Ther Adv Gastroenterol
2018, Vol. 11: 1–12
DOI: 10.1177/1756284818783600

High prevalence of irritable bowel syndrome-type symptoms in microscopic colitis: implications for treatment

John S. Kane, Andrew J. Irvine, Yannick Derwa, Olorunda Rotimi and Alexander C. Ford

Abstract

Background: Patients with microscopic colitis (MC) often present with abdominal pain and diarrhoea, and previous data suggest that there may be overlap between MC and irritable bowel syndrome (IBS). We evaluated the prevalence of IBS-type symptoms in patients with MC, and assess the impact of these symptoms on psychological health and quality of life.

Methods: We conducted a cross-sectional survey of individuals with a histological diagnosis of MC, collecting demographic data, Rome III IBS-type symptoms, and mood, somatization, and quality of life data.

Results: In total, 151 (31.6%) of 478 individuals with a new diagnosis of MC completed questionnaires, 52 (34.4%) of whom reported IBS-type symptoms. The commonest histological subtype was collagenous colitis (51.7%, $n = 78$), followed by lymphocytic colitis (39.1%, $n = 59$). Individuals with IBS-type symptoms had significantly higher levels of anxiety [Hospital Anxiety and Depression Scale (HADS) anxiety score 8.6 *versus* 5.1, $p < 0.001$], depression (HADS depression score 6.2 *versus* 3.6, $p = 0.001$), and somatoform-type behaviour (Patient Health Questionnaire 15 score 12.7 *versus* 8.0, $p < 0.001$) compared with individuals who did not. Those with IBS-type symptoms scored significantly worse across all domains of the 36-item Short Form questionnaire, except for physical functioning.

Conclusions: More than one third of individuals with MC reported IBS-type symptoms, although whether this is due to ongoing inflammation is unclear. These individuals had higher levels of anxiety, depression, and somatization, and impaired quality of life. Identifying concomitant IBS in individuals with MC may have important implications for management decisions.

Keywords: irritable bowel syndrome, microscopic colitis, psychological health, quality of life, somatization

Received: 1 March 2018; accepted in revised form: 21 May 2018.

Correspondence to:
John S. Kane
Leeds Gastroenterology Institute, 4th Floor, Bexley Wing, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK
jackjohnkane@googlemail.com

Andrew J. Irvine
Yannick Derwa
Leeds Gastroenterology Institute, St James's University Hospital, Leeds, UK

Olorunda Rotimi
Department of Histopathology, St James's University Hospital, Leeds, UK

Alexander C. Ford
Leeds Gastroenterology Institute, St James's University Hospital, Leeds, UK Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK

Introduction

Both microscopic colitis (MC) and irritable bowel syndrome (IBS) are important differential diagnoses in individuals presenting with chronic diarrhoea, especially among patients with a macroscopically normal colonoscopy. IBS is a chronic functional bowel disorder, often affecting younger individuals,[1] and characterized by abdominal pain in association with a disordered bowel habit.[2] The condition affects approximately 10–20% of individuals globally.[1] In contrast, MC often presents in middle age with chronic watery diarrhoea, and some studies suggest that the presence of abdominal pain is a negative predictor for MC.[3,4] In addition, MC is rarer and has a reported incidence of approximately 9 per 100,000 person years for the two main histological subtypes:[5] collagenous colitis (CC), characterized by a distinct subepithelial collagen band, and lymphocytic colitis (LC), with intraepithelial lymphocytosis.

Despite these differences in epidemiology, given the high prevalence of IBS, and the similarities in some of the presenting features, there is the

potential for substantial overlap of symptoms between IBS and MC. This issue is important as it could lead to confusion between the two, delaying the diagnosis and commencement of effective therapies in patients with MC,[6,7] or leading to unnecessary colonoscopy and biopsy in patients with probable IBS.[3] The degree of overlap between the two conditions has been examined in meta-analyses, with up to one in three individuals with MC reporting symptoms compatible with IBS.[8,9] However, there were few available studies examining this issue.

Individuals with a confirmed diagnosis of IBS are more likely to suffer from coexistent mood disorder, anxiety, and neuroticism compared with healthy individuals,[10] and to report lower quality of life.[11,12] When symptoms compatible with IBS are reported by patients with other organic gastrointestinal (GI) conditions, such as idiopathic inflammatory bowel disease (IBD), they appear to impact on both mood and quality of life. In a large cross-sectional study conducted among 378 patients with ulcerative colitis or Crohn's disease, levels of psychological comorbidity were significantly higher among those reporting IBS-type symptoms compared with patients with quiescent disease, and quality of life was reduced to a similar degree to that seen in patients with confirmed IBD activity.[13]

Although studies conducted among patients with MC have shown that quality of life is impaired in both CC and LC,[14–17] the prevalence of mood disorders, such as anxiety, depression, or somatization, is not clear. Data from another cross-sectional study, conducted among individuals with MC thought to be in disease remission clinically, demonstrated that some patients continue to report GI symptoms, which seem to impair health-related quality of life.[15] Furthermore, in a cross-sectional study of Swedish women, individuals with a diagnosis of MC plus concomitant IBS-like symptoms had a greater impairment in psychological wellbeing compared with those who did not report IBS-like symptoms, but the authors did not report levels of anxiety, depression, or somatization specifically.[18]

We therefore conducted this cross-sectional survey to further assess the prevalence of IBS-type symptoms and mood disorders in a large cohort of patients with a histological diagnosis of MC, and assess the impact of symptoms compatible with IBS on psychological health including levels of anxiety, depression, somatization, and health-related quality of life. Our *a priori* hypothesis was that the presence of IBS-type symptoms would impact negatively on mood and quality of life in patients with MC, as we have seen in patients with IBD in our centre.[13,19]

Materials and methods

Participants and setting

Potential participants were adult patients identified as having a new histological diagnosis of MC from histology reports after presenting to the Leeds Teaching Hospitals over a 6-year period, between January 2010 and December 2015. Our institution, based in the north of England, provides secondary care services to a population of 800,000 people. For all patients diagnosed with MC during this period we confirmed survival status, ensured there was no evidence of a diagnosis of cognitive impairment, and sought an up-to-date contact address, using hospital records.

Diagnosis of microscopic colitis

The diagnosis of MC was according to the following criteria: CC was defined as the presence of a subepithelial collagen band of at least 10 μm in thickness, in association with diffuse chronic inflammation; LC was defined using a threshold of more than 20 intraepithelial lymphocytes per 100 epithelial cells, with associated diffuse chronic inflammation, but no thickening of the subepithelial collagen band. Individuals, in whom the recorded pathology diagnosis did not specify the subtype of MC, were classified as 'MC, not otherwise specified (MC-NOS)' as, at our centre, the diagnoses of incomplete collagenous or lymphocytic colitis are not used. Other investigators have demonstrated that there is little interobserver variability in the diagnosis of MC.[20] Finally, individuals with a previous histology report suggesting a prior known diagnosis of MC were excluded from the analysis.

Data collection and synthesis

All potentially eligible participants were sent an invitation letter, participant information leaflet, written consent form, and a questionnaire by post. The postal survey took place between June 2016 and February 2017. All nonresponders to

the initial mail out received a second postal questionnaire. The study was approved by the local research ethics committee (Yorkshire & The Humber, Leeds West, United Kingdom) in January 2016.

Demographic data. All participants were asked to provide the following demographic data: sex, age, ethnicity, marital status, educational level, tobacco and alcohol use, and weight (in kg) and height (in m), which were used to calculate body mass index (BMI). We also asked participants to complete a checklist of medications previously reported as being associated with MC,[21] and respond to questions regarding the presence of common associated autoimmune diseases,[22] including coeliac disease, thyroid disease, rheumatoid arthritis, psoriasis, autoimmune hepatitis, and type 1 diabetes. Individuals were asked to record if they were given appropriate drug treatment after their diagnosis, and how effective they judged it to have been using a four-point Likert scale ('very effective', 'effective', 'no effect', or 'made symptoms worse'). These data were dichotomized into two groups: those with effective or very effective treatment and those without.

Reference standard used to define presence of IBS-type symptoms. Because our study was designed and commenced prior to the publication of the Rome IV criteria,[2] the presence of IBS-type symptoms was assessed *via* the Rome III criteria.[23] IBS-type symptoms were defined as present when participants reported abdominal discomfort or pain occurring at least 3 days per month over the past 3 months, with the onset of discomfort at least 6 months previously, and associated with two or more of the following: an improvement of pain or discomfort with the passage of stool, more or less frequent bowel movements, or looser or firmer stools.

Mood and somatization data. To assess for the presence of either anxiety or depression, participants were asked to complete the validated 14-item Hospital Anxiety and Depression Scale (HADS) questionnaire.[24] This includes seven questions screening for the presence of anxiety, and another seven questions for depression. Each question is scored from 0 to 3, resulting in a maximum potential score of 21 for anxiety or depression separately. The severity of anxiety and depression symptoms was then graded according to three categories: normal (total depression or anxiety scores 0–7), borderline normal (8–10), and abnormal ($\geqslant$11).

In order to assess for the presence of somatization we used the Patient Health Questionnaire 15 (PHQ-15), a validated questionnaire enquiring about the presence of 15 specific somatic symptoms occurring within the previous 4 weeks.[25] This is derived from the validated full PHQ tool, and has been seen to capture over 90% of physical symptoms described in the outpatient setting. Symptoms were graded into three levels of severity: 'not bothered at all' (scored as 0), 'bothered a little' (scored as 1), or 'bothered a lot' (scored as 2), giving a total possible score of 30. The severity of somatization was categorized into high (total score $\geqslant$15), medium (10–14), low (5–9), and minimal ($\leqslant$4) levels, as has been previously recommended.

Quality of life data. The medical outcomes study 36-item Short Form (SF-36) score is a validated questionnaire assessing both physical and mental health status,[26] and was used to assess health-related quality of life. The 36 questions are grouped into eight domains: physical functioning, role limitations due to physical health, role limitations due to emotional health, energy or fatigue, emotional wellbeing, social functioning, pain, and general health. Participants were asked to score each question from 0 to 100, with higher scores indicating more favourable quality of life.

Statistical analysis

We compared baseline demographic characteristics including medication, prevalence of IBS-type symptoms, HADS scores, PHQ-15 scores, SF-36 scores, and presence or absence of anxiety, depression, or somatization between subtypes of MC using a χ^2 test for categorical variables, and one-way analysis of variance (ANOVA) for continuous data. We then compared baseline demographic characteristics, HADS scores, PHQ-15 scores, SF-36 scores, and presence or absence of anxiety, depression, or somatization among those with IBS-type symptoms and those without, again using a χ^2 test for categorical variables and a one-way ANOVA for continuous data. As the PHQ-15 contains three GI symptoms, we repeated the analyses for the PHQ-12, which is the same questionnaire but with the three GI symptoms removed.[27] A two-tailed p value less than 0.01 was considered to be statistically significant for all

analyses, due to multiple comparisons. All statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Over the 6-year study period, a total of 568 patients were diagnosed with MC. We excluded 90 of these individuals, because 70 had died, 13 had a record of cognitive impairment, and 7 had a missing or incomplete home address. Therefore, 478 individuals were sent a postal questionnaire. We received 157 completed questionnaires after two mail outs, a response rate of 32.8% (Figure 1). Of these, six individuals had a previous histological diagnosis of MC prior to 2010 so were excluded from the final analysis. Overall, there were no significant differences between responders and nonresponders in terms of age, sex, or MC subtype. These data are provided in Table 1.

Among the 151 eligible responders, 78 (51.7%) individuals had a diagnosis of CC, 59 (39.1%) LC, and 14 (9.3%) MC-NOS. Of the eligible responders 74.8% ($n = 113$) were female, and had a mean age of 68.0 years [standard deviation (SD) $\pm$ 9.8]. Other data for all responders, and by MC subtype, are provided in Table 2. In all subtypes, there was a high frequency of individuals who reported taking a drug known to be a potential risk factor for MC; the most frequently reported medications being nonsteroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors (PPIs), with 98 (64.9%) patients taking either of these medications. The presence of any coexistent autoimmune disease was reported by 46 (30.5%) individuals. Regarding coeliac disease specifically, this was significantly more likely in LC [10 patients (16.9%)] compared with CC [1 patient (1.3%)] or MC-NOS (0 patients) ($p = 0.001$). Macroscopic features, such as ulceration, reduced vascularity, erythema, mucosal congestion, petechiae, or linear scarring were present at the index colonoscopy in 18 (11.9%) individuals with MC, including 5 (3.3%) individuals who had an endoscopic diagnosis of colitis. In terms of levels of anxiety, depression, and somatization, 15.1% of patients with MC reported abnormal levels of anxiety, 8.8% abnormal levels of depression, and 14.7%

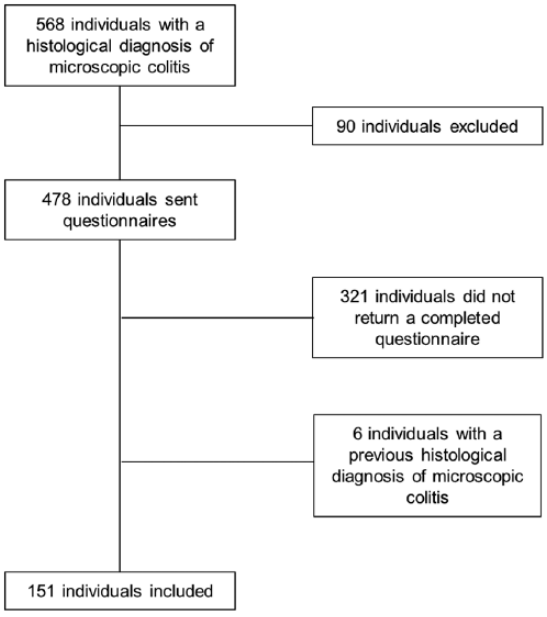

Figure 1. Flow chart of patients recruited into the study.

Table 1. Characteristics of responders and nonresponders.

	All responders ($n = 151$)	Nonresponders ($n = 321$)	p value*
Subtype of MC (%)			
Collagenous colitis	78 (51.7)	170 (53.0)	
Lymphocytic colitis	59 (39.1)	125 (38.9)	
MC-NOS	14 (39.1)	26 (8.1)	0.91
Mean age in years (SD)	68.0 (9.8)	65.4 (12.6)	0.03
Female sex (%)	113 (74.8)	232 (72.3)	0.32

*One way analysis of variance for continuous data and χ^2 for categorical data.
MC, microscopic colitis; MC-NOS, microscopic colitis, not otherwise specified; SD, standard deviation.

Table 2. Characteristics of patients with MC by subtype.

	Total ($n = 151$)	CC ($n = 78$)	LC ($n = 59$)	MC-NOS ($n = 14$)	*p* value*
Mean age in years (SD)	68.0 (9.8)	69.1 (9.1)	65.8 (10.2)	70.6 (10.8)	0.08
Female sex (%)	113 (74.8)	64 (82.1)	42 (71.2)	7 (50.0)	0.03
Married or cohabiting (%)	99 (65.6)	45 (57.7)	44 (74.6)	10 (71.4)	0.11
University graduate/professional (%)	36 (23.8)	17 (21.8)	17 (28.8)	2 (14.3)	0.43
Mean BMI (SD)	26.3 (4.8)	26.5 (5.1)	26.3 (4.6)	25.2 (4.2)	0.69
Tobacco user (%)	17 (11.3)	8 (10.3)	7 (11.9)	2 (14.3)	0.89
Alcohol user (%)	107 (70.9)	51 (65.4)	45 (76.3)	11 (78.6)	0.31
NSAID use (%)	52 (34.4)	29 (37.2)	20 (33.9)	3 (21.4)	0.52
PPI use (%)	70 (46.4)	38 (48.7)	26 (44.1)	6 (42.9)	0.83
Any associated drug (%)	130 (86.1)	70 (89.7)	49 (83.1)	11 (78.6)	0.37
Coeliac disease (%)	11 (7.3)	1 (1.3)	10 (16.9)	0 (0.0)	0.001
Any autoimmune disease (%)	46 (30.5)	19 (24.4)	23 (39.0)	4 (28.6)	0.18
Macroscopic features at endoscopy (%)	18 (11.9)	10 (12.8)	7 (11.9)	1 (7.1)	0.83
Reporting effective drug therapy (%)	64 (83.1)	39 (83.0)	20 (80.0)	5 (100)	0.55
Rome III IBS-type symptoms (%)	52 (34.4)	26 (33.3)	18 (30.5)	8 (57.1)	0.16
Mean HADS anxiety score (SD)	6.3 (4.6)	6.1 (4.1)	6.4 (5.0)	7.7 (5.5)	0.47
Anxiety categories (%)					
Normal	89 (61.0)	47 (61.0	34 (61.8)	8 (57.1)	
Borderline abnormal	35 (24.0)	23 (29.9)	10 (18.2)	2 (14.3)	
Abnormal	22 (15.1)	7 (9.1)	11 (20.0)	4 (28.6)	0.14
Mean HADS depression score (SD)	4.5 (4.3)	3.9 (3.5)	5.0 (5.2)	6.0 (4.2)	0.14
Depression categories (%)					
Normal	118 (79.7)	66 (85.7)	43 (75.4)	9 (64.3)	
Borderline abnormal	17 (11.5)	8 (10.4)	6 (10.5)	3 (21.4)	
Abnormal	13 (8.8)	3 (3.9)	8 (14.0)	2 (14.3)	0.16
Mean PHQ-15 score (SD)	9.5 (4.9)	9.8 (5.0)	8.8 (4.7)	11.3 (4.6)	0.21
PHQ-15 somatization categories (%)					
Mild	23 (15.3)	12 (15.4)	10 (16.9)	1 (7.7)	
Low	51 (34.0)	26 (33.3)	21 (35.6)	4 (30.8)	
Medium	54 (36.0)	27 (34.6)	21 (35.6)	6 (46.2)	
High	22 (14.7)	13 (16.7)	7 (11.9)	2 (15.4)	0.95

(Continued)

Table 2. (Continued)

	Total ($n = 151$)	CC ($n = 78$)	LC ($n = 59$)	MC-NOS ($n = 14$)	p value*
Mean SF-36 score (SD)					
Physical functioning	63.1 (30.5)	58.6 (31.7)	70.4 (26.8)	55.4 (35.6)	0.07
Role limitations physical health	47.1 (44.2)	50.0 (43.5)	56.9 (43.6)	39.6 (47.0)	0.11
Role limitations emotional problems	47.1 (44.4)	62.2 (45.3)	66.1 (43.8)	52.8 (43.7)	0.63
Energy/fatigue	50.8 (24.2)	51.6 (24.2)	53.2 (23.5)	34.5 (23.4)	0.06
Emotional wellbeing	71.1 (20.4)	72.9 (19.4)	71.5 (19.8)	59.1 (25.6)	0.08
Social functioning	70.2 (28.0)	66.3 (28.9)	77.0 (24.8)	63.5 (32.1)	0.06
Pain	56.4 (27.0)	54.6 (28.1)	60.3 (26.6)	49.2 (21.1)	0.29

*One-way analysis of variance for continuous data and χ^2 for categorical data.
BMI, body mass index; CC, collagenous colitis; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; LC, lymphocytic colitis; MC, microscopic colitis; MC-NOS, microscopic colitis, not otherwise specified; NSAID, nonsteroidal anti-inflammatory drugs; PHQ-15, Patient Health Questionnaire 15; PPI, proton pump inhibitor; SD, standard deviation; SF-36, Short Form 36.

high levels of somatization. There were no significant differences between MC subtypes, in terms of mood or quality of life data.

Prevalence of, risk factors for, and impact of IBS-type symptoms in patients with MC

Overall, 52 (34.4%) individuals reported IBS-type symptoms according to the Rome III criteria, with no significant difference between MC subtypes. Of the individual components of the Rome III criteria, only the presence of abdominal pain or discomfort for at least 1 day per week (67.3% *versus* 7.8%, $p < 0.001$) distinguished those with IBS-type symptoms from those without. There was a trend towards individuals with IBS-type symptoms being younger, and the frequency of individuals reporting use of PPIs was higher, although the result was not significant (Table 3). However, there was no significant association between IBS-type symptoms and macroscopic abnormalities seen at the index colonoscopy. Those with IBS-type symptoms had significantly higher levels of anxiety, depression, and somatization. The latter remained the case when the PHQ-12 was used, rather than the PHQ-15. In terms of quality of life, patients with MC who reported IBS-type symptoms also scored significantly worse across all domains of the SF-36, except for physical functioning.

In total, 77 individuals (51.0%) reported receiving drug therapy for MC, and 60 of these were prescribed glucocorticosteroids, including 52 (65.8%) individuals given budesonide and 8 (10.1%) given prednisolone. Other medications included loperamide in 15 (19.0%) and 5-aminosalicylates in 2 (2.5%). In those who were prescribed medication, 64 (83.1%) indicated their treatment was effective or very effective, but there was no significant difference seen with respect to the reported effectiveness of drug therapy received for MC, either according to subtype or between individuals reporting IBS-type symptoms and those who did not. There were also no significant differences in anxiety, depression, somatization, or quality of life in those reporting receiving effective or very effective drug treatment for MC compared with those describing that drug therapy was ineffective or worsened symptoms.

Discussion

This cross-sectional study has demonstrated that one third of patients with MC report IBS-type symptoms. Individuals with MC who reported these symptoms had significantly higher levels of anxiety, depression, and somatoform-type behaviour than those who did not. Health-related quality of life was significantly reduced in patients with IBS-type symptoms, and this was consistent across all domains of the SF-36, with the exception of physical functioning. The presence of macroscopic evidence of inflammation at the index colonoscopy did not seem to influence the likelihood of reporting these symptoms, nor did

Table 3. Characteristics of patients with MC according to presence or absence of IBS-type symptoms.

	IBS-type symptoms present ($n = 52$)	IBS-type symptoms absent ($n = 99$)	*p* value*
Subtype of MC (%)			
Collagenous colitis	26 (50.0)	52 (52.5)	
Lymphocytic colitis	18 (34.6)	41 (41.4)	0.16
MC-NOS	8 (15.4)	6 (6.1)	
Mean age in years (SD)	65.1 (10.2)	69.5 (9.3)	0.08
Female sex (%)	40 (76.9)	73 (73.7)	0.67
Married or cohabiting (%)	29 (55.8)	70 (70.7)	0.07
University graduate/professional (%)	11 (21.2)	25 (25.3)	0.57
Mean BMI (SD)	27.1 (5.3)	25.8 (4.4)	0.14
Tobacco user (%)	8 (15.4)	9 (9.1)	0.25
Alcohol user (%)	41 (78.8)	66 (66.7)	0.12
NSAID use (%)	18 (34.6)	34 (34.3)	0.97
PPI use (%)	31 (59.6)	39 (39.4)	0.02
Any associated drug (%)	46 (88.5)	84 (84.8)	0.54
Coeliac disease (%)	3 (5.8)	8 (8.1)	0.60
Any autoimmune disease (%)	16 (30.8)	30 (30.3)	0.95
Macroscopic features at endoscopy (%)	4 (7.7)	14 (14.1)	0.25
Reporting effective drug treatment (%)	21 (75.0)	43 (87.8)	0.15
Mean HADS anxiety score (SD)	8.6 (4.6)	5.1 (4.1)	<0.001
Anxiety categories (%)			
Normal	22 (42.3)	67 (71.3)	
Borderline abnormal	16 (30.8)	19 (20.2)	
Abnormal	14 (26.9)	8 (8.5)	0.001
Mean HADS depression score (SD)	6.2 (4.6)	3.6 (3.9)	<0.001
Depression categories (%)			
Normal	37 (72.5)	81 (83.5)	0.02
Borderline abnormal	5 (9.8)	12 (12.4)	
Abnormal	9 (17.6)	4 (4.1)	
Mean PHQ-15 score (SD)	12.7 (4.5)	8.0 (4.3)	<0.001
PHQ-15 somatization categories (%)			

(Continued)

Table 3. (Continued)

Anxiety categories (%)			
Mild	1 (2.0)	22 (22.2)	
Low	13 (25.5)	38 (38.4)	
Medium	22 (43.1)	32 (32.3)	
High	15 (29.4)	7 (7.1)	<0.001
Mean PHQ-12 score (SD)	8.6 (3.6)	5.8 (3.4)	<0.001
Mean SF-36 score (SD)			
Physical functioning	57.3 (32.2)	66.2 (29.4)	0.11
Role limitations physical health	30.7 (40.3)	54.8 (44.0)	0.003
Role limitations emotional problems	47.9 (46.6)	70.6 (41.4)	0.004
Energy/fatigue	42.8 (22.0)	55.0 (24.3)	0.006
Emotional wellbeing	62.2 (22.4)	75.9 (17.6)	<0.001
Social functioning	58.0 (28.5)	76.6 (25.6)	<0.001
Pain	45.0 (24.7)	62.2 (26.5)	<0.001
General health	44.7 (20.7)	61.1 (20.0)	<0.001

*One-way analysis of variance for continuous data, and χ^2 for categorical data.
BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; MC, microscopic colitis; MC-NOS, microscopic colitis, not otherwise specified; NSAID, nonsteroidal anti-inflammatory drugs; PHQ-15, Patient Health Questionnaire 15; PPI, proton pump inhibitor; SD, standard deviation; SF-36, Short Form 36.

having received an effective therapy for MC, although rates of IBS-type symptoms were generally higher among those patients who reported that prescribed therapy was either ineffective or made their symptoms worse.

This study surveyed a large population of patients with a histological diagnosis of MC, and recruited only individuals accessing secondary care services, rather than patients with more complex conditions referred for a tertiary care opinion. As a result, these data are likely to be representative of, and generalizable to, usual clinical practice. A further novel aspect is that this study was conducted in the United Kingdom, a geographical region from where epidemiological data concerning MC are sparse. In addition, we report data from a large MC cohort and examine the impact of IBS-type symptoms on levels of anxiety, depression, somatization, and health-related quality of life in both male and female patients with MC, using validated questionnaires.

Weaknesses of this study include the fact that we used the Rome III criteria for IBS,[23] which have now been superseded by the Rome IV criteria,[2] but this was unavoidable as our study was designed and commenced before the publication of the Rome IV criteria. In addition, we included individuals diagnosed with MC from 2010 onwards, and therefore recall bias may have affected the reporting of medication use and some of the other data we collected. However, the validated symptom and mood questionnaires we used do require contemporaneous answers. Data were not available regarding the results of investigations to exclude other causes of IBS-type symptoms, where these were requested. This means we cannot exclude the possibility that some individuals who reported these symptoms had an organic explanation, such as small intestinal bacterial overgrowth or bile salt malabsorption, both of which may present with symptoms that can be confused with diarrhoea-predominant IBS.[28–30] Participants in the study responded to a postal

questionnaire. This may have introduced volunteer bias, where those choosing to take part were intrinsically different from those who did not return a questionnaire, and only one in three potential participants returned a questionnaire, which may limit generalizability. It may be that those with more severe symptoms, low mood, or poor quality of life were more likely to return a questionnaire, and this potential bias may have contributed to our findings. It may also be that patients with MC with psychological comorbidity, such as anxiety, depression, and somatoform behaviour are more likely to report GI symptoms, and that this explains our findings. Studies that also recruit controls without psychological comorbidity would be required to examine this issue. Our study was limited by the lack of a control group, meaning we were unable to compare the levels of psychological comorbidity and impaired quality of life we observed. Finally, these symptoms may be a consequence of ongoing inflammation, although there was no significant difference seen with respect to the reported effectiveness of drug therapy received for MC between individuals with and without IBS-type symptoms.

Given the average age of over 60 years in our study population, it may be that other comorbidities have impacted on quality of life measures, although there should be no particular reason why these should affect the two groups of patients, with or without IBS-type symptoms, unequally. Furthermore, the trend towards individuals reporting IBS-type symptoms more frequently using PPI therapy could represent an important confounding factor, in terms of risk of developing MC. Colonic biopsy specimens were reviewed by several different GI pathologists, as this study was conducted in routine clinical practice, meaning that interobserver variability in the diagnosis of MC may have been introduced into the study. However, other investigators have demonstrated that there is little interobserver variability in the diagnosis of MC.[20] Finally, we did not collect MC disease activity data using a validated tool, such as the recently proposed MC disease activity index, as this was not available when this study was designed.[31] Therefore, we cannot exclude that the high prevalence of IBS-type symptoms observed in this group of patients was attributable to active MC, particularly given the fact that a diagnosis of IBS can only be given after exclusion of known structural causes of lower GI symptoms. This implies that symptoms of MC in general, rather than the fact that these are compatible with IBS, impacts negatively on mental health and quality of life.

Data on the impact of MC on quality of life have been reported both in clinical trials[16,17,32] and cross-sectional surveys.[14,15] Of these studies, three used the SF-36 questionnaire in individuals with MC and in healthy controls matched for age and sex.[14,17] Miehlke and colleagues, in two randomized clinical trials, reported greater impairment across all domains of the SF-36 for both LC and CC,[17] and Hjortswang and colleagues demonstrated significantly lower scores across all domains except physical functioning for individuals with CC.[14] In terms of the impact on psychological health, we are not aware of any other studies using the validated HADS or PHQ-15 questionnaires to examine for anxiety, depression, or somatization respectively, although Nyhlin and colleagues included an assessment of disease-related worry, as part of the short health questionnaire, and identified significantly higher levels in those with MC compared with healthy controls.[15] Furthermore, Roth and colleagues assessed the levels of overall psychological wellbeing in female patients with MC but did not compare levels with healthy controls.[18]

The prevalence of IBS-type symptoms seen in our study is very similar to that reported by a previous meta-analysis,[9] which included four studies,[6,7,33,34] and demonstrated a pooled prevalence of 33.4% in 420 individuals with MC. It should be noted that in this meta-analysis, only the study by Gu and colleagues used the Rome III criteria to define IBS-type symptoms, as we did, but included a smaller number of individuals with MC.[33] Only one study has attempted to assess the prevalence, and impact, of IBS-type symptoms in MC in relation to psychological wellbeing.[18] Roth and colleagues identified a higher prevalence of IBS-type symptoms in MC of 55%, and demonstrated that affected patients also reported greater impairments in psychological wellbeing, but it should be noted that this was only performed in female patients, and the authors did not examine for the presence of symptoms of anxiety or depression specifically.[18]

Unlike in classical IBD, where faecal calprotectin has been used to stratify individuals into those with active or quiescent disease,[13] there is no comparable biomarker in MC. Previous cross-sectional studies

have used a measure of self-reported stool frequency in order to define active MC.[14,15] Individuals designated as having active disease reported significantly impaired quality of life compared with those in clinical remission, and patients felt to be in remission had similar quality of life scores to healthy controls.[14,15] However, neither of these studies examined the role of potential concurrent IBS in the included individuals, and given that approximately 50–60% of individuals were classified as having active disease based on stool frequency alone, some of these may have met criteria for IBS. Interestingly, Nyhlin and colleagues reported that even those with MC in clinical remission were more likely to describe ongoing symptoms of abdominal pain, nocturnal diarrhoea, arthralgia, and myalgia despite an improvement in bowel frequency,[15] suggesting that some individuals could either have been wrongly classified as being in remission, or may have had concomitant IBS-type symptoms or somatoform-type behaviour.

Therefore, although it is challenging to distinguish whether individuals with MC meeting criteria for IBS have symptoms due to active MC or true concomitant IBS-type symptoms, there appears to be a distinct subset of individuals who experience persistent, troublesome symptoms more than 12 months after diagnosis and treatment of MC. With this in mind, it is interesting to note that among those who received effective therapy for MC, although rates of IBS-type symptoms were generally lower, mood and quality of life scores were no better than among those who reported their therapy as being ineffective or having made their symptoms worse. The relatively low rates of patients (51%) who reported receiving treatment for their MC in this study probably relates to two issues. First, in the UK, many patients over the age of 50 years with a change in bowel habit towards looser stools are referred for urgent colonoscopy on a suspected lower GI cancer pathway. They usually have random colonic biopsies taken, but if they do not have colorectal cancer they are discharged from follow up back to their primary care physician. Second, it is our clinical experience that many patients with MC who are prescribed a drug implicated in the aetiology of the condition will respond to withdrawal of the drug, and not need a specific treatment for MC. Overall, this suggests that even among patients with MC who may be in clinical remission, almost one in three will still report IBS-type symptoms, and this impacts on psychological health and quality of life. The aetiology of symptoms other than diarrhoea, such as abdominal pain, in patients with MC is not clear but could relate to underlying active inflammation, as well as previous low-grade inflammation leading to altered neuromuscular function, as has been seen in postinfectious IBS,[35] diverticular disease,[36] and even in inactive IBD.[37] It is also interesting to note that we did not detect any association between evidence of macroscopic inflammation at the index colonoscopy, and presence of IBS-type symptoms. Strategies to identify and treat the underlying cause of these symptoms may have significant implications for reducing healthcare-related costs in patients with MC. Furthermore, the finding that approximately 40% of individuals had either borderline or abnormal levels of anxiety, and 20% had borderline or abnormal levels of depression, suggests that drugs that act on the gut–brain axis or psychological therapies, which are beneficial in functional GI disorders,[38,39] may be helpful in this group of individuals with MC.

In summary, one third of patients with MC reported IBS-type symptoms. Whether this is due to ongoing inflammation is unclear, although this was the case even among those whose symptoms of MC had been well controlled by drug therapy. Further research is required to determine the relationship between MC and IBS-type symptoms, especially in terms of identifying methods to distinguish symptoms of genuine IBS from those of MC at the time of initial presentation, as well as those related to recurrent active MC, or potential coexistent functional GI problems, which may require alternative treatment strategies. This could include the use of scoring systems to identify patients with diarrhoea who are more likely to have MC rather than IBS,[3,4] and who therefore need expedited colonoscopy to obtain random colonic biopsies, disease activity tools,[31] or novel biomarkers. Furthermore, whether MC impacts negatively on patients' lives in other ways, as seen with the debilitating fatigue described in the other inflammatory bowel diseases,[40,41] requires investigation in the future.

Acknowledgements

JSK is guarantor. Specific author contributions: JSK and ACF devised the study. OR provided access to the histopathology database. JSK, AJI and YD conducted the data collection. JSK and ACF drafted the manuscript. All authors

contributed to and approved the final draft of the manuscript.

Funding

This work was supported by an investigator-initiated grant from Dr Falk Pharma UK Ltd (grant number: 108649).

Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

JohnS.Kane https://orcid.org/0000-0003-1066-2115

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