Article:
Kamp, EJ, Kane, JS and Ford, AC (2016) Irritable Bowel Syndrome and Microscopic Colitis: A Systematic Review and Meta-Analysis. Clinical Gastroenterology and Hepatology, 14 (5). pp. 659-668. ISSN 1542-7714

https://doi.org/10.1016/j.cgh.2015.09.031

Title: Irritable Bowel Syndrome and Microscopic Colitis: Systematic Review and Meta-analysis.

Short "running" title: IBS and Microscopic Colitis: Meta-analysis.

Authors: Eline J.C.A. Kamp[1], John S. Kane MBChB, MRCP[2, 3], Alexander C. Ford MBChB, MD, FRCP[2, 3].

[1]Radboud UMC, Radboud University, Nijmegen, The Netherlands.

[2]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

[3]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.

Grant support: None.

Abbreviations:

CC	collagenous colitis
CI	confidence interval
GI	gastrointestinal
IBS	irritable bowel syndrome
LC	lymphocytic colitis
MC	microscopic colitis
OR	odds ratio

Correspondence: Dr. Alex Ford

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +441132684963

Facsimile: +441132429722

Word count: 5803

Disclosures: EJCAK: none to declare. JSK: none to declare. ACF: none to declare.

Writing assistance: None

Author contributions: EJCAK, JSK, and ACF conceived and drafted the study. EJCAK and ACF collected all data. EJCAK and ACF analyzed and interpreted the data. EJCAK , JSK, and ACF drafted the manuscript. All authors contributed to and approved the final draft of the manuscript.

ABSTRACT

Objectives: Microscopic colitis (MC) and irritable bowel syndrome (IBS) share similar presenting symptoms. We examined the association between IBS and MC in a systematic review and meta-analysis.

Methods: We searched the medical literature to identify cross-sectional surveys or case-control studies reporting the association between MC and IBS in ≥50 unselected adult patients. We recorded the prevalence of IBS symptoms in patients with histologically confirmed MC, or the prevalence of histologically confirmed MC in patients with IBS. Data were pooled using a random effects model, and the association between MC and IBS was summarized using an odds ratio (OR) with a 95% confidence interval (CI).

Results: The search strategy identified 3,926 citations, of which 10 were eligible. The pooled prevalence of IBS in patients with MC was 33.4% (95% CI 31.5%-40.6%), but was not significantly higher in patients with MC than other patients with diarrhea (OR = 1.39; 95% CI 0.43-4.47). In three cross-sectional surveys, the pooled OR for MC in participants with IBS, compared with other patients with diarrhea, was 0.68 (95% CI 0.44-1.04). In four case-control studies prevalence of IBS in patients with MC was significantly higher than in asymptomatic controls (OR = 5.16; 95% CI 1.32-20.2).

Conclusions: One-third of MC patients reported symptoms compatible with IBS, but prevalence of IBS was no higher than other patients with diarrhea. Odds of MC were no higher in patients with IBS compared with other patients with diarrhea. The value of routine colonoscopy and biopsy to exclude MC in patients with typical IBS symptoms, unless other risk factors or alarm symptoms are present, remains uncertain based on this meta-analysis.

Keywords: diarrhea; irritable bowel syndrome; collagenous colitis; lymphocytic colitis; abdominal pain.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional disorder of the gastrointestinal (GI) tract characterized by abdominal pain or discomfort and altered bowel habit. [1] It is one of the most commonly diagnosed functional GI disorders, affecting approximately 10% of the general population, [2] and with a female predominance in most studies. [3] The condition can be associated with significant emotional distress, impaired health-related quality of life, disability, and high health care costs. [4-7] No known structural or anatomical explanation accounts for the pathophysiology of IBS, although several mechanisms have been proposed, including low-grade mucosal inflammation, visceral hypersensitivity, alterations in fecal flora, and bacterial overgrowth. [8-11]

Management guidelines for IBS recommend that a positive diagnosis is made using symptom-based diagnostic criteria, [12, 13] in an attempt to minimize fruitless and repeated invasive investigation. The current gold-standard for diagnosing IBS are the Rome III criteria, [1] but their accuracy has only been assessed in one study to date, [14] and their performance in predicting IBS was modest. In recent years, interest in the potential for a missed organic GI diagnosis in patients with suspected IBS has increased. Previous studies have suggested that symptoms compatible with IBS may co-exist in patients with several organic GI diseases, such as inflammatory bowel disease, coeliac disease, or bile acid diarrhea, [15-17] and that some patients who meet criteria for IBS may have one of these underlying organic diseases. [18-21]

Microscopic colitis (MC) consists of two primary subtypes: collagenous and lymphocytic colitis. Collagenous colitis (CC) differs from lymphocytic colitis (LC) in that it presents a sub-epithelial collagen band adjacent to the basal membrane, whereas the hallmark of LC is a dense lymphocytic infiltration in the epithelium. The condition is commoner in women, [22] is a frequent cause of an altered bowel habit towards looser stools, [23, 24] and is often accompanied by abdominal pain. [25-27] The incidence of MC has been reported as 2.6 to 21.0

per 100,000 per year. [28-30] It has three key elements: a clinical history of chronic watery diarrhea, normal or almost normal macroscopic appearances of the colon at colonoscopy, and a distinct histological pattern. [31]

Microscopic colitis and IBS may therefore share similar presenting symptoms and in both conditions the mucosa at colonoscopy is normal. Treatment options for these conditions are quite different, so making a prompt diagnosis of MC has important management implications. The aim of this systematic review and meta-analysis was to examine the prevalence of IBS in individuals with histologically confirmed MC, as well as the prevalence of histologically confirmed MC in patients with IBS.

METHODS

Search strategy and study selection

A search of the medical literature was performed using MEDLINE (1946 to 1st May 2015), EMBASE (1974 to 1st May 2015), EMBASE Classic, Web of Science, and the Cochrane library to identify all publications reporting the association between IBS and MC. Included studies recruited ≥50 unselected adults (>18 years), and had to report either the prevalence of IBS symptoms in patients with histologically confirmed MC, or the prevalence of histologically confirmed MC in patients with IBS (see Box 1).

For studies that reported the prevalence of IBS in patients with MC, individuals had to report symptoms compatible with IBS according to the Manning, [32] Kruis, [33] Rome I, [34] II, [35] or III criteria, [1] and have a confirmed histological diagnosis of MC after examination of colonic biopsies. Studies could be case series, case-control studies, or cross-sectional surveys, but those reporting the prevalence of IBS before a diagnosis of MC was established were not eligible for inclusion. Controls in these studies, where enrolled, were individuals undergoing complete colonoscopy and without MC after histological interpretation of colonic biopsies.

For studies reporting the prevalence of MC in patients with IBS according to the Manning, Kruis, Rome I, II, or III criteria, complete colonoscopy and colonic biopsies had to be performed in all recruited individuals. Case series were ineligible for these analyses, as we felt that such studies would recruit highly selected groups of atypical patients meeting criteria for IBS and would overestimate the prevalence of MC in IBS. Therefore eligible studies could only be of a case-control or cross-sectional design. Controls in these studies were required to be individuals who did not meet criteria for IBS who were also undergoing complete colonoscopy, and in whom colonic biopsies were obtained.

The medical literature was searched using the following terms: irritable bowel syndrome, spastic colon, irritable colon, functional adj5 bowel, Manning, Rome 1, Rome I, Rome 2, Rome II, Rome 3, Rome III, and Kruis. These were combined using the set operator "OR". Studies relevant to MC were identified using the following terms: microscopic colitis, lymphocytic colitis, collagenous colitis, and colitis. Again, these were combined together using the set operator "OR". These two searches were then combined using the "AND" set operator. There were no restrictions according to publication status, or language.

All articles were assessed for relevance to the study question and potentially relevant papers were retrieved and examined in more detail. All abstracts of the identified articles were screened and evaluated. A recursive search of the reference lists of all relevant papers and included articles was also conducted, and foreign language articles were translated, where required. Both screening of identified studies and assessment for eligibility were performed in duplicate by two investigators independently, using predesigned eligibility forms. Any disagreement between investigators was resolved by consensus.

Data extraction

Data were extracted independently by two investigators onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA) and discrepancies were resolved by consensus. For each eligible study, the following data were extracted: year of publication, country, setting, number of centers, study design (case series, cross-sectional survey or case-control study), and criteria used to define IBS.

For studies reporting the prevalence of IBS symptoms in patients with MC we recorded the number of participants with MC, and the number of controls without MC (where enrolled). We then calculated the prevalence of IBS symptoms in all subjects with MC and in

all controls without MC. This was also done separately for LC and CC, where individual studies reported these data.

For studies reporting the prevalence of MC in patients with IBS, we recorded the number of participants with IBS, and the number of subjects without IBS. We then extracted the prevalence of MC in those with IBS, and in those without IBS. Again, this was also done separately for LC and CC, where individual studies reported these data.

Quality assessment for case-control studies was performed using the Newcastle-Ottawa scale, [36] which judges quality based on the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest.

Data synthesis and statistical analysis

The degree of agreement between the two investigators, in terms of judging study eligibility, was measured using the Kappa statistic. The proportion of subjects with MC who reported IBS symptoms was combined to give a pooled prevalence of IBS for all patients with MC. We compared the prevalence of IBS symptoms in patients with MC, and those without MC, using an odds ratio (OR) and 95% confidence intervals (CI). We also examined the prevalence of MC in individuals with IBS, again with data combined to give a pooled prevalence. In addition, for cross-sectional surveys and case-control studies we compared the prevalence of MC in patients with IBS, and those without, using an OR and 95% CIs. These analyses were performed separately according to study type. If there were no subjects with MC in the control group of a single study, 0.5 was added to all four cells for the purposes of the analysis, as ORs cannot be calculated from zero values. We conducted a subgroup analysis including only patients with diarrhea-predominant IBS (IBS-D) to investigate whether this had any effect on the pooled prevalence of MC.

Heterogeneity between studies was assessed using the I^2 statistic with a cut-off of 50%, and the χ^2 test with a P value <0.10 used to define a statistically significant degree of heterogeneity. [37] Data were pooled using a random effects model, [38] to give a more conservative estimate of the prevalence of IBS in MC, and the prevalence of MC in patients with IBS. Stats-Direct version 2.7.2 was used to generate Forest plots of pooled prevalences and pooled ORs with 95% CIs. Evidence of publication bias was assessed for by applying Egger's test to funnel plots, [39] where a sufficient number of studies (≥10) were available. [40]

RESULTS

The search strategy yielded 3,926 citations (Figure 1), of which 57 potentially relevant articles were retrieved and assessed in more detail. Of these, 10 met our eligibility criteria and were included. [14, 41-49] There were two case-control studies that met all eligibility criteria, except for the fact that colonic biopsies were not obtained in controls, so these were ineligible for inclusion. [50, 51] Agreement between reviewers was excellent (Kappa statistic = 0.79). There were four studies reporting the prevalence of IBS symptoms in patients with MC, [41, 44, 48, 49] two of which were case series, [44, 48] one a case-control study, [49] and one a cross sectional survey. [41] There were three cross-sectional surveys reporting the prevalence of MC in patients with IBS, [14, 41, 42] one of which also reported the prevalence of IBS in patients with MC and was included in the aforementioned analysis. [41] Finally, there were four case-control studies reporting the prevalence of MC in patients with IBS. [43, 45-47] Quality assessment for all five case-control studies according to each of the domains of the Newcastle-Ottawa scale is provided in Supplementary Table 1.

Prevalence of IBS Symptoms in Patients with MC

Four studies, involving a total of 1,056 individuals, reported data on the prevalence of IBS in patients with MC. [41, 44, 48, 49] Detailed characteristics of these studies are provided in Table 1. To define IBS, three studies used the Rome II criteria, [44, 48, 49] and one used the Rome III criteria. [41] There were a total of 420 individuals with histologically confirmed MC recruited into these studies, and the pooled prevalence of IBS in all four studies was 33.4% (95% CI 17.2% to 52.0%), but with significant heterogeneity between studies (I^2 =93.6%, P < 0.001). With only four studies, it was not possible to conduct subgroups analyses to explore reasons for the observed heterogeneity. The prevalence of IBS in individual studies varied from 13.8% to 55.7%. Only one study reported the prevalence of IBS in patients with CC and

LC separately, which were 21.4% (6/28) and 11.5% (6/52), respectively.[41] We contacted authors of another two studies in order to try to obtain these data, but unfortunately these were not available. [48, 49]

Two of the four studies also reported the prevalence of IBS among other patients with diarrhea in whom random colonic biopsies were normal. [41, 49] These studies included a total of 218 patients with MC, of whom 85 (39.0%) had IBS, compared with 129 (20.3%) of 636 patients without MC. The pooled OR for IBS was not significantly higher in those with MC compared with those without (1.39; 95% CI 0.43 to 4.47). There were too few studies to assess for heterogeneity or evidence of publication bias.

Prevalence of MC in Patients with IBS Compared with Patients without IBS in Cross-sectional Surveys

There were a total of 1,758 participants in the three cross-sectional surveys that reported the prevalence of MC in patients with IBS. [14, 41, 42] Detailed characteristics of these studies are provided in Table 2. All studies used the Rome III criteria to define IBS, and all individuals underwent complete colonoscopy. Of the 1,758 patients who underwent a colonoscopy, there were 144 patients (8.2%) found to have MC after interpretation of colonic biopsy specimens. The pooled prevalence of MC among patients with IBS was 7.4% (95% CI 1.5% to 17.2%), but with significant heterogeneity between studies (I^2 = 90.9%, P < 0.001). The prevalence of MC in patients with IBS in individual studies varied from 2.4% to 11.5%. The pooled OR for MC in participants with IBS, compared with those without, was 0.68 (95% CI = 0.44 to 1.04) (Figure 2), with no significant heterogeneity between study results (I^2 = 0%, P = 0.88). There were too few studies to assess for evidence of funnel plot asymmetry.

All three studies reported the prevalence of MC in only the 397 patients with IBS-D. [14, 41, 42] The pooled prevalence for MC in patients with IBS-D was 8.3% (95% CI 3.5% to

15.0%), but with significant heterogeneity between studies (I^2 = 76.1%, P = 0.02). The proportion of subjects with IBS-D with MC ranged from 3.8% to 11.5% in individual studies. When all studies were pooled the OR for MC in those with IBS-D, compared with those without IBS symptoms, was 0.79 (95% CI 0.51 to 1.23), with no significant heterogeneity between studies (I^2 = 0%, P = 0.75). With only three studies, it was not possible to assess for publication bias.

Two of the three studies, containing a total of 1,655 participants, reported the prevalence of CC and LC in individuals with IBS and those without. [14, 41] The pooled prevalence of CC in 659 patients with IBS was 2.7% (95% CI 0.01% to 10.0%), and for LC it was 3.2% (95% CI 0.3% to 9.0%). The pooled OR for CC in participants with IBS, compared with those without, was 1.34 (95% CI 0.59 to 3.02), and the pooled OR for LC was lower at 0.49 (95% CI 0.26 to 0.93).

Prevalence of MC in Patients with IBS Compared with Patients without IBS in Case-Control Studies

The four case-control studies included a total of 604 subjects, 365 (60.4%) of whom were cases with IBS, and 239 controls without. [43, 45-47] Detailed study characteristics are provided in Table 3. Presence of IBS was confirmed using the Rome III criteria in three studies, [43, 45, 47] and the Manning criteria in the remaining study. [46] Controls had no history of IBS and were asymptomatic individuals who were undergoing colonoscopy for reasons not related to IBS, including investigation of anemia, functional dyspepsia, adenoma surveillance, or familial colorectal cancer screening. The pooled prevalence of MC in patients with IBS was 7.1% (95% CI 1.8% to 15.6%), but with significant heterogeneity between studies (I^2 = 80.3%, P = 0.002). The prevalence of MC in patients with IBS in individual studies varied from 1.4% to 23.3%. The pooled OR for MC was significantly higher in cases with IBS

compared with controls without (5.16; 95% CI 1.32 to 20.2) (Figure 3), with no significant heterogeneity between studies (I^2 = 0%, P = 0.88). There were too few studies to assess for evidence of funnel plot asymmetry.

All four studies reported the prevalence of MC in only those patients with IBS-D. [43, 45-47] There were 211 patients with IBS-D. The pooled prevalence of MC was higher than in all patients with IBS (9.2%; 95% CI 2.7% to 19.1%), but again with significant heterogeneity between the individual studies (I^2 = 77.0%, P = 0.005). In only cases with IBS-D, the pooled OR for MC was again higher compared with controls without (6.51; 95% CI 1.66 to 25.5). There was no significant heterogeneity detected between studies (I^2 = 0%, P = 0.57), but again there were too few studies to assess for evidence of funnel plot asymmetry.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis that has attempted to synthesize data from all available studies examining the association between IBS and MC in adults. We examined the prevalence of IBS in individuals with histologically confirmed MC, as well as the prevalence of histologically confirmed MC in patients with IBS. When data were pooled from four studies, one in three individuals with MC reported IBS symptoms. However, data from two case-control studies demonstrated that this was not significantly higher than the prevalence of IBS in individuals without MC. Data from three cross-sectional surveys demonstrated no increase in the odds of MC in patients with IBS compared with patients without, with no significant heterogeneity between studies. When CC and LC were considered separately, similar findings were observed, with non-significant ORs. In contrast, when data were pooled from the four case-control studies that reported the prevalence of MC in patients with IBS, the prevalence of MC was significant higher in cases with IBS compared with asymptomatic controls without IBS. When only patients meeting criteria for IBS-D were considered, the OR increased further.

In this systematic review and meta-analysis we carried out an exhaustive search strategy and a recursive search of the reference lists of all relevant papers and the selected articles, meaning that we were able to pool data from nearly 3,000 individuals. We defined clear inclusion criteria for the included studies, and both the screening process and data extraction were done in duplicate by two independent investigators. We also contacted the primary author of two studies in order to obtain extra information, but unfortunately the data of interest were not available. The studies were conducted in countries all over the world, so data can be applied to patients in different regions. Finally, we used a random effects model, instead of a fixed effects model, in order to provide a more conservative estimate of the prevalences and ORs.

It is necessary to consider the limitations of the present meta-analysis when interpreting the results. The number of available and eligible studies limited the ability to conduct exhaustive subgroup analyses, and therefore reasons for the significant heterogeneity detected between included studies in some analyses remain obscure. However, when comparing the prevalence of MC in patients with IBS or IBS-D with patients without IBS in cross-sectional surveys, there was no significant heterogeneity detected. The heterogeneity in other analyses may relate to a combination of geographical differences in the populations under study, characteristics of included individuals, and methodological differences between studies, such as inclusion and exclusion criteria. In addition, the patients were derived from secondary or tertiary care, which may not be representative of patients in the community. However, the results are likely to be generalizable to gastroenterologists consulting with patients with histologically-confirmed MC, or IBS, in usual clinical practice. Another limitation includes the fact that, in the cross-sectional surveys included in the meta-analysis, the decision to perform colonoscopy and obtain biopsies was at the discretion of the responsible physician. This could mean that there were certain features identified by the responsible physicians in the symptom history, such as older age group, recent onset of symptoms, or prescribed medications, or after physical examination that alerted them to a higher probability of MC. A final limitation is the quality of the eligible case-control studies, which was assessed according to the Newcastle-Ottawa scale, and was suboptimal (Supplementary Table 1).

As mentioned in the results, the large case-control study by Chey et al. was not included in our meta-analysis. This study investigated the diagnostic yield of colonoscopy and mucosal biopsy in patients with non-constipated IBS, [50] and reported that colonoscopy and biopsies identified MC in only 1.5% of patients with IBS. There were 451 controls without IBS but, unfortunately, for practical and cost-related reasons they did not obtain random

colonic biopsies in the control group. As a result, this study was ineligible for our meta-analysis. Moreover, they only took biopsies from the recto-sigmoid region, so this may have underestimated the true prevalence of MC. Studies are conflicting on this issue, with some reporting that MC will be missed in up to 40% of patients unless right-sided biopsies are also obtained, [52-54] although recently Bjornbak et al. demonstrated that <2.5% of cases of MC would have been missed if only the left colon had been biopsied. [55]

Some pathophysiological processes may explain why patients with MC report symptoms that are in keeping with a diagnosis of IBS. There are several causes proposed for the pain experienced by patients with IBS, such as visceral hypersensitivity and abnormal central pain processing. It seems that there is also chronic low-grade mucosal inflammation in patients with IBS. A systematic review demonstrated a potential role of low-grade inflammation as a mediator in the pathogenesis of IBS, [8] providing support for inflammation in the etiology, as well as in the induction of symptoms, in both MC and IBS, which may explain why patients present with similar symptoms.

Our study shows that in unselected patients with diarrhea, it may not be desirable to perform colonoscopy to exclude MC in all those individuals with symptoms meeting criteria for IBS, as the prevalence is no higher than in other symptomatic patients with diarrhea but who do not meet criteria for IBS. It would therefore be useful if patients with a higher risk of MC could be identified on clinical grounds, and prioritized for colonoscopy and biopsies. In a large multicenter prospective study, conducted in France, reporting the characteristics of a cohort of patients with MC, and comparing their characteristics with those of patients with IBS-D or other functional bowel disorders with diarrhea, age ≥50 years, coexistent autoimmune disease, female gender, medications such as proton pump inhibitors or non-steroidal anti-inflammatory drugs, presence of weight loss, longer duration of diarrhea, and nocturnal symptoms were all associated with MC. [56] Performing a receiver operating

characteristics curve analysis using these data demonstrated an area under the curve of 0.80, and identified that if the presence of two or more risk factors was used to decide whether or not to obtain random colonic biopsies, sensitivity to detect MC was 93.5%, but random colonic biopsies were avoided in 47.8% of patients with diarrhea. [57] In a similar study Kane et al. derived and validated a novel diagnostic scoring system to distinguish patients with MC from those with functional bowel disease on the basis of clinical data. [22] This scoring system had a sensitivity of 90.5% and a specificity of 45.3% when the optimal cut-off of ≥8 was used. The authors concluded that applying the diagnostic scoring system would obviate the need for random colonic biopsies in 37%–49% of patients without MC, and reduce the total costs associated with excluding MC in this group of patients.

We analyzed data from cross-sectional surveys, case-series, and case-control studies conducted in secondary and tertiary care. The difference in direction of effect of the ORs that we observed in cross-sectional surveys and case-control studies is likely due to the selection of the control groups. The patients without IBS in the cross-sectional surveys had diarrhea, while the controls in the case-control studies were asymptomatic. It is self-evident that patients with diarrhea will be more likely to have MC than asymptomatic individuals. This is also likely to explain why the prevalence of MC in patients with IBS-D was higher than among all patients with IBS regardless of subtype. There were few studies that reported the association between IBS and the subtypes of MC. Well-designed studies with a larger population are warranted to determine this association with LC and CC, separately.

The findings of this meta-analysis may be clinically useful. In the majority of included studies the authors concluded that patients with IBS should have colonoscopy and biopsies to exclude MC. However, the results of our meta-analysis could instead be interpreted as supporting current recommendations that colonoscopy is not warranted in all patients with IBS, and should be reserved for those with aforementioned risk factors for MC, or alarm

features such as GI bleeding, anemia, recent onset change in bowel habit, or family history of colorectal cancer. It should also be remembered that when patients with existing IBS develop new or altered symptoms, indicating the possibility of a de novo organic GI condition, colonoscopy should not be delayed with the assumption that these symptoms are due to IBS alone.

In conclusion, data from this systematic review and meta-analyses demonstrate that one in three patients with MC report IBS symptoms, but IBS symptoms were not more common in patients with MC compared with individuals without MC. Case control studies demonstrated a significantly higher prevalence of MC among patients with IBS, compared with asymptomatic individuals, but in cross-sectional surveys, there was no significant difference in prevalence of MC in patients with IBS compared with patients with diarrhea undergoing colonoscopy. Based on current evidence the utility of colonoscopy and random biopsies to exclude MC in patients presenting with typical symptoms of IBS, in the absence of known risk factors for MC or alarm features, is debatable. Better designed studies examining this issue are required before any firm conclusions can be drawn.

ACKNOWLEDGEMENTS

None.

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FIGURE LEGENDS

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review and Meta-analysis.

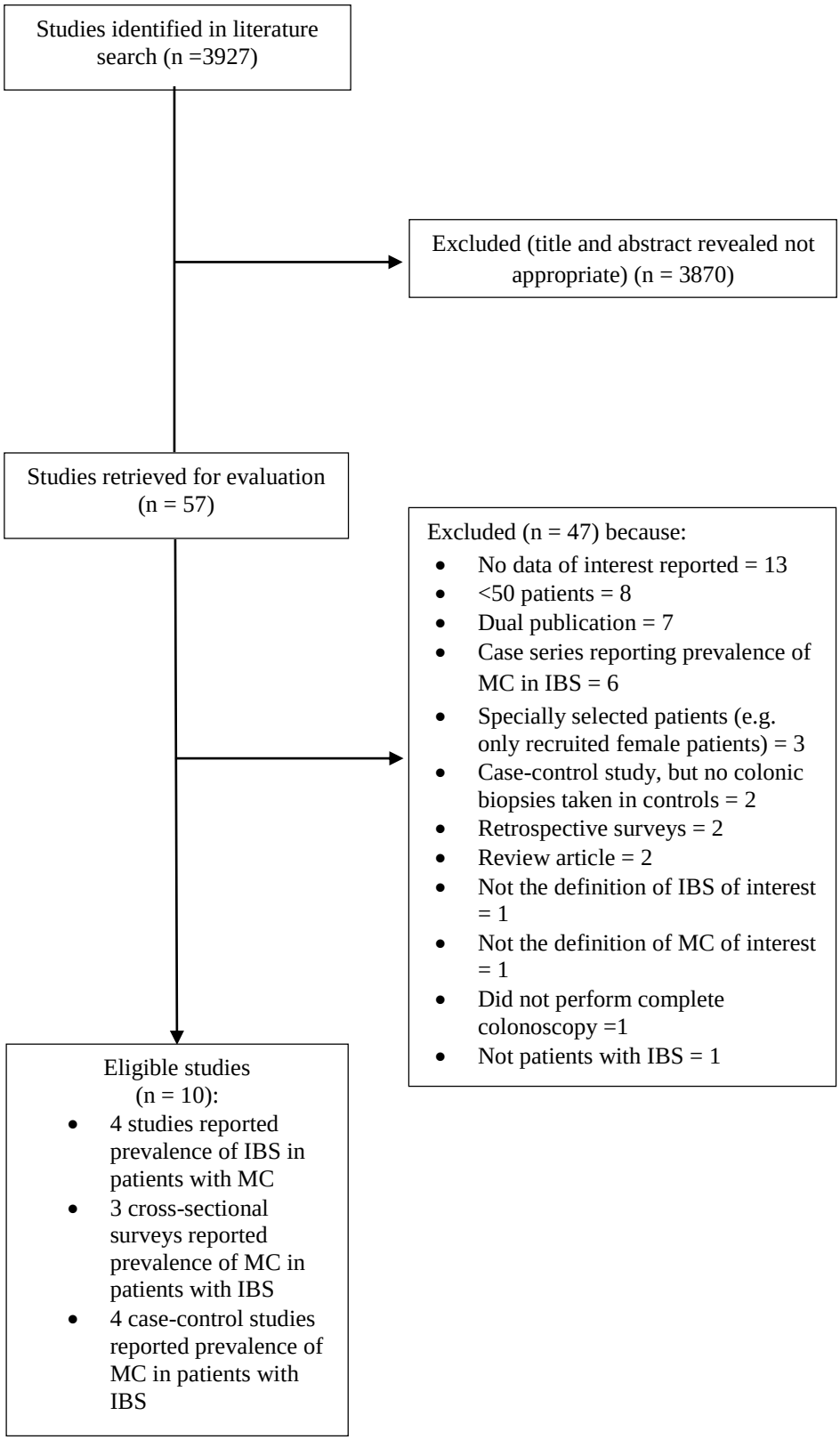

Figure 2. Odds Ratio for MC Among Patient with IBS versus Patients without IBS in Cross-sectional Surveys.

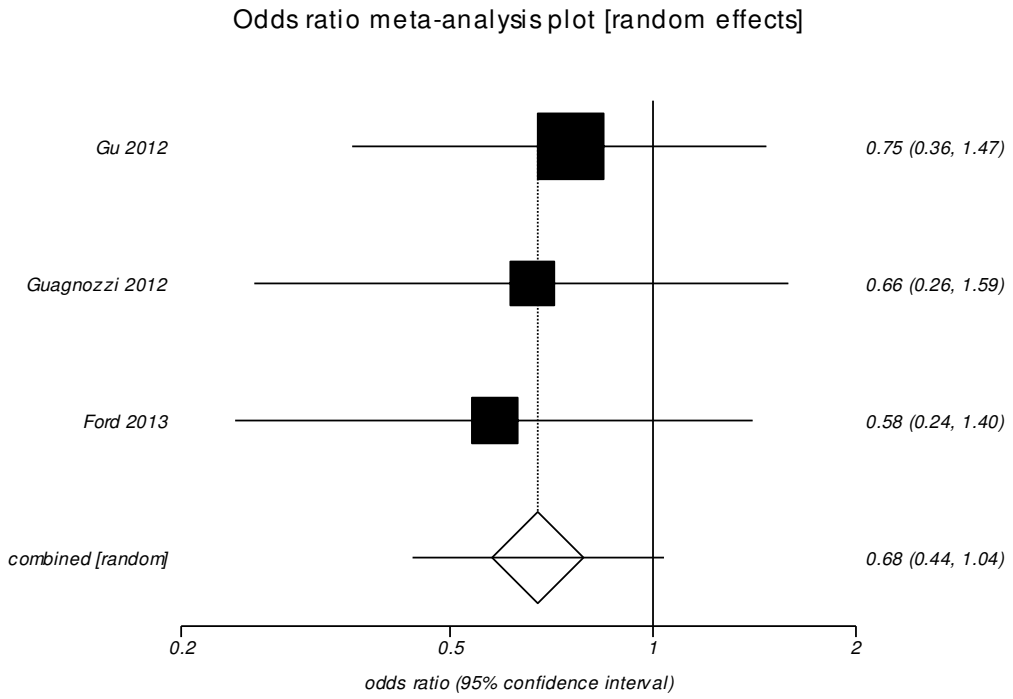

Figure 3. Odds Ratio for MC Among Patient with IBS versus Patients without IBS in Case-control Studies.

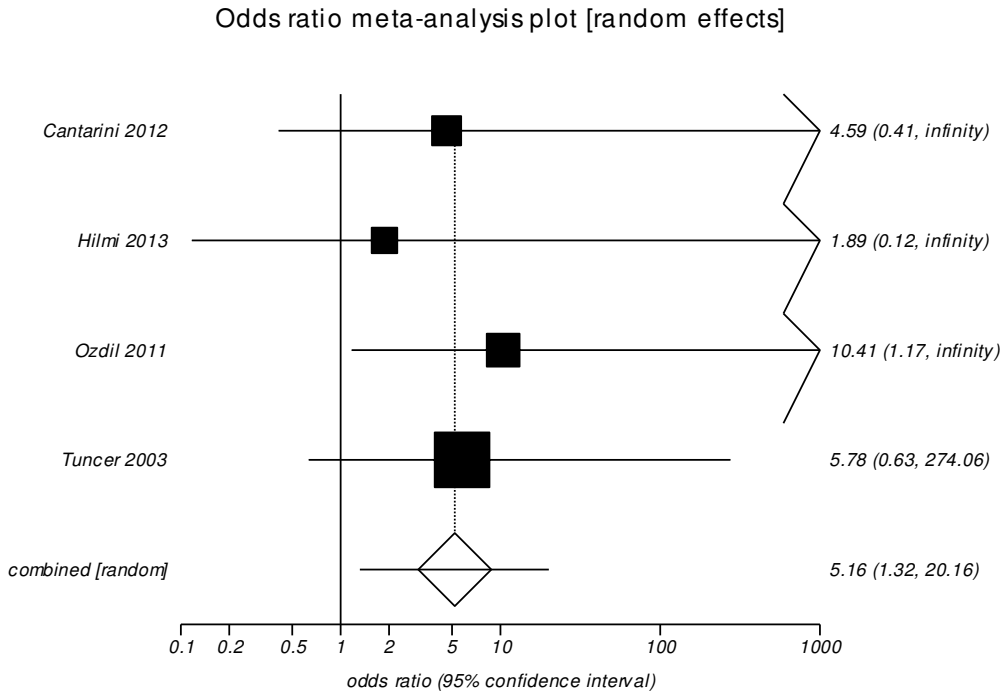

Table 1. Characteristics of Studies Reporting the Prevalence of IBS in Patients with MC.

Study	Country and Setting (Number of Centers)	Study Type	Source of Controls	Criteria Used to Define IBS	Number of Subjects with Histologically-confirmed MC (LC, CC)	Number of MC Subjects with IBS (%)	Number of Control Subjects	Number of Control Subjects with IBS (%)
Madisch 2005 [44]	Germany, tertiary care (1)	Case series	N/A	Rome II	82 (8, 74)	23 (28.0)	N/A	N/A
Limsui 2007 [49]	USA, tertiary care (2)	Case-control	Other patients with diarrhea	Rome II	131 (84, 47)	73 (55.7)	110	37 (33.6)
Gu 2012 [41]	China, secondary and tertiary care (2)	Cross-sectional survey	Other patients with diarrhea	Rome III	87 (59, 28)	12 (13.8)	526	92 (17.5)
Abboud 2013 [48]	USA, tertiary care (2)	Case series	N/A	Rome II	120	46 (38.3)	N/A	N/A

Table 2. Characteristics of Cross-sectional Surveys Reporting the Prevalence of MC in Patients with IBS.

Study	Country, Setting (Number of Centers)	Criteria Used to Define IBS	Comparison Group	Number of Subjects with IBS	Number of Subjects with IBS with MC (%)	Number of Subjects without IBS	Number of Subjects without IBS with MC (%)
Gu 2012 [41]	China, secondary and tertiary care (2)	Rome III	Other patients with diarrhea undergoing colonoscopy	104	12 (11.5)	509	75 (14.7)
Guagnozzi 2012 [42]	Spain, secondary care (1)	Rome III	Other patients with diarrhea undergoing colonoscopy	84	9 (10.7)	150	23 (15.3)
Ford 2013 [14]	Canada, secondary and tertiary care (2)	Rome III	Other patients with diarrhea undergoing colonoscopy	555	12 (2.2)	356	13 (3.7)

Table 3. Characteristics of Case-control Studies Reporting the Prevalence of MC in Patients with IBS.

Study	Country, Setting (Number of Centers)	Criteria Used to Define IBS	Source of Controls Who Also Underwent Complete Colonoscopy	Number of Cases with IBS	Number of Cases with IBS with MC (%)	Number of Controls without IBS	Number of Controls without IBS with MC (%)
Tunçer 2003 [46]	Turkey, secondary and tertiary care (2)	Manning	Patients with functional dyspepsia or needing colorectal cancer screening	30	7 (23.3)	20	1 (5)
Ozdil 2011 [45]	Turkey, secondary care (2)	Rome III	Asymptomatic patients with a family history of colorectal cancer or a history of anemia	226	7 (3.1)	152	0 (0)
Cantarini 2012 [47]	Italy, tertiary care (1)	Rome III	Asymptomatic patients	35	3 (8.6)	21	0 (0)
Hilmi 2013 [43]	Malaysia, tertiary care (1)	Rome III	Asymptomatic patients needing colorectal cancer or polyp surveillance	74	1 (1.4)	46	0 (0)