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Diagnostic Yield of Colonoscopy in Patients with Symptoms Compatible with Rome IV Functional Bowel Disorders

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Short title: Colonoscopy in Functional Bowel Disorders

Diagnostic Yield of Colonoscopy in Patients with Symptoms Compatible with Rome IV Functional Bowel Disorders

ABSTRACT

Background: There is little data on the diagnostic yield of colonoscopy in patients with symptoms compatible with functional bowel disorders (FBDs). Previous studies have only focused on diagnostic outcomes of colonoscopy in those with suspected irritable bowel syndrome using historic Rome I-III criteria, whilst having partially assessed for alarm features and shown markedly conflicting results. There is also no colonoscopy outcome data for other FBDs, such as functional constipation or functional diarrhea.

Aims: Using the contemporaneous Rome IV criteria we determined the diagnostic yield of colonoscopy in patients with symptoms compatible with a FBD, stratified diligently according to the presence or absence of alarm features

Methods: Basic demographics, alarm features, and bowel symptoms using the Rome IV diagnostic questionnaire were collected prospectively from adults attending out-patient colonoscopy in 2019. Endoscopists were blinded to the questionnaire data. Organic disease was defined as the presence of inflammatory bowel disease, colorectal cancer, or microscopic colitis.

Results: 646 patients fulfilled symptom-based criteria for the following Rome IV FBDs: IBS (56%), functional diarrhea (27%) and functional constipation (17%). Almost all had alarm features (98%). The combined prevalence of organic disease was 12%, being lowest for functional constipation and IBS-constipation (~6% each), followed by IBS-mixed (~9%), and highest amongst functional diarrhea and IBS-diarrhea (~17% each); p=0.005. The increased prevalence of organic disease in diarrheal versus constipation disorders was accounted for by microscopic colitis (5.7% vs. 0%, p<0.001) but not inflammatory bowel disease (7.2% vs. 4.0%, p=0.2) or colorectal cancer (4.2% vs. 2.3%, p=0.2). However, one-in-four chronic diarrhea patients - conceivably at risk for microscopic colitis - did not have colonic biopsies taken. Finally, only 11 of 646 (2%) patients were without alarm features, in whom colonoscopy was normal.

Conclusion: Most patients with symptoms of FBDs who are referred for colonoscopy have alarm features. The presence of organic disease is significantly higher in diarrheal versus constipation disorders, with microscopic colitis largely accounting for the difference whilst also being a missed diagnostic opportunity. In those patients without alarm features, the diagnostic yield of colonoscopy was nil.

Key words: Colonoscopy; Functional Bowel Disorders; Rome criteria; Microscopic colitis; Inflammatory Bowel Disease; Colorectal Cancer

WHAT YOU NEED TO KNOW

BACKGROUND

The diagnostic yield of colonoscopy in patients with symptoms compatible with functional bowel disorders (FBDs) is limited and with discrepant outcomes. This diagnostic confusion may be attributed to minimal assessment of alarm features.

FINDINGS

Most patients with symptoms of FBDs who are referred for colonoscopy have alarm features. The presence of organic disease at colonoscopy is significantly higher in diarrhoeal versus constipation disorders, largely accounted for by microscopic colitis although it remains frequently overlooked. In those without alarm features, the diagnostic yield of colonoscopy was nil.

IMPLICATIONS FOR PATIENT CARE

This study highlights the yield of colonoscopy in patients with symptoms compatible with a Rome IV functional bowel disorder, with and without alarm features.

Introduction: Functional bowel disorders (FBDs) is an umbrella term for a group of conditions characterised by chronic lower gastrointestinal symptoms that occur in the absence of organic disease.[1] The lower gastrointestinal symptoms include diarrhea, constipation, abdominal pain, and bloating or distension. Based on the symptom pattern, FBDs can be subdivided under the contemporaneous Rome IV classification into one of six diagnoses: irritable bowel syndrome (IBS), functional constipation (FC), functional diarrhea (FD), functional abdominal bloating/distension, opioid induced constipation, and unspecified functional bowel disorder.[1] Those with IBS can be further stratified into predominant diarrhea (IBS-D), constipation (IBS-C), and mixed bowel habits (IBS-M).[1] A recent large epidemiological study has shown that one-in-four adults fulfil symptom based criteria for a Rome IV FBD, of which the vast majority are accounted for by IBS, FD and FC.[2] These highly prevalent disorders are common in young to middle aged adults, in particular women, and significantly disrupt quality of life.[3] As such, patients commonly seek healthcare advice, with FBDs (such as IBS) accounting for at least a third of all gastroenterology cases seen in primary care, with a subsequent third of these being referred onto secondary care for further evaluation.[3] Hence, the economic burden of FBDs is considerable,[4] and of importance towards reducing health care costs within clinical practise is making a timely diagnosis without recourse to expensive and invasive tests.[5]

A diagnosis of a FBD can be made in patients with compatible symptoms and who have had organic diseases excluded.[1] Examples of organic diseases which can mimic FBDs and be detected by colonoscopy include colorectal cancer, inflammatory bowel disease and - in those with diarrhea - also microscopic colitis. However, given that FBDs are extremely common (relative to the aforementioned colonic pathologies) a clinical conundrum is to avoid over-investigating and inappropriately subjecting all patients with suspected FBDs to a colonoscopy as it is a costly, difficult procedure with appreciable risks.[5] In fact, it has historically been estimated that a third of potentially inappropriate colonoscopies are undertaken in patients with FBDs, such as IBS.[6,7] Hence, guidelines advocate a cost effective and judicious approach towards diagnosing FBDs, recommending that patients with compatible symptoms should initially be screened for "alarm features" - as listed in table 1 - prior to deciding on the need for further investigations.[1,8-11] Only individuals with alarm features need a colonoscopy to exclude organic disease before physicians commit to a diagnosis of a FBD. All other patients should be reassured, given a prompt diagnosis of a FBD, and avoid having colonoscopies.

Adhering to such guidelines seems logical, but its evidence base is in fact limited and with markedly conflicting data (detailed in Supplementary table A).[12-18] Previous studies, conducted in Asia and North

America, have solely focused on diagnostic outcomes of colonoscopy in those with suspected IBS using historic Rome I-III criteria, except for a study from Nepal which used the Rome IV criteria albeit before it had been translated and validated to non-English speaking languages. They also appear to have partially assessed for alarm features, such as failing to enquire about family history of GI cancer/inflammatory bowel disease and not performing laboratory tests for inflammation, leading to widely discrepant colonoscopy outcome data and subsequent clinical uncertainty. For example, the diagnostic yield of colonoscopy in suspected IBS subjects supposedly without alarm features is reported to be reassuringly low at 0% to a worrisomely high 15% (i.e. approximately one in seven), which in some instances was comparable to those with alarm features. Surprisingly, some groups also appear to have performed a greater proportion of colonoscopies in patients without alarm features than with alarm features, which is contrary to our own anecdotal clinical experience (Supplementary table A).[12-18] Finally, there is no colonoscopy outcome data for other FBDs, such as functional constipation or functional diarrhea, which have become increasingly prevalent following the recent publication of the Rome IV criteria and commonly seek healthcare.[2]

Thus, we aimed to perform the first study to evaluate the diagnostic yield of colonoscopy across the spectrum of FBDs whilst using the contemporaneous Rome IV criteria, and having stratified diligently in accordance with the presence or absence of alarm features. We hypothesised that most patients with suspected FBDs attending for colonoscopy will exhibit alarm features and have appreciable organic diseases to be found, whilst those without alarm features will be a minority and in whom the diagnostic yield of colonoscopy will be negligible.

Methods & Materials:

Study design and participants: This prospective cross-sectional study was undertaken at Sheffield Teaching Hospitals, United Kingdom, over an 8-month period between January to August 2019. The gastroenterology department is accredited by the national Joint Advisory Group for its high-quality gastrointestinal endoscopy services, and comprises 35 independent colonoscopists and performs around 8000 colonoscopies per year.

English-speaking adults aged ≥18 years referred by their secondary-care GI physician for an out-patient colonoscopy (excluding those as part of the national bowel cancer screening programme) were invited to self-complete a questionnaire at home enquiring for basic demographics, past gastrointestinal history, alarm symptoms, and bowel symptoms compatible with FBDs according to the Rome IV diagnostic questionnaire.[19] Patients were asked to return the questionnaire on the day of their colonoscopy, where clinical chart review and laboratory-based alarm features that had been requested at the discretion of the referring physician were also entered into the questionnaire template (see table 1). Colonoscopists were blinded to the questionnaire data, with organic disease being defined - following endoscopic and histological confirmation - as the presence of inflammatory bowel disease, colorectal cancer, or microscopic colitis.

Statistical analysis: The primary analysis determined the prevalence of alarm features, and diagnostic yield of colonoscopy, in patients who had symptoms compatible with a Rome IV FBD. In order to put these findings into context, we used those patients without symptoms compatible with a FBD as a comparative group.

The secondary analysis assessed the relative influence of individual alarm features on the diagnostic yield for organic disease in those with symptoms compatible with FBDs. This was executed using a multivariable logistic regression model, with all alarm features entered into the model as a single block. We also evaluated the diagnostic yield for organic disease following the accumulation of alarm features, with the latter arbitrarily stratified into no alarm features, few (1-2), and many (≥3) to provide adequate sample sizes for meaningful comparison. Finally, we assessed differences in the type of organic disease seen in younger patients compared with those ≥45 years.

Statistical analysis was carried out using SPSS version 25.0 software, with significance set at a p-value of <0.05. Categorical variables were summarized by descriptive statistics, including total numbers and percentages, with comparisons between groups performed using the chi-square test or exact fisher test. Continuous variables were summarized by mean and standard deviation, with difference

between two independent groups performed using the unpaired student T-test. Data following multivariable logistic regression analysis was presented as adjusted odds ratios, with 95% confidence intervals.

Results

Study participants

As shown in the study flow chart in figure 1 we sent out 3000 questionnaires of which 1329 were returned with complete data. We subsequently excluded 412 patients who had declared a pre-existing gastrointestinal condition (e.g. known inflammatory bowel disease/microscopic colitis/colorectal cancer/polyps) as that would potentially account for them being referred for a colonoscopy. This left 917 patients who were without pre-existing GI disease, of which 271 did not meet criteria for a Rome IV FBD whilst 646 had symptoms compatible with one of the following Rome IV FBDs; IBS (n=360), FD (n=177) and FC (n=109). Of the 360 patients with suspected IBS, 160 were IBS-D, 129 IBS-M, and 71 IBS-C.

Patient characteristics, prevalence of alarm features, and the diagnostic yield of colonoscopy

Patients attending for colonoscopy who had symptoms compatible with a Rome IV FBD were significantly more likely to be female (61% vs. 41%, p<0.0001) and of younger age (mean-age 55 yrs vs. 62 yrs, p<0.0001) compared with those not meeting criteria for a Rome IV FBD; table 2. The presence of at least one alarm feature was almost ubiquitous across both groups, although those without symptom criteria for a FBD were less likely to report weight loss or nocturnal symptoms but more likely to have iron deficiency anaemia. On reflection, this pattern is to be expected as relatively asymptomatic patients are commonly triaged for colonoscopy following routine annual medical reviews, which incidentally detects anaemia.

Probing specifically into those patients referred for a colonoscopy with symptoms compatible with a Rome IV FBD, almost all exhibited alarm features (n=635 of 646; 98%), and this was seen irrespective of the FBD subtype; see supplementary table B. The most common alarm features were age ≥45 years (75%), nocturnal symptoms (40%), rectal bleeding (33%), unintentional weight loss (24%) and family history of either GI cancer (19%) or IBD (6.5%); if age was removed as a criterion for an alarm feature then the other alarm features were still present in 86% of cases. Only 11 of 646 (2%) had no alarm features on either clinical or laboratory assessment.

With regards to the overall diagnostic yield of colonoscopy, there was a trend for a higher prevalence of organic disease in those with symptoms compatible with a Rome IV FBD compared to those without (12.2% vs. 8.1%, p=0.07). For individual organic diseases, a significantly higher prevalence of IBD (6.2% vs. 2.2%, p=0.012) and microscopic colitis (2.9% vs. 0%, p=0.004) was seen in those meeting criteria for a FBD, whilst colorectal cancer was less common (3.1% vs. 5.9%, p=0.046).

The diagnostic yield of colonoscopy in patients who have symptoms compatible with Rome IV FBDs, stratified according to the presence or absence of alarm features

In patients with symptoms compatible with Rome IV FBD who had alarm features, the diagnostic yield of colonoscopy for an organic disease was approximately 12% (n=79 of 635). However, difference in outcomes were noted according to the subtype of FBD, with the lowest prevalence of organic disease being for those with suspected functional constipation and IBS-constipation (~6% each), followed by IBS-mixed (~9%), and highest amongst functional diarrhea and IBS-diarrhea (~17% each); p=0.005. The increased prevalence of organic disease at colonoscopy in diarrheal versus constipation disorders was accounted for by microscopic colitis (5.7% vs. 0%, p<0.001) but not inflammatory bowel disease (7.2% vs. 4.0%, p=0.2) or colorectal cancer (4.2% vs. 2.3%, p=0.2); figure 2. On further scrutiny of the patients with chronic diarrhea (n=332), we assessed what proportion without IBD or colorectal cancer (n=38) had colonic biopsies taken for microscopic colitis; of 294 potential cases, colonic biopsies were obtained in 214 (73%) but not in 80 (27%) of cases. There was no difference in those who did and did not have biopsies taken, with regards to female gender (61% vs. 54%, p=0.3) and age ≥45 years (80% vs. 82%, p=0.7), both of which are recognized associations for microscopic colitis and suggest that in some it may have been a missed opportunity.[20] If we were to re-analyse the data in only those where colonic biopsies were taken then the prevalence of microscopic colitis increases from 5.7% (n=19/332) to 8.9% (n=19/214). Finally, of the 11 patients who were without alarm features, there was no organic disease seen at colonoscopy.

We next examined the relative influence of alarm features on the yield for organic disease at colonoscopy in patients with symptoms compatible with FBDs (table 3). Here we noted that, following multivariate analysis, the presence of rectal bleeding, abnormal physical examination, and raised inflammatory markers were all independent predictors of an organic disease, whilst other factors such as age, fevers, nocturnal symptoms, weight loss, family history of IBD or GI cancer, and anaemia were not.

We also examined the impact of accumulating alarm features on the diagnostic yield of colonoscopy for organic disease (Supplementary table C). As previously mentioned, 2% were without alarm features with the remaining 98% having alarm features that were sub-divided as being a few (47%) or many (51%). With the accumulation of alarm features, the likelihood of organic disease increased in a stepwise manner, going from 0% in those without alarm features, to 10% in those with a few alarm features, and reaching as high as 15% in those who had many alarm features (i.e. three or more).

The type of organic GI disease seen according to age category

We noted there to be a significant difference in the type of organic disease being seen in those under the age of 45 years compared with those over 45 years (figure 3). In the younger group who presented with symptoms compatible with a FBD, and were found to have an organic GI disease, the predominant disease subtype was IBD. In contrast, in the older group found to have organic disease there was a similar representation of approximately a third each of IBD, colon cancer, and microscopic colitis ($p < 0.0001$).

Discussion

By undertaking a large prospective study, whereby alarm features were thoroughly assessed using clinical criteria and laboratory tests, we addressed the uncertainty within the literature regarding to the diagnostic yield of colonoscopy for suspected FBDs. We have clarified the discrepant data that exists for IBS, whilst being the first study to provide outcomes in those with possible FC and FD, all of which was performed using the contemporaneous Rome IV criteria. We have shown that most patients with symptoms of FBDs who are referred for colonoscopy have alarm features, with the diagnostic yield of organic disease being approximately 12%. Moreover, the diagnostic yield of colonoscopy was lowest for disorders of constipation (~6%) and highest for diarrheal disorders (~17%), with the difference largely accounted for by microscopic colitis, and not by IBD or colorectal cancer. Yet, microscopic colitis remains potentially underestimated as 1-in-4 patients with chronic diarrhea did not have colonic biopsies taken. In the small cohort of patients without alarm features, the diagnostic yield for colonoscopy was nil. As a secondary analysis, we noted the relative influence of individual alarm features towards predicting subsequent organic disease at colonoscopy, with rectal bleeding/abnormal GI examination/ raised inflammatory markers carrying the greatest weight, although appreciably most will still have normal findings. We also observed a stepwise increase in diagnostic yield with the accumulation of alarm features. Finally, we showed that whilst age was not independently associated with organic disease, the subtype of organic disease varied according to age category, with IBD being the predominant organic disease seen in younger individuals, whereas in those over the age of 45 years there was a similar representation of IBD, colon cancer, and microscopic colitis

It can only be speculated as to why previous groups have had large proportions of patients with suspected IBS and no alarm features undergoing colonoscopy, and why their diagnostic yield for organic disease was markedly variable (Supplementary table A).[12-18] There may be differences in endoscopy referral patterns between countries, with our study being the first to be conducted within the United Kingdom which is a publically funded healthcare system, and this may not apply to those studies performed within North America. A potentially more plausible argument is that previous studies may have failed to comprehensively assess alarm features leading to incorrect assignment.[12-18] This assumption would be further supported by studies from elsewhere noting the vast majority of patients attending out-patient consultation clinics do have alarm features when thoroughly assessed.[21]

Nevertheless, we show that a small fraction of patients with symptoms compatible with FBDs and no alarm features will still undergo a colonoscopy despite the low diagnostic yield, and reasons for this

may include ongoing patient concerns. However, a study in 458 patients found no independent association between a negative colonoscopy and reassurance or improved health-related quality in IBS patients aged <50 years.[22] Similarly, a positive diagnostic strategy in those without alarm feature is non-inferior to a diagnosis of exclusion.[23] This type of clinical scenario may benefit from an alternate approach whereby having a simple diagnostic biomarker to "rule in" IBS or an alternate FBD will help eliminate any potential uncertainties and avoid unnecessary colonoscopic examinations. However, diagnostic biomarkers for this purpose are currently in the pipeline and require further validation.[24]

This study also highlights the importance of taking microscopic colitis into consideration in those with diarrheal symptoms who undergo colonoscopy. This is of increasing clinical relevance following the change in criteria from Rome III to Rome IV, whereby IBS-D now represents a third of all IBS subtypes, and FD has risen by almost five-fold within the general population.[2] We found that ~6% of patients with symptoms compatible with a diarrheal-type FBD had microscopic colitis, and this was similar for suspected IBS-D and FD. This important finding suggests that colonic biopsies should be taken in diarrheal cases irrespective of the presence or absence of frequent abdominal pain, the latter being the differentiating factor between IBS-D and FD using the stringent Rome IV criteria.[1] Previous studies using historic Rome criteria have reported a much lower prevalence of microscopic colitis (supplementary table A), which may be accounted for by potentially missing the opportunity to obtain colonic biopsies or diluting IBS-D patients alongside those with IBS-M.[12-18] In fact, a weakness of our study is that we may have also potentially underestimated the true prevalence of microscopic colitis, as a quarter of eligible cases did not have colonic biopsies taken; on re-analyses of the data the prevalence could be as high as ~9% instead of the ~6% quoted. Nevertheless, as this was a pragmatic study design whereby the need for biopsies was left to the discretion of the endoscopist, we feel that our findings convey day-to-day practise and can be generalised to other centres represented by a large and varied endoscopy workforce. Unfortunately, over-looking microscopic colitis is a recognised concern, with a third of cases having previously been misdiagnosed as IBS.[25,26] Hence, greater awareness and education is necessary, and hopefully our study sheds light on this.[26]. Moroever - whilst outside the scope of this paper - there are non-colonic disorders that should be taken into consideration in patients with chronic diarrheal disorders such as coeliac disease and idiopathic bile acid diarrhea which account for roughly 4% and 25% of cases, respectively.[27,28] Another limitation is that the presence of alarm features (e.g. anaemia, unintentional weight loss) was collected as binary outcome data, and it would have also been useful to collect data according to different threshold levels to help further optimize predicting organic disease at colonoscopy. Finally, our study was

performed in secondary care and the findings may not be applicable outside these clinical settings (e.g. general population).

In conclusion, this prospective study reveals that most patients with symptoms of FBDs who are referred for colonoscopy have alarm features. The presence of organic disease in this cohort ranges from 6% in constipation to 17% in diarrheal disorders. However, in those with chronic diarrheal disorders, greater awareness of microscopic colitis is needed. Very few patients undergo colonoscopy without alarm features and in these no organic disease was seen.

Table 1: Alarm features in subjects with lower gastrointestinal symptoms that should prompt colonic investigations for organic disease

| |
|---|
| Age of symptom onset ≥ 45 years |
| Recent change in bowel habit |
| Rectal bleeding in the absence of documented bleeding haemorrhoids or anal fissures |
| Unintentional weight loss |
| Nocturnal bowel symptoms |
| Family history of colorectal cancer or inflammatory bowel disease |
| Abnormal GI examination (i.e. palpable abdominal/rectal mass or lymphadenopathy) |
| Evidence of iron deficiency anaemia on blood testing |
| Evidence of inflammation on blood or stool testing |

Figure 1: Study flow chart
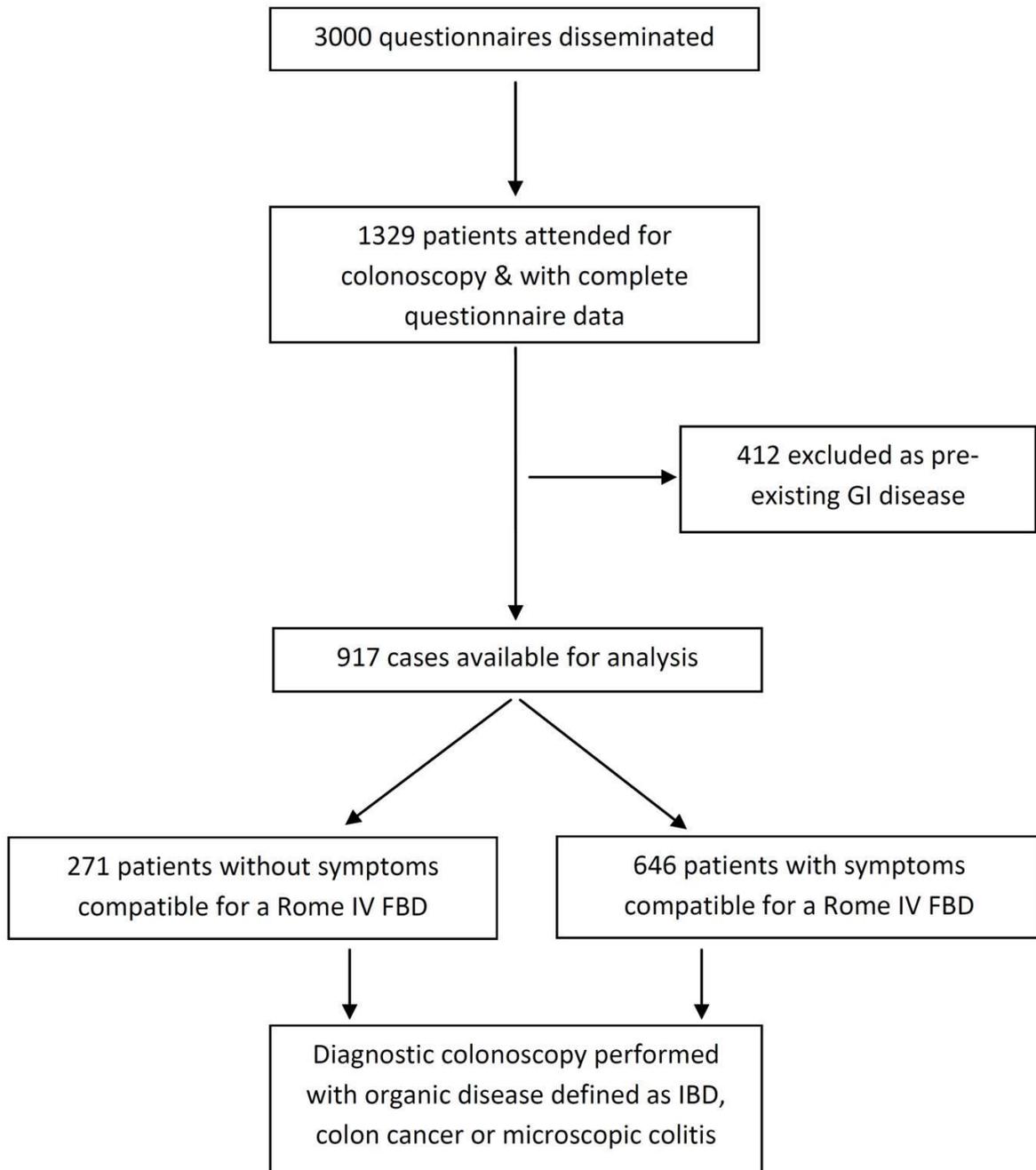
Table 2: Basic characteristics, alarm features, and diagnostic yield of colonoscopy in patients with and without symptoms compatible for a Rome IV FBD

	Symptoms not compatible with a Rome IV FBD (n=271)	Symptoms compatible with a Rome IV FBD (n=646)	P-value
Demographics			
Female	112 (41%)	391 (61%)	<0.0001
Mean age (SD)	62 (13.6)	55 (17)	<0.0001
White	249 (92%)	598 (93%)	0.98
Alarm Features			
Age ≥ 45 years	241 (89%)	483 (75%)	<0.0001
Unintentional weight loss	36 (13%)	152 (24%)	<0.0001
Nocturnal symptoms	25 (9%)	258 (40%)	<0.0001
Rectal bleeding	78 (29%)	215 (33%)	0.18
Fevers	7 (2.6%)	49 (8%)	0.004
Family history of GI cancer	63 (23%)	125 (19%)	0.18
Family history of IBD	7 (2.6%)	42 (6.5%)	0.02
Abnormal GI examination	11 (4%)	24 (3.7%)	0.35
Iron deficiency anaemia	106/244 (43%)	138/633 (22%)	<0.0001
Raised inflammatory markers (serum/stool)	79/171 (46%)	251/534 (47%)	0.85
Presence of any alarm feature	271 (100%)	635 (98%)	0.03
Diagnostic yield of colonoscopy			
IBD	6 (2.2%)	40 (6.2%)	0.012
Microscopic colitis	0 (0%)	19 (2.9%)	0.004
Colorectal cancer	16 (5.9%)	20 (3.1%)	0.046
Any of the above organic diseases	22 (8.1%)	79 (12.2%)	0.07

Figure 2: Diagnostic yield of colonoscopy in patients with symptoms compatible with Rome IV FBDs and exhibiting alarm features
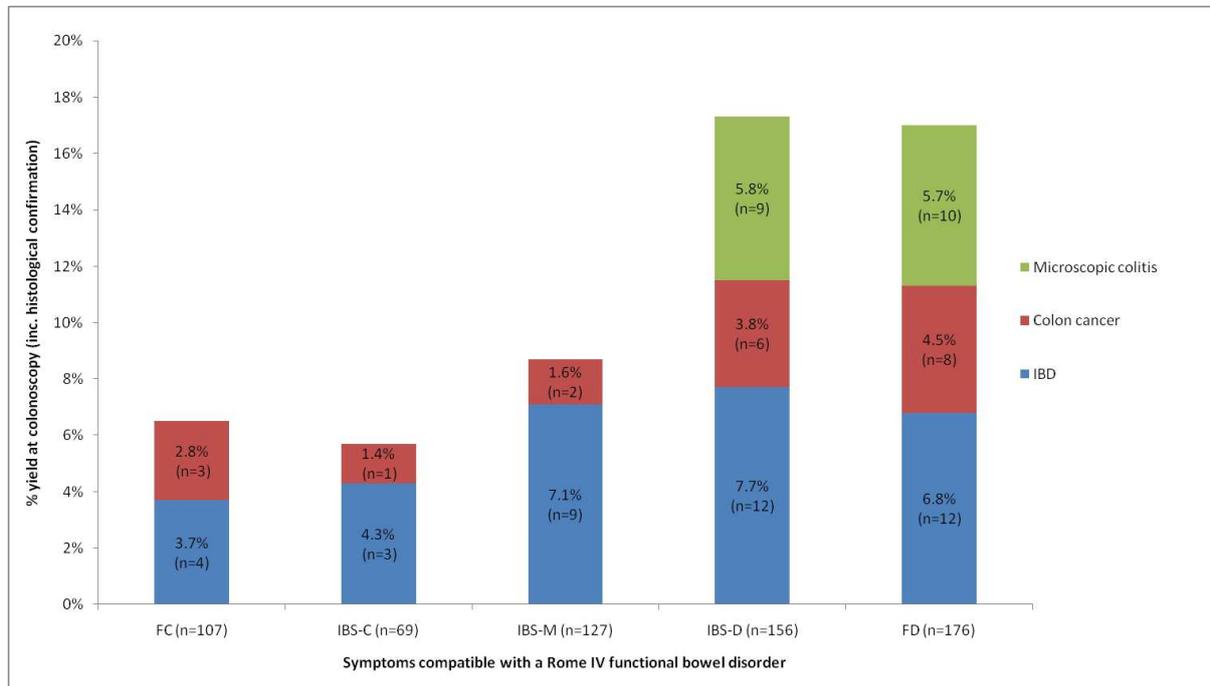
Table 3: Relative influence of alarm features on the likelihood of organic disease at colonoscopy in patients presenting with symptoms compatible with a Rome IV FBD (n=646)

	Organic disease at colonoscopy	Unadjusted OR (95% C.I)	Adjusted OR (95% C.I)
Age ≥45 years, (n=483)	51 (10.6%)	0.6 (0.35-0.9)	0.8 (0.5-1.5)
Unintentional weight loss, (n=152)	19 (12.5%)	1.0 (0.6-1.8)	0.9 (0.5-1.6)
Nocturnal symptoms, (n=258)	40 (15.5%)	1.6 (1.02-2.6)	1.4 (0.8-2.4)
Rectal bleeding, (n=215)	38 (18%)	2.0 (1.3-3.3)	1.8 (1.0-3.0)
Fevers, (n=49)	5 (10%)	0.8 (0.3-2.1)	0.6 (0.2-1.6)
Family history of GI cancer, (n=125)	10 (8%)	0.6 (0.3-1.1)	0.5 (0.2-1.2)
Family history of IBD, (n=42)	5 (12%)	0.97 (0.37-2.5)	0.9 (0.3-2.6)
Abnormal GI examination, (n=24)	8 (33%)	3.8 (1.6-9.4)	4.3 (1.5-12.2)
Iron deficiency anaemia, (n=138)	20 (14.5%)	1.2 (0.7-2.2)	1.3 (0.7-4.2)
Raised inflammatory markers (serum/stool), (n=251)	49 (19.5%)	2.6 (1.6-4.4)	2.4 (1.4-4.2)

Figure 3: The type of organic disease at colonoscopy in patients under and over the age of 45 years
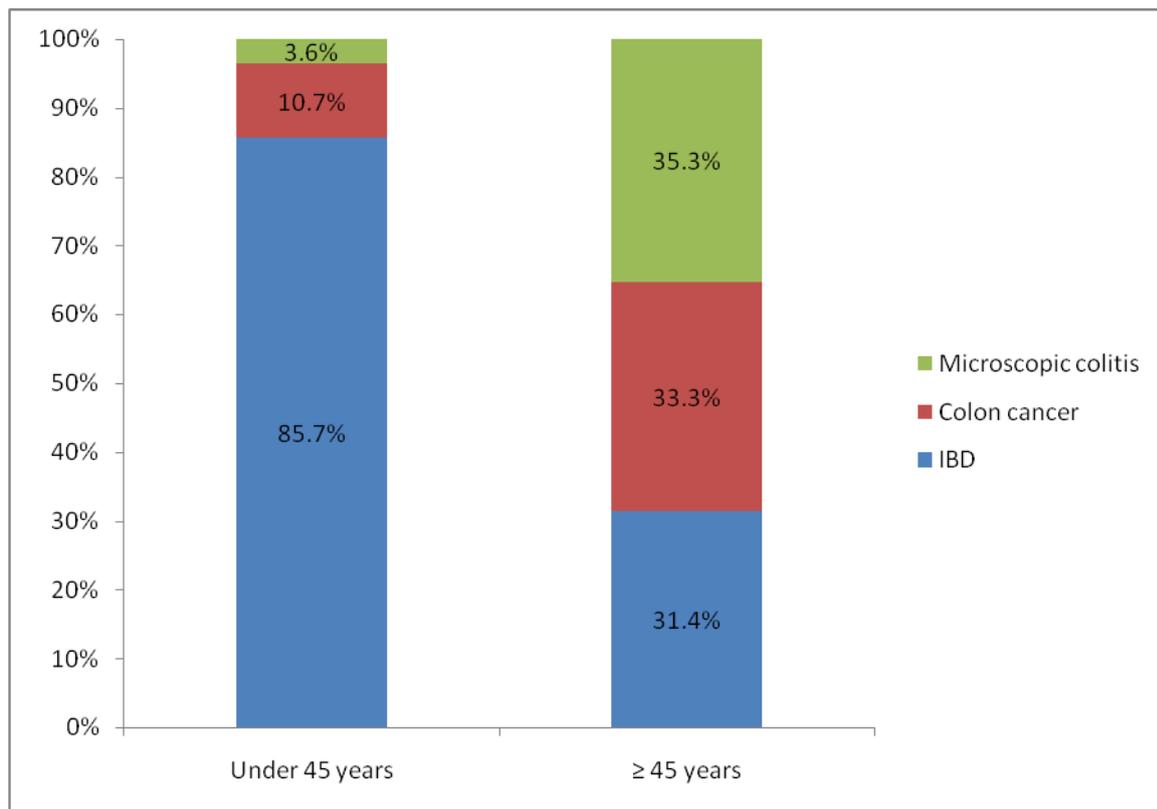
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Supplementary Table A: Studies evaluating diagnostic yield of colonoscopy in patients with symptoms compatible with a functional bowel disorder

Author, (Year) Country, Design, Criteria	Number of cases			Alarm features	FBD	Diagnostic yield for inflammatory bowel disease (IBD), colorectal cancer (CRC), and microscopic colitis (MC)		
	Total	With alarm features	Without alarm features			Overall	With alarm features	Without alarm features
Paudel et al[12] (2018) Nepal, Prospective Single centre, Rome IV	140	0 (0%)	140 (100%)	- Onset at >50 years of age - Weight loss - Blood in stool - Family history of IBD	IBS	N/A	N/A	IBD (2.1%), CRC (0.7%), MC (0.7%), total (3.5%)
Patel et al[13] (2015), Canada, Prospective, Dual centre, Rome III	559	423 (76%)	136 (24%)	- Weight loss >4.5kg in last yr - Blood in stools - Whether a doctor had told them they were anaemic - Family history of CRC	IBS IBS-D IBS-M IBS-C	IBD (19%), CRC (3%), MC (2%), total (24%) IBD (24%), CRC (2%), MC (4%), total (30%) IBD (18%), CRC (3%), MC (2%), total (23%) IBD (8%), CRC (3%), MC (0%), total (11%)	IBD (22%), CRC (3%), MC (2%), total (27%) IBD (28%), CRC (3%), MC (4%), total (35%) IBD (21%), CRC (3%), MC (2%), total (26%) IBD (7%), CRC (5%), MC 0%), total (12%)	IBD (10%), CRC (1%), MC (2%), total (13%) IBD (11%), CRC (0%), MC (4%), total (15%) IBD (10%), CRC (2%), MC (2%), total (14%) IBD (10%), CRC (0%), MC (0%), total (10%)
Ishihara et al[14] (2012), Japan, Prospective, Multi centre, Rome III	203	58 (29%)	145 (71%)	- Age ≥ 50 years	IBS	CRC (2.5%), IBD (3.4%), total (5.9%)	IBD (0.7%), CRC (3.4%), total (4.1%)	IBD (10.3%), CRC (0%), total (10.3%)
Gu et al [15] (2011) China Retrospective Single centre, Rome III	2323	0 (0%)	2323 (100%)	- Rectal bleeding - Anaemia - Weight loss - Fever -Family history of CRC - Onset at >50 years of age	IBS	N/A	N/A	IBD (6.9%) CRC (0.2%), total (7.1%)
Chey et al[16] (2010), USA, Prospective, Multi centre, Rome III	466	0 (0%)	466 (100%)	-Unexplained weight loss (10lb over 6 months) - Fever - Blood in stools - Family history of CRC, celiac disease and IBD	IBS-M/ IBS-D	N/A	N/A	IBD (0.4%), CRC (0%), MC (1.5%), total (1.9%)

Akhtar et al[17] (2006), USA, Retrospective Single centre, Rome I-II	622	622 (100%)	0 (0%)	- Change in character and intensity of abdominal pain - Persistent diarrhea, especially nocturnal - Change in bowel habits - Blood in stools - weight loss - anaemia - Non-specific symptoms not responding to therapy	IBS	N/A	IBD (7.6%), CRC (4.2%), MC (2.6%), total (14.4%)	N/A
Vanner et al[18] (1999) Canada, Retrospective, Single centre, Rome I-II	86	56 (65%)	30 (35%)	-Relevant abnormalities on physical examination - Documented weight loss - Nocturnal symptoms - Blood in stools - History of antibiotic use - Family history of CRC	IBS	IBD (3.5%), CRC (1.2%), total (4.7%)	IBD (5.4%), CRC (1.8%), total (7.2)	IBD (0%), CRC (0%), total (0%)

Supplementary Table B: Basic characteristics and the presence of alarm features in patient with symptoms compatible with Rome IV FBDs

	Total (n=646)	IBS (n=360)	IBS-C (n=71)	IBS-M (n=129)	IBS-D (n=160)	FD (n=177)	FC (n=109)
Demographics							
Female	391 (61%)	245 (68%)	50 (70%)	88 (68%)	107 (67%)	84 (48%)	62 (57%)
Mean age (SD)	55 (17)	51 (18)	52 (19)	49 (19)	52 (16)	60 (14)	62 (14)
White	598 (93%)	327 (91%)	117 (91%)	117 (91%)	151 (94%)	167 (94%)	104 (95%)
Alarm features							
Age ≥ 45 years	483 (75%)	234 (65%)	47 (66%)	81 (63%)	106 (66%)	155 (88%)	94 (86%)
Unintentional weight loss	152 (24%)	99 (28%)	18 (25%)	37 (29%)	44 (28%)	36 (20%)	17 (16%)
Nocturnal symptoms	258 (40%)	197 (55%)	27 (38%)	72 (55%)	99 (62%)	51 (29%)	10 (9%)
Rectal bleeding	215 (33%)	134 (37%)	23 (32%)	58 (42%)	53 (33%)	51 (29%)	30 (27.5%)
Fevers	49 (8%)	40 (11%)	7 (10)	18 (14%)	15 (9%)	4 (2%)	5 (5%)
Family history of GI cancer	125 (19%)	71 (20%)	14 (20%)	24 (19%)	33 (21%)	34 (19%)	20 (18%)
Family history of IBD	42 (6.5%)	29 (8%)	2 (3%)	15 (12%)	12 (7.5%)	7 (4%)	6 (5.5%)
Abnormal GI examination	24 (3.7%)	10 (2.8%)	1 (1.4%)	3 (2.3%)	6 (3.8%)	8 (4.5%)	6 (5.5%)
Iron deficiency anaemia	138/633 (22%)	61/358 (17%)	11/71 (15.5%)	25/127 (20%)	25/160 (16%)	41/172 (24%)	36/103 (35%)
Raised inflammatory markers (serum/stool)	251/534 (47%)	157/319 (49%	23/60 (38%)	66/119 (55.5%)	68/140 (49%)	63/143 (44%)	31/72 (43%)
Presence of any alarm feature	635 (98%)	352 (98%)	69 (97%)	127 (98%)	156 (98%)	176 (99%)	107 (98%)

Footnote: The column for IBS (n=360) is data accumulated across the columns for IBS-C (n=71), IBS-M (n=129) and IBS-D (n=160)

Supplementary Table C: Diagnostic yield of colonoscopy in subjects with symptoms compatible with FBDs (n=646) according to the number of alarm features

Number of alarm features	Number of patients	Diagnostic yield of colonoscopy (%)	P-value
0 (none)	11	0 (0%)	
1-2 (few)	307	30 (10%)	0.03
≥3 (many)	328	49 (15%)	