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Systematic review with meta-analysis: diagnostic overlap of microscopic colitis and functional bowel disorders

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SUMMARY

Background
Microscopic colitis shares certain common clinical manifestations with functional bowel disorders, especially diarrhoea-dominant irritable bowel syndrome (IBS) and functional diarrhoea. However, the exact relationship between microscopic colitis and functional bowel disorders has not been systematically assessed.

Aim
To conduct a systematic review and meta-analysis on the diagnostic overlap between functional bowel disorders and microscopic colitis.

Methods
We searched MEDLINE, EMBASE and SCOPUS databases, as well as the abstract books of the major gastroenterology meetings, to investigate the prevalence of microscopic colitis among patients with functional bowel disorders (considering all subtypes of both disorders) and vice versa. Data were pooled with a random-effects model.

Results
Of 227 references identified, data were collected from 26 studies and a total of 5,099 adult patients. The pooled prevalence any type of functional bowel disorders in patients who present diagnostic criteria of microscopic colitis was 39.1% (95% CI: 22.8–56.6%; I^2: 97%) and was higher for lymphocytic colitis than for collagenous colitis (40.7% vs. 28.4%, respectively; $P = 0.58$). The prevalence of microscopic colitis in functional bowel disorders patients was 7% (95% CI: 3.6–11.4%), reaching 9.8% (95% CI: 4.4–17.1%; I^2: 95%) in patients exhibiting diarrhoea-dominant IBS, nonsignificantly higher than microscopic colitis rates among patients with constipation-dominant IBS (1.3%) or mixed-dominant IBS (1.9%).

Conclusions
There is a significant overlap of symptoms between microscopic colitis and functional bowel disorders, especially in diarrhoeal subtypes. The high proportion of microscopic colitis among diarrhoea-dominant functional syndromes should serve as a call for more active diagnosis in selected patients.

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INTRODUCTION

Microscopic colitis (MC) is a term used to identify a group of chronic inflammatory bowel disorders characterised by chronic or recurrent watery diarrhoea in the absence of abnormal radiological examinations, with normal or near-normal endoscopic appearance and specific microscopic abnormalities in colonic biopsies.[1–3] The disorder comprises two major subtypes: lymphocytic colitis and collagenous colitis. The incidence and prevalence of MC have increased over time, making it a common cause of chronic watery diarrhoea worldwide, now estimated to be present in 10–20% of these patients, who otherwise present with a macroscopically normal colon.[4–7] Research over the past decade has indicated an increasing incidence for lymphocytic colitis and collagenous colitis, with some studies noting an incidence at least as high as that of ulcerative colitis and Crohn's disease.[8]

Patients with functional bowel disorders such as irritable bowel syndrome (IBS) – mainly the diarrhoea subtype (IBS-D) – or functional diarrhoea share similar symptoms and endoscopic results with MC patients, with both disorders having a substantial negative impact on health-related quality of life.[9–11]

Irritable bowel syndrome is the most prevalent functional bowel disorder found in the general population worldwide; it is also the most common reason for referral to gastroenterology departments.[12] Its prevalence ranges from 6.2% to 25%, which makes it approximately 100 times more frequent than MC.[13]

As in the case of MC, no distinctive biological, endoscopic or physiological parameters have been defined for IBS, and, in the absence of a colonoscopy with colonic mucosal biopsies, there is no marker for an accurate differential diagnosis between the two conditions.[14] Currently, diagnosis of IBS is symptom-based, with diagnostic criteria for each IBS-subtype as well as for functional diarrhoea. These criteria have been developed to reduce the need for an exhaustive investigation in patients who present no alarm symptoms. However, few validation studies have been carried out on the current gold-standard, symptom-based criteria for diagnosing IBS, namely the Rome III criteria.[15] Indeed, the largest validation study performed to date found only modest accuracy of these criteria in predicting the presence of true IBS.[16]

As opposed to MC, for which corticosteroid-based therapy with budesonide is currently the most effective treatment,[17] therapeutic interventions in IBS are based on antispasmodic agents, changes in dietary habits, and management of stressor conditions, taking into consideration the complex interaction between the digestive, immune and nervous systems in IBS patients.[18]

Interest in proper identification of underlying organic gastrointestinal disease among patients with suspected IBS has increased over the last decade due to the potential implications for its therapeutic management. In particular, several recent studies have reported a diagnostic overlap between MC and IBS (especially in patients with IBS-D or functional diarrhoea) with conflicting results.[19–22] In fact, increased awareness on the part of clinicians, endoscopists and pathologists alike is needed to reach a definitive diagnosis of MC due to the relationship between MC and IBS has neither been universally documented nor assessed according to the latest updated studies.

The aim of this study was to evaluate the frequency of overlap between the diagnostic criteria of IBS or functional diarrhoea and MC. To achieve this goal, we systematically assessed: (i) the prevalence of patients that fulfil the diagnostic criteria for IBS or functional diarrhoea in histologically confirmed MC patients and (ii) the prevalence of histologically confirmed MC patients among patients who fulfilled the diagnostic criteria for IBS or functional diarrhoea.

METHODS

This systematic review has been registered in the PROSPERO international prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; register no. CRD42014014195), and has been reported in accordance with the PRISMA statements.[23]

Selection of studies

A systematic literature search was performed independently by two researchers (AA and AJL) in three major bibliographic databases (PUBMED, EMBASE and Scopus) up to January 2015. The search was not restricted to English language manuscripts. A pre-determined protocol was used in accordance with the quality standards of reporting meta-analyses of observational studies in epidemiology.[24]

Comprehensive search criteria were used to identify articles dealing with the relationship between MC and functional bowel disorders (IBS and functional diarrhoea) in adult populations, including studies that used every available diagnostic criteria for IBS. We consulted the thesauri for MEDLINE (MESH) and EMBASE (EMTREE) using the following search strategy: (micro-

scopic colitides OR microscopic colitis OR collagenous colitis OR lymphocytic colitis) AND [("rome" AND "1") OR ("rome" AND "2") OR ("rome" AND "3") OR ("rome"AND "ii") OR ("rome"AND "iii") OR "manning" OR "kruis" OR "irritable bowel syndrome" OR "functional diarrhea" OR "functional diarrhoea" OR ("functional" AND ("disease" OR "disorders")] AND ("epidemiology" OR "prevalence" OR "proportion" OR "frequency" OR "incidence" OR "demography").

In the SCOPUS database, only free text searches with truncations were carried out. We also examined the reference lists from retrieved articles and abstracts of conference proceedings (annual abstract books from the American Gastroenterology Association or Digestive Disease Week, as well as meetings of the American College of Gastroenterology and United European Gastroenterology societies from January 2000 up to January 2015) to identify additional relevant studies. Two reviewers (AA & AJL) independently screened the database search for titles and abstracts. If any of the reviewers felt that a title or abstract met the study eligibility criteria, the full text of the study was retrieved.

Inclusion criteria

Randomised controlled trials, observational prospective and retrospective studies, and case series reports were included if data on the fulfilment of diagnostic criteria for MC (and its variants) and functional bowel disorders (independent of the diagnostic criteria used) were provided. Studies evaluating the proportion of MC patients who simultaneously presented with diagnostic criteria for functional bowel disorders and vice versa were selected. Variations both in the histological criteria used for MC and the clinical criteria used to define functional bowel disorders were taken into account, especially in the case of IBS subtypes.

Exclusion criteria

Our analysis excluded reviews that provided no original data, along with clinical guidelines and consensus documents. Studies not carried out on humans, or those providing duplicated information (i.e. repeated abstracts presented at different congresses or abstracts published later as a full paper) and subsets of patient cohorts from a previously published article by the same group of authors were also excluded.

Quality assessment

Cohort studies, case series and case reports were evaluated for quality if the article described (i) the diagnostic criteria considered for MC and functional bowel disorders, (ii) patients' demographic data and (iii) the proportion of patients in whom both disorders overlapped. Likewise, diagnostic criteria for both conditions had to be specifically stated in the text along with the time frame(s) and the clinic or clinics in which the study was carried out. Quality assessment was checked with a specific evaluation form for observational studies developed by our group and based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement[25] and critical appraisal tools from the Critical Appraisal Skill Program (CASP). A study was considered to be at low risk for bias if each of the bias items could be categorised as low risk. On the contrary, studies were judged to have a high risk of bias if even one of the items was deemed high risk. Two investigators (DG and AA) independently gave each eligible study an overall rating of high, low or unclear risk of bias, and if disagreements emerged, a third reviewer (AJL) was consulted.

Data extraction

Three reviewers (DG, AA, & AJL) independently extracted relevant information from each eligible study using a standardised data extraction sheet and then proceeded to cross-check the results. The data extracted included the trial study areas, the last name of the first author, publication year, type of primary disease investigated (MC or FBDs), as well as their respective subtypes [lymphocytic colitis or collagenous colitis; IBS-D, IBS with constipation (IBS-C) subtype; mixed IBS (IBS-M) subtype and functional diarrhoea], age and gender of the study participants, sample size, methodological design and study period, whenever possible. At the same time, data on the key outcomes, including proportion of MC patients who fulfilled the criteria for functional bowel disorders or vice versa, were extracted from all included studies. Disagreements between reviewers regarding data extraction were resolved through discussion. When necessary, the authors of the various studies were contacted by e-mail for additional information.

Statistical analysis

Estimations of the prevalence of MC within functional bowel disorders or vice versa were summarised with the aid of random effects meta-analysis weighted for inverse variance following DerSimonian and Laird's method. Summary estimates and 95% CIs were calculated for the prevalence of MC within functional bowel disorders and vice versa.

Heterogeneity between studies was assessed by means of a Chi-square test (Cochran *Q* statistic) and quantified with the I^2 statistic. Generally, I^2 was used to evaluate the level of heterogeneity, assigning the categories low, moderate, and high to I^2 values of 25%, 50% and 75%, respectively.[26] Publication bias was evaluated with the aid of a funnel plot, the asymmetry of which was assessed with Begg–Mazumda's rank test[27] along with the Egger[28] and Harbord tests.[29]

For the primary outcomes, planned subgroup analyses were performed based on the primary disease studied (MC or FBDs) and their subtypes (lymphocytic colitis or collagenous colitis, and IBS-D, IBS-C, IBS-M, as well as functional diarrhoea). The diagnostic criteria used by authors for each disorder were also considered. A subgroup analysis was performed with regard to quality (risk of bias) and type of document (full-length article vs abstract presented at conference proceedings). Calculations were made with StatsDirect statistical software version 2.7.9 (StatsDirect Ltd, Cheshire, UK). The standard errors for prevalence and incidence of all studies were estimated. Differences in estimates on the frequency of subtypes of functional bowel disorders among MC patients (and its respective subtypes), and vice versa, were calculated with the aid of random-effects meta-regression using aggregate-level data, carried out with STATA 12.0 (Statacorp, College Station, TX, USA) software.

RESULTS

The search strategy yielded 227 references; 190 were excluded after examining the title and abstract because they did not fulfil the inclusion criteria. Among the remaining 37 documents retrieved for complete evaluation, six were excluded due to repeated or duplicated information, and seven more were discarded due to a lack of data for calculation. However, two new documents were retrieved after reference tracking. In the end, 26 studies (comprising 23 full papers and three abstracts, nine of which dealt primarily with MC[18, 19, 29–35] while the remaining 17 focused on functional bowel disorders[7, 21, 22, 36–49]) were included in the quantitative summaries of our systematic review (Figure 1). Eleven studies were carried out in Europe, seven in North

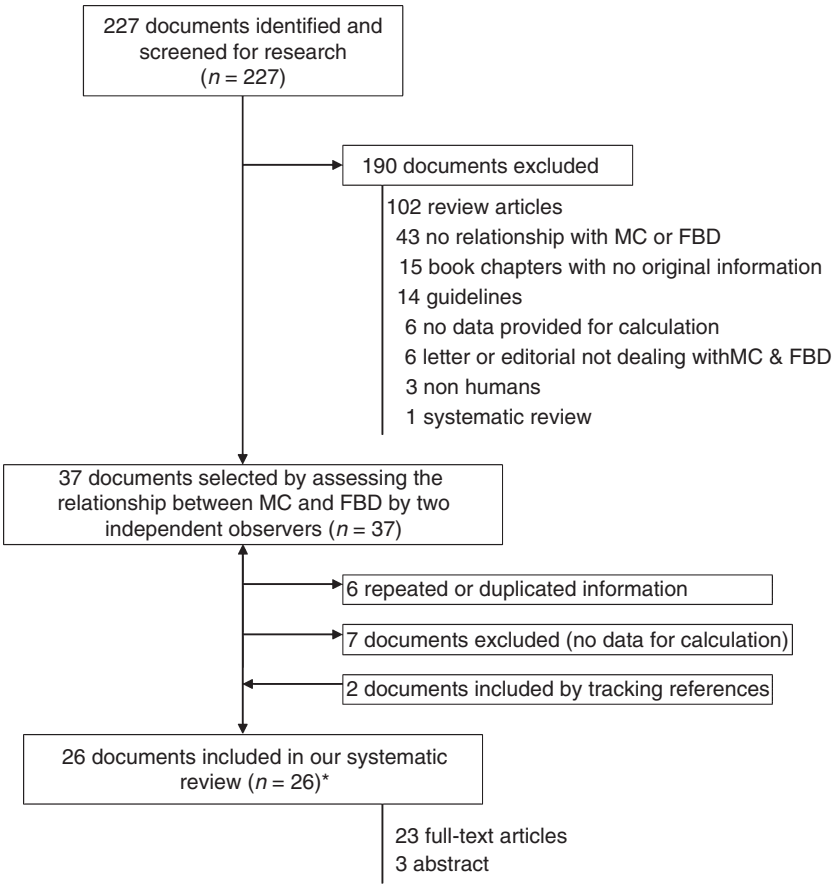

Figure 1 | Flow chart for the process of identifying studies included in and excluded from the systematic review.

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America, six in Asia, one in the Middle East (Iran) and one in New Zealand. Most of the papers retrieved were prospective observational case−control studies, with only one sub-analysis from a randomised controlled trial. Detailed characteristics of the included studies are summarised in Tables S1 and S2.

Overall, data from 5099 individual adult patients (among whom 1507 had received a primary diagnosis of MC and 3592 a primary diagnosis of functional bowel disorders) were retrieved, with sample sizes ranging from 30 to 968 cases. The definitions used for MC and functional bowel disorders were inconsistent across various studies; thus, although the currently accepted histological criteria for defining MC according to the European MC study group guidelines[1] (i.e. ≥20% intraepithelial lymphocytes and/or ≥10 μm sub-epithelial collagen band) were used in almost all the studies, four studies used a value of >10% intraepithelial lymphocytes. Regarding functional bowel disorders, IBS-D was predominantly diagnosed according to Rome III[50] criteria (11 studies), although eight studies used the Rome II[51] criteria. Despite these differences in diagnostic criteria, they were considered similar enough to combine patients in summary meta-analyses.

Prevalence of functional bowel disorders among MC patients

Nine studies reported on the prevalence of functional bowel disorders among patients with MC,[19, 20, 30–35, 52] with most of them concentrating on diarrhoea-predominant subtype IBS (Table S1). Two of the studies also provided data on functional diarrhoea[34, 52]; an additional one[20] was only included in the subgroup analyses because it exclusively provided data for collagenous colitis but not for overall MC.

Overall, the prevalence of any type of functional bowel disorders in patients with MC was 39.1% (95% CI: 22.9–56.6%) (Figure 2a); this value was not significantly higher for patients with lymphocytic colitis (40.7%; 95% CI: 8.2–78.9) (Figure 2b) than for those with collagenous colitis (28.4%; 95% CI: 8.4–54.5%) (P = 0.58) (Figure 2c).

When analyses were restricted to IBS-D, it was found to be present in 32.5% (95% CI: 18.1–48.8%) of patients with MC (Figure S1a). No significant differences were observed between the prevalence of diagnostic criteria for IBS-D in patients presenting with lymphocytic colitis (24%; 95% CI: 4–53.7%) (Figure S1b) and that of patients suffering from collagenous colitis (22.5%; 95% CI: 5.8–45.9%) (Figure S1c). A similar proportion of patients with MC also had symptoms that overlapped with functional diarrhoea (22.8%, 95% CI: 0.6–63%) (Figure S1d). All the previous results are summarised in Table 1. High heterogeneities, with I^2 values over 90%, were documented in all cases.

Prevalence of MC among patients fulfilling diagnostic criteria for functional bowel disorders

Seventeen of the documents retrieved provided data on the prevalence of MC (including both lymphocytic colitis and collagenous colitis) among patients fulfilling the diagnostic criteria for functional bowel disorders (Table S2); most of these provided differentiated information for different IBS subtypes. One[37] of the articles was included only in the subgroup analysis, but not in the overall analysis because exclusively provided data for lymphocytic colitis but not for overall MC.

The overall prevalence of MC among patients with all types of functional bowel disorders was 7% (95% CI: 3.6–11.4%) (Figure 3); the prevalence value was slightly higher in patients with lymphocytic colitis (4.3%) than in those with collagenous colitis (1.4%) (P = 0.42).

When functional bowel disorders were classified by their dominant symptoms, the prevalence of MC among IBS-D patients was 9.8% (95% CI: 4.4–17.1%), higher than MC rates among patients with IBS-C (1.3%; 95% CI: 0.04–4.4) or IBS-M (1.9%; 95% CI: 0.1–5.5) (P = 0.119). Table 2 provides detailed information regarding summary estimates on the prevalence of MC and its subtypes in patients with various functional bowel disorders.

Globally, MC was diagnosed in 9% (95% CI: 4.5–14.9%) of patients with diarrhoea-predominant functional bowel disorders (IBS-M + IBS-D + functional diarrhoea).

Publication bias

Funnel plot analyses of studies assessing the prevalence of MC among patients with functional bowel disorders revealed no significant publication bias, with the P value for Begg−Mazumda's rank test being 0.55, P value for Egger test being 0.20, while for the Harbord bias test it was 0.10. In contrast, significant publication bias was found when prevalence of symptoms diagnostic of functional bowel disorders among patients with MC was assessed, according to Begg−Mazumda's rank test, Egger test and Harbord bias test, with P values of 0.0086, 0.0005 and 0.052 respectively (Figure S2).

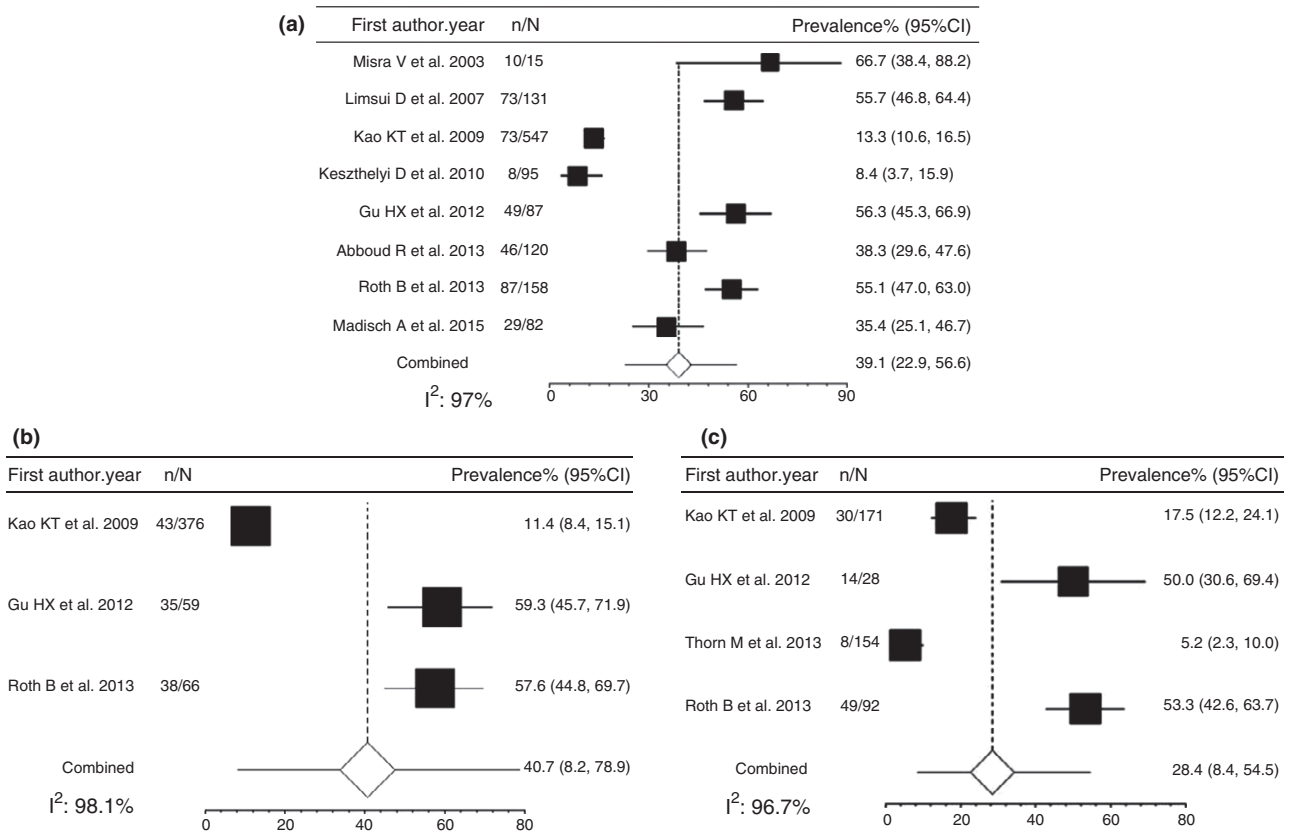

Figure 2 | Summary estimates for the prevalence of functional bowel disorder and its subtypes among patients with an established diagnosis of microscopic colitis, according to clinical and histopathological criteria (a) in patients with MC, (b) in patients with lymphocytic colitis; (c) in patients with collagenous colitis. An I^2 value (statistical heterogeneity) of >75% indicates a high variability in intra-study differences of the overall effect size.

DISCUSSION

This meta-analysis of 26 published studies demonstrates the presence of a significant diagnostic overlap between MC and functional bowel disorders, especially for the predominant diarrhoeic IBS subtypes. This overlap was doubly documented in that the prevalence rate of MC among patients fulfilling the diagnostic criteria for functional bowel disorders was found to be 7% (but reaching a prevalence of 9.8% in IBS-D patients) while IBS symptoms were observed in 39% of MC patients.

Accurate diagnosis of IBS and other functional bowel disorders is based on clinical data and simple diagnostic techniques; a colonoscopy is not usually performed unless there are signs and/or symptoms suggestive of an organic pathology. Such signs include late onset (in patients 50 years of age and older), diarrhoea of <12 months' duration with nocturnal stool, absence of abdominal pain and weight loss. As both MC and functional bowel disorders manifest with similar clinical presentations, our results indicate that colonoscopies with random mucosal biopsies should perhaps be considered on a larger proportion of functional bowel disorders patients, especially in IBS-D subtype, also without alarm signs/symptoms in order to rule out a diagnosis of MC. However, it will be important in the future to identify specific combined panel of clinical and molecular risk factors that allow to identifying those patients at higher risk to develop MC. Actually, the usefulness of conducting a more exhaustive investigation to reach a definite functional bowel disorders diagnosis and rule out MC in these patients remain controversial. On the one hand, a symptom-based approach not only brings down the cost of managing functional patients,[53] but it may also reduce the stress involved in undergoing medical testing (which often reinforces abnormal illness-type behavior[54]) and eliminate the need to reassure patients with a negative test result (which has been shown to have only a minimal reassurance effect in functional patients[55]). On the

Table 1 | Summary estimates and 95% CIs for the frequency of symptoms fulfilling diagnostic criteria of functional bowel disorders in general, irritable bowel syndrome with diarrhoea subtype and functional diarrhoea, among patients with an established primary diagnosis of microscopic colitis

Type of functional condition	Overall %	*n*	I^2
Functional bowel disorders* among MC patients	39.1 (22.8–56.6)	8	97
Functional bowel disorders* among LC patients	40.7 (8.2–78.9)	3	98.1
Functional bowel disorders* among CC patients	28.4 (8.4–54.5)	4	96.7
IBS-D among MC patients	32.5 (18.1–48.8)	8	96.7
IBS-D among LC patients	24 (4–53.7)	3	93.7
IBS-D among CC patients	22.5 (5.8–45.9)	4	96.2
FD among MC patients	22.8 (0.6–63)	2	–

FD, functional diarrhoea; IBS-D, irritable bowel syndrome with diarrhoea; MC, microscopic colitis.

* Functional bowel disorders comprise the addition of patients with diarrhoeic, constipated, mixed and unclassified subtypes of irritable bowel syndrome, as well as functional diarrhoea.

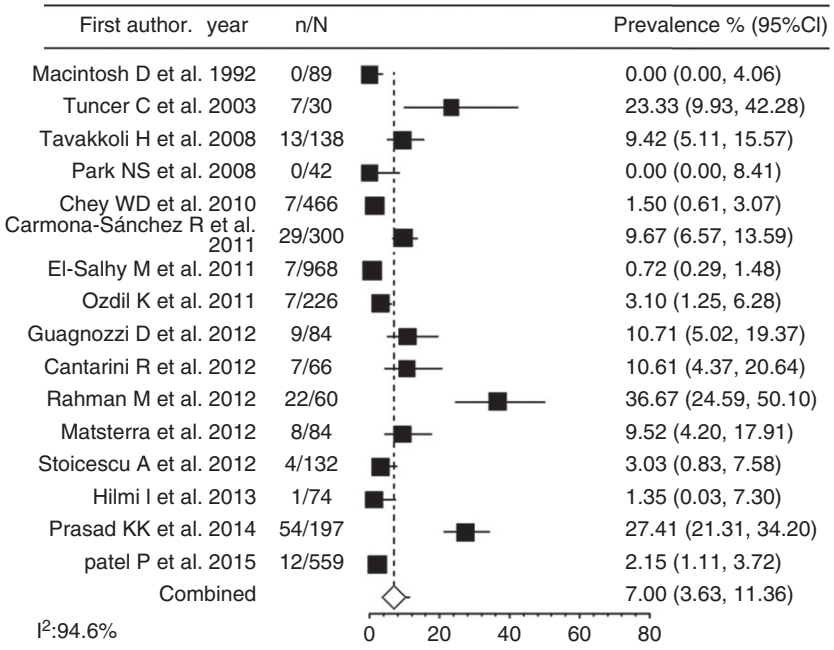

Figure 3 | Summary estimates for the prevalence of microscopic colitis among patients with functional bowel disorders. An I^2 value (statistical heterogeneity) of >75% indicates a high variability in intra-study differences of the overall effect size.

other hand, although MC is a benign inflammatory bowel disease, it can greatly affect patient health-related quality of life[10] and the cost-effectiveness ratio of colonic biopsies in the case of chronic watery diarrhoea has demonstrated superiority to that of other universally accepted procedures[56]. Moreover, an increasing number of studies investigating the potential for missing an organic gastrointestinal disease in patients with functional bowel disorders, especially in IBS patients, have produced heterogeneous results, especially with regard to an diagnosis of MC. In particular, a recent study on the prevalence of organic disease, including MC, in a selected group of IBS patients who met the Rome III criteria and who presented no alarm features documented a 15% prevalence rate for organic disease,[49] with Crohn's disease, coeliac disease, and MC being the most common in these patients. In contrast, several other studies have shown conflicting results, with either lower or higher prevalence of organic disease in IBS patients.[41] A previous systematic review of the utility of diagnostic tests in IBS patients concluded that colonic evaluation rarely identifies organic disease in patients who meet the symptom-based criteria for IBS.[57] However, only one of the studies included in that systematic review evaluated the use of mucosal biopsies; in all the others, only rectal biopsies were performed. It has been well documented that rectal biopsies may have a low sensitivity for diagnosing MC, giving normal results in 8% and 43% of

Table 2 | Summary estimates and 95% CIs for the prevalence of microscopic colitis, and its subtypes lymphocytic colitis and collagenous colitis among patients with symptoms that fulfil diagnostic criteria of functional bowel disorders

Type of condition	Overall %	*n*	I^2
MC among patients with functional bowel disorders*	7 (3.6–11.4)	16	94.6
LC among patients with functional bowel disorders*	4.3 (1.9–5.6)	13	91
CC among patients with functional bowel disorders*	1.4 (0.5–2.8)	12	79.8
Subgroups analysis			
MC among IBS-D patients	9.8 (4.4–17.1)	10	95
MC among IBS-C patients	1.3 (0.04–4.4)	5	78.9
MC among IBS-M patients	1.9 (0.1–5.5)	4	80.8
MC among diarrhoeic functional disorders patients (IBS-M + IBS-D + FD)	9 (4.5–14.9)	12	95.1
LC patients			
LC among IBS-D patients	5.4 (1.5–11.5)	7	93.5
LC among IBS-C patients	0.3 (0.01–1.1)	3	0
LC among IBS-M patients	0.4 (0.06–2.6)	2	–
LC among diarrhoeic functional disorder patients (IBS-M + IBS-D + FD)	4.9 (1.6–9.7)	8	93.2
CC patients			
CC among IBS-D patients	2.1 (0.5–4.9)	7	86.2
CC among IBS-C patients	0.1 (0.004–0.7)	3	0
CC among IBS-M patients	0.1 (0.002–0.7)	2	–
CC among diarrhoeic functional disorder patients (IBS-M + IBS-D + FD)	2.1 (0.6–4.6)	8	87.6

CC, collagenous colitis; FD, functional diarrhoea; IBS-D, irritable bowel syndrome with diarrhoea subtype; IBS-C, irritable bowel syndrome with constipation subtype; IBS-M, mixed irritable bowel syndrome subtype; LC, lymphocytic colitis; MC, microscopic colitis;

* Functional bowel disorders comprise the addition of patients with diarrhoeic, constipated, mixed and unclassified subtypes of irritable bowel syndrome, as well as functional diarrhoea.

lymphocytic colitis and collagenous colitis cases, respectively,[58] with biopsies from the ascending and transverse colon being the most accurate.[6, 59]

The results of our meta-analysis of seventeen studies primarily assessing patients with functional bowel disorders showed that MC could be the underlying condition in a significant proportion in 7% of these patients, regardless of the subtype studied. However, when only patients presenting with IBS-D subtype were taken into account, the prevalence of MC reached 9.8%. Limited information is available on the prevalence of MC among patients with functional diarrhoea,[45] in whom a prevalence of 9% has been described. Despite the fact that MC was being mostly diagnosed in patients with IBS-D, it is worth noting that it was also diagnosed in a very small proportion of patients with IBS-C. This indicates the need to broaden the level of suspicion of MC to include patients with nondiarrhoeic symptoms only in specific cases with a changing pattern of predominant symptoms along the time. At any rate, our meta-analysis shows that approximately one of five patients with diarrhoeic functional bowel disorders present with underlying MC. Furthermore, most of the studies supporting this claim are prospective in design, with 47% of them using the most recent Rome III criteria to define a diagnosis of IBS.

The literature contains repeated reports of an almost identical presentation for lymphocytic colitis and collagenous colitis,[7, 60–63] although the prevalence of lymphocytic colitis among patients with a primary diagnosis of IBS was higher than that of collagenous colitis in our meta-analysis. While there are several specific histological differences that distinguish lymphocytic colitis from collagenous colitis, both entities have a considerable clinical and therapeutic overlap.[64] It is still unclear whether collagenous colitis and lymphocytic colitis should be considered two distinct entities or different subtypes of the same disease, since recent research has identified differences in the pathological mechanisms underlying the development and maintenance of the two subtypes, albeit in a common pathogenetic context.[65, 66]

The pathogenesis of MC is considered to be multifactorial, probably secondary to an abnormal immune reaction which appears in predisposed individuals and is triggered by various luminal factors.[3, 67, 68] The mechanism through which the altered mucosal immune

response generates the dominant symptoms of the disease (diarrhoea) in MC without the development of significant, macroscopic mucosal damage is still under investigation, but suggests a proximity to the pathogenetic mechanisms of diarrhoea in IBS patients. In fact, there is increasing evidence to support an inflammatory process in the pathogenesis of IBS, as 72% of patients with the disease present with a low-grade inflammation in the lamina propria and mucosa; however, this occurs to a lesser extent than in MC.[67] Furthermore, although several studies have shown that increasing amounts of intraepithelial lymphocytes can be seen in patients diagnosed with post-infectious IBS,[69] these levels do not reach the cut-off density needed to reach a diagnosis of MC. Finally, some authors have postulated on the implication of the neuroendocrine system in the pathogenesis of MC after finding an increase in the colonic serotonin-positive cell density, which probably results from the interaction between lymphocytes and enterochromaffin cells.[70] Serotonin is known to accelerate intestinal motility and to promote the secretion of both water and electrolytes, with a secondary compensatory increase in the expression of peptide YY, as has also been observed in LC patients.[71] Still, despite the clinical overlap between MC and IBS, a clear relationship between both disorders at an aetiopathological level has not been sufficiently studied.

Our research has three main strengths: first, it compiles results from an exhaustive literature search in three major databases as well as in the abstract books of the three major gastroenterology congresses. Second, all recovered studies were critically appraised according to their methodological aspects. Finally, different investigators independently extracted the data from the studies included.

The possibility of not recovering all the relevant information published on the overlap of MC and functional bowel disorders could be considered as one of the main limitations of our study, along with a risk of publication bias that remains according to funnel plot analysis. The wide heterogeneity found in meta-analytical calculations from the studies we retrieved should be taken into account when interpreting current result. Furthermore, risks of bias in the studies included in our systematic review were assessed with a nonvalidated evaluation tool, because commonly accepted criteria that have proven validity for this purpose are not currently available. Our tool is based on the application of some items of the STROBE Statement and CASP forms for critical appraisal of observational studies, in the same way that new pilot checklists recently proposed.[72, 73] The utilisation of our tool can be justified because, at least, it was useful in the assessment of designing and conducting observational studies.

In addition, not all studies retrieved in our systematic search employed the currently accepted diagnostic criteria for MC,[74] with older studies using a lower intraepithelial lymphocytes cut-off value to reach a diagnosis of lymphocytic colitis (>15% instead of >20%)[41, 75] as well as a thicker cut-off measurement of the sub-epithelial fibrous band to define collagenous colitis (>15 μm instead of >10 μm).[38] Seven of the retrieved studies did not even specify the cut-off values for IELs density and sub-epithelial fibrous band thickness. Although there is no real consensus on how thick the collagenous band should be or the exact density of intraepithelial lymphocytes needed for a diagnosis of MC,[74] the European MC Consensus Guidelines have established that >20 intraepithelial lymphocytes per 100 epithelial cells and a sub-epithelial fibrous band >10 μm in thickness, over the above other criteria, are required to warrant a diagnosis of lymphocytic colitis and collagenous colitis, respectively.[1] Still, even with these variations, the criteria used by the studies included in our systematic review were considered homogeneous enough to be combined and summarised in meta-analytical calculations.

Finally, it is important to highlight that different criteria for defining a diagnosis of functional bowel disorders, especially IBS and its sub-types, were used in the source studies included in our meta-analysis as a reflection of the evolving process of defining IBS diagnostic criteria along the last years. Despite the fact that this syndrome was first described 150 years ago, the concept of using clinical criteria to establish a definitive diagnosis of IBS was first suggested by Manning in 1978.[76] Subsequently, the process of developing consensus-based criteria has matured throughout three generations, culminating with the publication of the Rome criteria in 1992, their revision in 2000,[51] and, most recently, their updated revision in 2005, to provide us with the Rome III criteria,[50] which currently represent the gold standard for IBS diagnosis. Thus, variations in diagnostic criteria throughout the time period covered by our systematic review (from 1992 to 2015) were considered to reflect the evidence-based process of developing IBS diagnostic criteria over time. Despite broad variations in the reported prevalence of IBS when criteria different from the oldest available criteria were used,[77] we consider the results to be similar enough to be combined in meta-analytical summaries. In any case, Rome III criteria were used to define and clas-

sify IBS in the majority of the retrieved documents; the subgroup analysis provided us with additional elements of control to achieve accurate estimations.

In conclusion, our research has demonstrated a wide overlap between MC and functional bowel disorders symptoms, which suggests that ruling out a diagnosis of MC by means of colonoscopy and adequate mucosal biopsies should always be considered, especially in patients with IBS-D subtype. This would improve both the treatment and follow-up management of these patients, thereby preventing further unnecessary studies and/or inappropriate therapy. With regard to MC, we should focus our attention on identifying associated functional symptoms that coexist in a significant proportion of patients in order to improve health-related quality of life through a combined therapeutic approach. In the absence of accurate, non-invasive biomarkers, there should be increased awareness of the importance of suspecting and diagnosing MC in patients suffering from functional bowel disorders with predominant diarrhoea subtypes; further revisions of the Rome criteria are also needed to reduce the pre-test probability of missing a diagnosis of MC in patients with functional bowel disorders.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Summary estimates for the prevalence of functional bowel disorder and its subtypes among patients with an established diagnosis of MC, according to clinical and histopathological criteria (a) analyses restricted to IBS-D and MC; (b) analyses restricted to IBS-D and lymphocytic colitis; (c) analyses restricted to IBS-D and collagenous colitis; (d) analyses restricted to functional diarrhoea and MC).

Figure S2. Begg's funnel plot of studies assessing overlap in the diagnosis of functional bowel disorders and microscopic colitis according to Begg−Mazumda's rank test, Egger test and Harbord bias test (a) functional bowel disorders among patients with established diagnosis of microscopic colitis; (b) microscopic colitis among patients with symptoms concordant with functional bowel disorders. The solid line in the center is the natural logarithm of pooled diagnostic overlap rates; the two oblique lines are pseudo 95% confidence intervals.

Table S1. Demographics and characteristics of studies included in our systematic review and meta-analysis that assessed the prevalence of functional bowel disorders (irritable bowel syndrome with its subtypes and functional diarrhoea) among patients with an established primary diagnosis of microscopic colitis.

Table S2. Demographics and characteristics of studies included in our systematic review and meta-analysis that assessed the prevalence of microscopic colitis among patients with symptoms fulfilling diagnostic criteria for irritable bowel syndrome of functional diarrhoea.

AUTHORSHIP

Guarantor of the article: Dr D Guagnozzi is acting as the submission's guarantor and she takes responsibility for the integrity of the work.

Author contributions: All the three authors have contributed to the same element of the work: performed the research, collected and analysed the data, designed the research study and wrote the paper, and contributed to the design of the study.

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