-type symptoms with an FC <250mcg/g were defined as having quiescent disease, regardless of disease activity indices. Those with normal disease activity indices and FC ≥250mcg/g were defined as having occult inflammation, regardless of IBS-type symptoms. Finally, those with abnormal disease activity indices with an FC ≥250mcg/g were defined as having active disease, regardless of IBS-type symptoms.

Anxiety, Depression, Somatoform Symptom, and Quality of Life Data

We recorded anxiety and depression symptom data via the hospital anxiety and depression scale (HADS),(28) containing seven questions screening for the presence of anxiety symptoms, and seven for depression symptoms. The total HADS score ranges from a minimum of 0 to a maximum of 21 for both anxiety and depression. Severity was categorised, according to HADS anxiety or depression score, into normal (total score 0-7), borderline normal (8-10), and abnormal (≥11).(28) We collected somatoform symptom data via the patient health questionnaire-15 (PHQ-15).(29) Severity of each symptom is rated as “not bothered at all” (score 0), “bothered a little” (score 1), or “bothered a lot” (score 2). Therefore, the total PHQ-15 score

ranges from 0 to 30. Somatoform symptom severity was categorised into high (total PHQ-15 ≥15), medium (10–14), low (5–9), or minimal (≤4). We assessed health-related quality of life using the validated 36-item short-form (SF-36) questionnaire.(30) We collected these data at baseline and both follow-up points.

Longitudinal Objective Assessment of IBD Activity and Healthcare Utilisation

A sole investigator (KMF), blinded to baseline questionnaire data, reviewed each participant's medical records during longitudinal follow-up. An objective assessment of disease activity was made, during which we extracted the following end points, along with the date of their occurrence: glucocorticosteroid prescription or flare of disease activity based on a physician's global assessment; escalation of medical therapy due to uncontrolled IBD activity, hospitalisation due to uncontrolled IBD activity; and intestinal resection due to uncontrolled IBD activity. Changes to medication without evidence of uncontrolled IBD activity (e.g., based on the results of therapeutic drug monitoring), or surgery for isolated perianal CD, were not judged to be relevant. We also recorded the number of each of these events of interest, the number of IBD-related clinic appointments, helpline calls, and the number of radiological and endoscopic investigations performed for assessment of disease activity to examine healthcare utilisation.

Longitudinal Assessment of IBS-type Symptoms

We recorded the presence or absence of symptoms compatible with Rome III-defined IBS at both the first and second points of follow-up.(26) Using these questionnaire data we were able to classify individuals as having never reported IBS-type symptoms, having IBS-type symptoms that resolved, having fluctuating IBS-type symptoms, having new onset IBS-type

symptoms, or having persistent IBS-type symptoms throughout the study period (Supplementary Table 1).

Statistical Analysis

Baseline demographic characteristics, HADS scores, PHQ-15 scores, and presence or absence of symptoms of anxiety or depression, or somatoform-type behaviour were compared between IBD patients reporting IBS-type symptoms those with quiescent disease, those with occult inflammation, and those with active disease using a χ^2 test for categorical variables and a one-way analysis of variance (ANOVA) for continuous data. The same comparisons were made between these groups for each of the four objective disease activity outcomes and all measures of healthcare utilisation during longitudinal follow-up. Independent predictors of reporting IBS-type symptoms at one or more points during follow-up were assessed by multivariate logistic regression, controlling for all baseline demographic characteristics, medications, and the presence or absence of baseline abnormal anxiety, depression, or somatoform symptom scores, with the results expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Independent predictors of the occurrence of any of the objective disease activity outcomes of interest were determined by multivariate Cox regression analysis controlling for baseline demographics, baseline IBD activity, medications, and presence or absence of baseline abnormal anxiety, depression, or somatoform symptom scores. The results were expressed as hazard ratios (HR) with 95% CIs. We performed sensitivity analyses using a FC <100mcg/g to define those who reported IBS-type symptoms as having IBD with IBS-type symptoms. We considered a 2-tailed P-value of <0.01 to be statistically significant. All statistical analyses were performed using SPSS for Windows version 26.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, we recruited 760 individuals, of whom 363 (47.8%) individuals (mean age 49.4 years (range 17 to 86 years), 211 (58.1%) female, 200 (55.1%) CD) provided complete IBS-type symptom and disease activity indices data and a FC sample at baseline. There were 87 patients reporting IBS-type symptoms at baseline (5 (5.7%) IBS with constipation, 27 (31.0%) IBS with diarrhoea, and 55 (63.2%) IBS with mixed stool pattern). In terms of the natural history of IBS-type symptom data, 217 (59.8%) individuals responded to the first follow-up questionnaire and 160 (44.1%) to the second, with a mean follow-up duration of 6.1 years. In total, 125 (34.4%) patients provided IBS-type symptom data at all three time points. Those who responded to all three questionnaires were more likely to be a university graduate or professional and to be receiving anti-tumour necrosis factor (TNF)-α drugs at baseline, and less likely to have abnormal depression scores at baseline than those who did not respond, but there were no other significant differences (Supplementary Table 2).

In terms of the number of the original 363 individuals for whom longitudinal follow-up data were available in their medical records for each of the IBD activity endpoints studied, this varied between 308 (84.8%) (flare of disease activity or need for glucocorticosteroids) and 352 (97.0%) (intestinal resection due to uncontrolled IBD activity) with a mean duration of follow-up of 6.3 years. When comparing patient characteristics, those with IBS-type symptoms at baseline were significantly more likely to be female, to have higher levels of symptoms of anxiety or depression, and higher levels of somatoform symptom reporting (Table 1). There were no other significant differences according to other baseline characteristics including IBD-related medications at baseline, type of IBD, or disease location, behaviour, or extent.

Natural History of IBS-type Symptoms

Among the 217 patients providing IBS-type symptom data at both baseline and the first point of follow-up, 63 had IBS-type symptoms at baseline, of whom 36 (57.1%) reported IBS-type symptoms at follow-up (Supplementary Figure 1). Among the 154 patients without IBS-type symptoms at baseline, 65 (42.2%) developed IBS-type symptoms at follow-up. Among the 160 patients providing data at baseline and second follow-up, 40 had IBS-type symptoms at baseline, of whom 24 (60.0%) still had IBS-type symptoms at second follow-up (Supplementary Figure 2). Among 120 patients without IBS-type symptoms at baseline, 45 (37.5%) developed IBS-type symptoms at second follow-up. Overall, based on data from 125 individuals at all three time points, 41 (32.8%) never reported IBS-type symptoms, 15 (12.0%) had IBS-type symptoms at baseline that resolved, 19 (15.2%) had fluctuating IBS-type symptoms, 35 (28.0%) had new onset IBS-type symptoms after baseline, and 15 (12.0%) had persistent IBS-type symptoms (Figure 1).

Therefore, in total, 84 (67.2%) patients reported IBS-type symptoms at one or more points during follow-up. Those with a previous intestinal resection (OR = 7.31; 95% CI 1.61 to 33.3) and with borderline abnormal anxiety scores at baseline (OR = 11.5; 95% CI 2.02 to 65.7) were more likely to report IBS-type symptoms on one or more occasion during the study. Those with IBS-type symptoms at one or more points during follow-up had significantly worse HADS, PHQ-15, and SF-36 scores across almost all domains at last point of follow-up than those who never reported IBS-type symptoms (Supplementary Table 3).

Impact of IBS-type Symptoms at Baseline on Disease Activity During Longitudinal Follow-up

In total, 163 (52.9%) of 308 patients needed a prescription for glucocorticosteroids or had a flare of disease activity during a mean duration of follow-up of 4.2 years (range 7 days to 8.7 years). Rates were significantly higher in those with active disease at baseline (p=0.002 for trend) (Table 2). After multivariate Cox regression analysis, rates remained highest in those with active disease at baseline (HR = 3.35; 95% CI 1.93 to 5.81, p<0.001), but were not significantly higher among those with IBS-type symptoms at baseline (HR = 1.45; 95% CI 0.96 to 2.18) (Table 2 and Figure 2a). Younger age (HR per year = 0.98; 95% CI 0.97 to 0.99, p<0.001) was associated with a reduced likelihood of need for glucocorticosteroid prescription or flare. Results were similar when using a FC of <100mcg/g (Supplementary Table 4).

Of 329 patients with complete data, 168 (51.1%) required escalation of medical therapy due to uncontrolled IBD activity over a mean follow-up period of 4.2 years (range 4 days to 8.7 years). Again, rates were significantly higher among those with active disease at baseline (p<0.001 for trend) (Table 2). After multivariate Cox regression, escalation rates were significantly higher in those with active disease at baseline (HR = 3.01; 95% CI 1.88 to 4.84, p<0.001) but not those with IBS-type symptoms at baseline (HR = 1.15; 95% CI 0.75 to 1.76) (Table 2 and Figure 2b). Younger age (HR per year = 0.99; 95% CI 0.97 to 1.00, p=0.007) was associated with a reduced likelihood of escalation of medical therapy. Results were similar when using a FC of <100mcg/g (Supplementary Table 4).

In total, 68 (19.4%) of 351 patients required hospitalisation over a mean follow-up period of 5.9 years (range 7 days to 8.7 years). Hospitalisation rates were highest among those with active disease at baseline and those with IBS-type symptoms at baseline, although this was not

statistically significant (p=0.028 for trend) (Table 2). After multivariate Cox regression, rates were highest among those with active disease at baseline (HR = 2.56; 95% CI 1.21 to 5.40) and those with IBS-type symptoms at baseline (HR = 2.36; 95% CI 1.15 to 4.83) although these differences were not statistically significant (Table 2 and Figure 2c). Glucocorticosteroid use at baseline was associated with an increased likelihood of hospitalisation (HR = 2.46; 95% CI 1.28 to 4.74, p=0.007). Using a FC of <100mcg/g, rates of hospitalisation were significantly higher among those with active disease at baseline (HR = 3.11; 95% CI 1.40 to 6.94), but not those with IBS-type symptoms (HR = 1.98; 95% CI 0.78 to 5.03) (Supplementary Table 4).

Finally, of 352 patients, 30 (8.5%) underwent intestinal resection for uncontrolled IBD activity, during a mean follow-up of 6.3 years (range 28 days to 8.7 years). Progression to intestinal resection was greatest in those with active disease at baseline, although this was not statistically significant (p=0.021 for trend) (Table 2). After multivariate Cox regression, rates were highest among those with active disease at baseline (HR = 3.61; 95% CI 1.16 to 11.2) although these differences were not statistically significant (Table 2 and Figure 2d). Glucocorticosteroid use at baseline was associated with an increased likelihood of intestinal resection (HR = 3.86; 95% CI 1.43 to 10.4, p=0.008). Results were similar using a FC of <100mcg/g (Supplementary Table 4).

Impact of IBS-type Symptoms at Baseline on Healthcare Utilisation During Longitudinal Follow-up

When compared with patients with quiescent disease at baseline, mean number of flares 2.4; SD ± 2.0) (p<0.001 for trend), mean number of glucorticosteroid prescriptions (1.4; SD ± 1.5) (p=0.001 for trend), and mean number of escalations (1.7; SD ± 1.3) (p<0.001 for trend)

were all significantly higher among those with active disease at baseline (Table 3). Mean number of outpatient appointments were significantly higher among those with IBS-type symptoms (10.3; SD ± 5.9) and those with active disease at baseline (11.8; SD ± 6.8) (p<0.001 for trend). Mean number of endoscopic investigations was significantly higher among those with IBS-type symptoms at baseline (1.3; SD ± 1.4) (p=0.003 for trend) and there was a trend towards higher rates of radiological investigations in those with IBS-type symptoms (0.9; SD ± 1.2) and those with active disease (1.2; SD ± 1.5) (p=0.018 for trend). Sensitivity analyses using a FC <100mcg/g were similar (Supplementary Table 5).

DISCUSSION

This longitudinal follow-up study recruiting patients with well-characterised IBD demonstrates that IBS-type symptoms are extremely common, affecting up to two-thirds of patients during >6 years of follow-up. These symptoms impacted significantly on anxiety, depression, and somatoform symptom reporting, and quality of life during longitudinal follow-up. However, importantly, there was no significant adverse effect of IBS-type symptoms at baseline on any of the endpoints of disease activity we examined. Although rates of occurrence of some of the endpoints we studied, such as need for glucocorticosteroids or flare of disease activity, or hospitalisation, were higher among those with IBS-type symptoms at baseline, these were not significantly different from those with quiescent disease, and the mean number of these events was only significantly higher in those with active disease at baseline. Despite this, rates of consultations and investigations were significantly higher among those with IBS-type symptoms at baseline.

Although we recruited over 300 patients with well-characterised IBD and classified the presence or absence of IBS-type symptoms rigorously, including the use of a FC at baseline, there are some limitations. The FC cut off of ≥250mcg/g used to define the presence of active mucosal inflammation is contentious, despite it being advocated by expert consensus,(27) and having been used by previous researchers.(31, 32) However, we conducted sensitivity analyses using an FC ≥100mcg/g to define active disease, with similar findings. In addition, FC may correlate poorly with disease activity in ileal CD,(33) although the group with IBS-type symptoms at baseline contained one of the lowest proportions with ileal CD. We were unable to assess calprotectin longitudinally, which may mean that some patients reporting IBS-type symptoms during follow-up were experiencing a flare of disease activity. Our assessment of

anxiety, depression, and somatoform symptom scores and quality of life scores during longitudinal follow-up was based on questionnaire responses at a single point in time. Hence, any fluidity of the association between baseline IBS-type symptom and abnormal anxiety, depression, or somatoform symptom scores or impaired quality of life cannot be assessed. This suggests that, in susceptible individuals, the association between IBS-type symptoms and psychological co-morbidity is likely to be durable. Although we obtained longitudinal follow-up data for between 85% and 97% of involved individuals for the disease activity endpoints of interest, questionnaire data were only provided by 60% and 44% of participants at 2 and 6 years. However, this is in line with data from other longitudinal follow-up studies conducted by our group over similar time frames.(34-36) Finally, there may have been volunteer bias, with those with IBS-type symptoms being more likely to respond to follow-up questionnaires, although as this was not the sole focus of the follow-up study we feel this is unlikely.

To our knowledge, there has been only one other study conducting longitudinal follow-up in patients with IBD who report IBS-type symptoms to assess their impact on the natural history of the condition.(16) This Swedish study recruited 94 patients with newly diagnosed UC and followed them up on an annual basis for 3 years. During longitudinal follow-up, between 11% and 23% of patients reported IBS-type symptoms, and these were associated with lower quality of life and impairments in psychological health, but not with subsequent disease activity, as assessed by FC. The current study results are, therefore, in line with those of both the study by Jonefjall *et al.*,(16) and our previous follow-up of these individuals.(17) However, given the multitude of endpoints we assessed it contributes further to knowledge in this field. IBS-type symptoms affected two-thirds of patients during the study and were persistent, based on being present at all three time points assessed, in almost one-in-eight participants. Although their

presence at baseline was not associated with the occurrence or absolute number of any of the adverse disease activity outcomes we studied, they were associated with increased healthcare utilisation. Given that other investigators have postulated that these symptoms are likely to be due to ongoing disease activity,(7) these findings are important.

Based on our results, management strategies for these symptoms are required, to reduce healthcare resource use and to improve psychological health and quality of life among those who experience them. Whether it is these impairments in psychological health and quality of life that drive the higher rates of consultations and investigations seen in those reporting IBS-type symptoms is unclear, but plausible. It may be that gut-brain axis activation is involved and, if so, this may represent a therapeutic target, as has been discussed elsewhere.(37-39) Trials of gut-brain behavioural therapies and neuromodulators have, to date, been disappointing,(40-43) but none of these have targeted this patient group specifically. An ongoing trial in the UK aims to study the efficacy of neuromodulators in such a population, recruiting patients with stable UC who have chronic diarrhoea despite optimal medical therapy.(44)

In summary, this study expands on previous work conducted by our group, and others, examining the natural history of IBS-type symptoms in patients with IBD and demonstrating their impact on both psychological health and quality of life. Although this is an extension of a prior study, the findings remain important. The previous study may have been underpowered to detect significant differences for rarer events, such as hospitalisation and surgery. With a substantial increase in the study duration, more of the events of interest have accrued, yet there was still no significant effect of IBS-type symptoms on adverse disease activity outcomes during 6 years of longitudinal follow-up. This increases our confidence that such symptoms do not contribute deleteriously to the natural history of IBD. In addition, rates of healthcare utilisation

remained significantly higher among those who reported these symptoms at baseline. The consistent association between psychological co-morbidity and IBS-type symptoms observed in this patient cohort over time, and the lack of any clear relationship with objective measures of disease activity, suggests that activation of the gut-brain axis, rather than ongoing inflammation, is both the cause and a potential therapeutic target.

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Table 1. Disease Activity Status at Baseline and Characteristics of IBD Patients After FC Analysis Using a Cut Off <250mcg/g.

	Quiescent IBD (n=131)	IBD with IBS-type Symptoms (n=87)	IBD with Occult Inflammation (n=83)	Active IBD (n=62)	P value*
Mean age in years (SD)	49.5 (16.9)	46.3 (15.1)	51.6 (18.5)	50.5 (16.1)	0.21
Female sex (%)	66 (50.4)	63 (72.4)	43 (51.8)	39 (62.9)	0.006
Married or co-habiting (%)	88 (67.2)	55 (64.0)	54 (65.1)	43 (69.4)	0.90
University graduate/professional (%)	40 (30.5)	23 (26.4)	19 (23.8)	17 (27.9)	0.75
Tobacco user (%)	10 (7.6)	19 (21.8)	13 (15.9)	9 (14.5)	0.029
Alcohol user (%)	89 (68.5)	57 (65.5)	52 (62.7)	36 (58.1)	0.54
IBD type (%)					
CD	66 (50.4)	56 (64.4)	49 (59.0)	29 (46.8)	
UC	65 (49.6)	31 (35.6)	34 (41.0)	33 (53.2)	0.091
CD location (%)					
Ileal	10 (15.2)	13 (23.2)	13 (26.5)	11 (37.9)	
Colonic	24 (36.4)	21 (37.5)	14 (28.6)	5 (17.2)	
Ileocolonic	32 (48.5)	22 (39.3)	22 (44.9)	13 (44.8)	0.21
Non-stricturing, non-penetrating CD (%)	58 (87.9)	47 (83.9)	43 (87.8)	22 (75.9)	0.46
Perianal Crohn's disease present (%)	6 (9.1)	3 (5.4)	3 (6.1)	3 (10.3)	0.78

UC extent (%)					
Proctitis	16 (24.6)	10 (32.3)	11 (32.4)	8 (24.2)	
Left-sided	32 (49.2)	15 (48.4)	13 (38.2)	14 (42.4)	
Extensive	17 (26.2)	6 (19.4)	10 (29.4)	11 (33.3)	0.83
Current 5-ASA use (%)	72 (55.0)	48 (55.2)	40 (48.2)	31 (50.0)	0.72
Current immunomodulator use (%)	42 (32.1)	37 (42.5)	24 (28.9)	20 (32.3)	0.25
Current anti-TNF-α use (%)	23 (17.6)	18 (20.7)	8 (9.6)	9 (14.5)	0.23
Current glucocorticosteroid use (%)	11 (8.4)	9 (10.3)	11 (13.3)	8 (12.9)	0.66
Previous intestinal resection (%)	23 (17.6)	23 (26.4)	11 (13.3)	12 (19.4)	0.17
Anxiety categories (%)					
Normal	85 (64.9)	30 (34.5)	53 (63.9)	30 (48.4)	
Borderline abnormal	23 (17.6)	20 (23.0)	17 (20.5)	11 (17.7)	
Abnormal	23 (17.6)	37 (42.5)	13 (15.7)	21 (33.9)	<0.001
Depression categories (%)					
Normal	111 (84.7)	56 (64.4)	71 (86.6)	39 (62.9)	
Borderline abnormal	12 (9.2)	15 (17.2)	6 (7.3)	8 (12.9)	
Abnormal	8 (6.1)	16 (18.4)	5 (6.1)	15 (24.2)	<0.001

PHQ-15 somatoform symptom categories (%)					
Mild	32 (25.2)	2 (2.4)	17 (22.1)	2 (3.4)	
Low	47 (37.0)	16 (19.0)	36 (46.8)	14 (24.1)	
Medium	32 (25.2)	37 (44.0)	23 (29.9)	25 (43.1)	
High	16 (12.6)	29 (34.5)	1 (1.3)	17 (29.3)	<0.001

*p value for χ^2 for comparison across all four groups for categorical data and for one-way ANOVA for continuous data.

Table 2. Clinical Outcomes of Patients According to IBD Activity Status (FC <250mcg/g) at Baseline.

	Quiescent IBD	IBD with IBS-type Symptoms	IBD with Occult Inflammation	Active IBD	P Value
Glucorticosteroid prescription or flare of disease activity (%)	59/126 (46.8)	49/82 (59.8)	31/70 (44.3)	24/30 (80.0)	0.002*
Multivariate HR for glucorticosteroid prescription or flare of disease activity (95% CI)	1.00 (reference)	1.45 (0.96 – 2.18)	0.97 (0.60 – 1.56)	3.35 (1.93 – 5.81)†	<0.001
Escalation of medical therapy due to uncontrolled IBD activity (%)	58/127 (45.7)	43/83 (51.8)	33/77 (42.9)	34/42 (81.0)	<0.001*
Multivariate HR for escalation of medical therapy due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.15 (0.75 – 1.76)	1.00 (0.63 – 1.59)	3.01 (1.88 – 4.84)†	<0.001
Hospitalisation due to uncontrolled IBD activity (%)	16/127 (12.6)	20/83 (24.1)	14/80 (17.5)	18/61 (29.5)	0.028*
Multivariate HR for hospitalisation due to uncontrolled IBD activity (95% CI)	1.00 (reference)	2.36 (1.15 – 4.83)	1.34 (0.60 – 3.02)	2.56 (1.21 – 5.40)	0.041

Intestinal resection due to uncontrolled IBD activity (%)	6/127 (4.7)	8/83 (9.6)	5/80 (6.3)	11/62 (17.7)	0.021*
Multivariate HR for intestinal resection due to uncontrolled IBD activity (95% CI)	1.00 (reference)	1.76 (0.54 – 5.75)	1.08 (0.27 – 4.41)	3.61 (1.16 – 11.2)	0.096

*χ^2 for comparison across all four groups.

†p<0.01 versus reference category.

Table 3. Healthcare Utilisation According to IBD Activity Status (FC <250mcg/g) at Baseline.

	Quiescent IBD	**IBD with IBS-type Symptoms**	**IBD with Occult Inflammation**	**Active IBD**	***p* value***
Mean number of flares of disease activity (SD)	1.1 (1.8)	1.5 (1.8)	1.2 (1.6)	2.4 (2.0)	<0.001
Mean number of glucocorticosteroid prescriptions (SD)	0.6 (1.3)	0.8 (1.4)	0.6 (1.1)	1.4 (1.5)	0.001
Mean number of escalations (SD)	0.8 (1.2)	1.0 (1.3)	0.9 (1.1)	1.7 (1.3)	<0.001
Mean number of hospitalisations (SD)	0.2 (0.6)	0.3 (0.8)	0.2 (0.5)	0.4 (0.9)	0.051
Mean number of intestinal resections (SD)	0.1 (0.3)	0.1 (0.3)	0.1 (0.2)	0.2 (0.4)	0.045
Mean number of outpatient appointments (SD)	8.1 (6.4)	10.3 (5.9)	7.9 (6.4)	11.8 (6.8)	<0.001
Mean number of helpline calls (SD)	4.2 (7.7)	5.5 (6.4)	4.7 (5.5)	5.4 (5.5)	0.51
Mean number of radiological investigations (SD)	0.5 (1.1)	0.9 (1.2)	0.9 (1.7)	1.2 (1.5)	0.018
Mean number of endoscopic investigations (SD)	0.9 (1.1)	1.3 (1.4)	0.6 (0.9)	1.1 (1.2)	0.003

**p* value for one-way ANOVA.

Figure 1. Natural History of Rome III IBS-type Symptoms in 125 Individuals with IBD During 6.3 years of Longitudinal Follow-up.

Figure 2a. Survival Plot of the Impact of IBS-type Symptoms at Baseline on Glucocorticosteroid Prescription or Flare of Disease Activity.

Figure 2b. Survival Plot of the Impact of IBS-type Symptoms at Baseline on Escalation of Medical Therapy Due to Uncontrolled IBD Activity.

Figure 2c. Survival Plot of the Impact of IBS-type Symptoms at Baseline on Hospitalisation Due to Uncontrolled IBD Activity.

Figure 2d. Survival Plot of the Impact of IBS-type Symptoms at Baseline on Intestinal Resection Due to Uncontrolled IBD Activity.