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TITLE PAGE

Title: A Validated Diagnostic Scoring System to Predict Microscopic Colitis.

Short "running" title: A Scoring System for Microscopic Colitis.

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Abbreviations:

CI	confidence interval
GI	gastrointestinal
MC	microscopic colitis
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PPI	proton pump inhibitor
PPV	positive predictive value
SD	standard deviation

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ABSTRACT

Background & Aims: Diarrhea is a common indication for colonoscopy. In patients with a macroscopically normal colon, random colonic biopsies are obtained to exclude microscopic colitis (MC), but yield is low as most patients have functional disease. We derived and validated a diagnostic scoring system to predict MC, reducing need for random biopsies.

Methods: Adult patients with chronic diarrhea undergoing colonoscopy in Leeds, UK were included. All demographic and symptom data were collected retrospectively. Those significantly associated with the presence of MC were assigned an item score, which were combined to create a total score. The sensitivity and specificity of this diagnostic scoring system was studied in separate derivation and validation cohorts, and impact of applying the score on costs of diagnosing MC was examined.

Results: In the derivation cohort, age ≥50 years, female gender, proton pump inhibitor or non-steroidal anti-inflammatory drug use, presence of weight loss, and absence of abdominal pain were significantly associated with MC. Creating a diagnostic scoring system, with a score ranging from -8 to +38, the optimal cut off to predict MC was ≥+8. In the validation cohort sensitivity was 90.5% and specificity 45.3%. Total costs associated with excluding MC were reduced by >£7,000. The area under the receiver operating characteristics curve was 0.76.

Conclusions: By combining known risk factors for MC we have created a diagnostic scoring system identifying those requiring colonic biopsies, as well as those in whom biopsies can be avoided, reducing costs of excluding MC in this patient group.

Keywords: diarrhea; irritable bowel syndrome; collagenous colitis; lymphocytic colitis; sensitivity; specificity.

INTRODUCTION

The incidence of microscopic colitis (MC) has been reported as 2.6 to 21.0 per 100,000 per year. (1-3) A recent European consensus on the histopathological diagnosis of inflammatory bowel disease classifies the entity as having three key elements: a clinical history of chronic watery diarrhea, normal or almost normal endoscopic appearance of the colon, and a distinct histological pattern. (4) Histologically MC can be subdivided into collagenous colitis with a characteristic thick band of collagen under the surface epithelium, or lymphocytic colitis, in which there is a diffuse increase in intraepithelial lymphocytes. Once diagnosed, treatment with budesonide, a glucocorticosteroid, is effective in managing both subtypes. (5-7)

However, chronic diarrhea is common in the community, affecting between 2% and 9% of individuals. (8-11) In population-based surveys such as these, the majority of people will have functional bowel disease, with no underlying organic cause. Despite this, many patients will be referred for colonoscopy, because diarrhea is an alarm symptom that is thought to be indicative of colorectal cancer. (12) In the absence of any structural explanation for diarrhea at colonoscopy, most endoscopists would obtain random colonic biopsies in order to exclude the presence of MC. In referral populations it is estimated that between 4% and 13% of chronic diarrhea patients will have MC following colonoscopy. (13) However, with a large number of patients with chronic diarrhea being referred for colonoscopy, and a yield of less than 20% for diagnosing MC, the cost of obtaining and analyzing multiple biopsies is high.

There are some potential risk factors for MC, with studies suggesting that age ≥50 years, co-existent autoimmune disease (including celiac disease), female gender, medications such as proton pump inhibitors (PPIs) or non-steroidal anti-inflammatory drugs (NSAIDs), the presence of weight loss or nocturnal symptoms are all associated

with MC. (14-16) However, none of these epidemiological studies has attempted to explore ways of predicting which patients will be found to have MC after interpretation of random colonic biopsy specimens.

Colonoscopy usually cannot be avoided in patients with diarrhea, but the ability to identify a subset of patients at higher risk of MC has the potential to reduce the number of patients in whom biopsies are taken, and therefore reduce both the duration of the colonoscopy and the costs associated with the orientation and interpretation of biopsies. The aim of this study was therefore to derive and validate a diagnostic scoring system to predict patients at increased likelihood of MC based on identified risk factors, in whom biopsies would be mandated, but which may also obviate the need for random colonic biopsies in a group of individuals with chronic diarrhea who are deemed to be at low risk of MC, and are therefore more likely to have functional bowel disease.

METHODS

Participants and Setting

The study was conducted among individuals with chronic diarrhea referred for colonoscopy at the endoscopy units in Leeds Teaching Hospitals NHS Trust, West Yorkshire over a 2-year period between 2011 and 2012. There are three endoscopy units, at Leeds General Infirmary, St. James's University Hospital, and Wharfedale General Hospital, which are staffed by the same team and follow identical clinical protocols. The hospitals provide secondary care services to a local population of almost 800,000 people in the North of England. The relevant local research ethics committee in Leeds was approached, and confirmed that ethical approval was not required for a retrospective study such as this.

Data Collection and Synthesis

Demographic and Symptom Data

All subjects undergoing colonoscopy for diarrhea in 2011 and 2012 who had a macroscopically normal colonic mucosa, and in whom random colonic biopsies were judged as being warranted by the colonoscopist, were identified from the hospitals' histopathology database. Patients with organic disease seen at colonoscopy such as colorectal cancer, ulcerative colitis, or Crohn's disease were not included in this study. We used patients presenting with diarrhea in 2011 as the derivation cohort, and patients presenting in 2012 as the validation cohort. Medical records of all individuals found to have MC after interpretation of colonic biopsy specimens, as well as a random selection of those with a macroscopically normal colonoscopy and no

evidence of MC and selected based on clinical case records number using SPSS for Windows version 21.0 (SPSS Inc, Chicago, IL, USA), were reviewed retrospectively, including hospital notes, and laboratory and histopathology results. Demographic and symptom data were recorded. Demographic data of interest included the age of the patient at the time of colonoscopy, gender, current use of PPIs or NSAIDs, and history of celiac disease (either biopsy-proven or positive celiac serology). Symptom data collected included the presence of weight loss, nocturnal diarrhea, or abdominal pain.

Colonoscopic and Histopathological Data

All included patients underwent complete colonoscopy to the caecum or terminal ileum. The endoscopy units employ colonoscopes from both Olympus and Fujinon. Bowel preparation was either a combination of polyethylene glycol and sodium picosulfate, or polyethylene glycol alone, depending on renal function. Random colonic biopsies were taken in all included patients, the number of which was at the discretion of the endoscopist, although departmental policy is to take two from the right colon, two from the left colon, and two from the rectum. All specimens were interpreted by experienced GI histopathologists.

Reference Standard

The presence of MC was diagnosed according to the following criteria: collagenous colitis was defined as the presence of a subepithelial collagen band of ≥10μm in thickness and associated diffuse chronic inflammation; lymphocytic colitis was defined using a threshold of >20 intra-epithelial lymphocytes per 100 epithelial cells and associated diffuse chronic inflammation, but no thickening of the

subepithelial collagen band. Other investigators have demonstrated that there is little inter-observer variability in the diagnosis of MC. (17)

Statistical Analysis

The associations between demographic and symptom data and the presence of MC were explored using univariate analysis, and the results were expressed as odds ratios (OR) with a 95% confidence interval (CI). Statistical analyses were performed using SPSS. Those variables that demonstrated statistically significant univariate odds ratios were included in a diagnostic scoring system to predict the presence of MC.

In order to create the diagnostic scoring system, the regression coefficients of all these statistically significant predictors were changed into item assigned scores by dividing with the smallest coefficient (0.155), and rounding up to the nearest integer. These individual item scores were then summed to create a total score, which signified the summary measure of risk for MC. This is similar to the methodology used to create other predictive scores in gastroenterology, including scores to predict peptic ulcer perforation, mortality after GI hemorrhage, and need for endoscopic intervention in patients with GI hemorrhage. (18-20)

The primary aim of the study was to describe the performance of this diagnostic scoring system in predicting the presence of MC. The optimal cut off to diagnose MC was assessed for this scoring system using a receiver operating characteristics (ROC) curve as the point at which there was the best tradeoff between sensitivity and false positive rate, (21) and the total area under the curve was calculated. These analyses were performed using StatsDirect version 2.7.2 (StatsDirect Ltd, Sale, Cheshire, England). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), and their 95%

confidence intervals (CIs), were calculated for the optimal cut off using a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA). These calculations were checked using Meta-DiSc® version 1.4 (Universidad Complutense, Madrid, Spain). We also assessed the cost of diagnosing each case of MC using NHS reference costs for colonic biopsies from 2011 to 2012, with a cost of £43 per set of biopsies taken (£1 = $1.6). (22) The potential impact of using the diagnostic scoring system on both the total cost and the cost per case of MC was then calculated.

RESULTS

Derivation cohort

In total, 476 (22.1%) of 2151 patients with chronic diarrhea undergoing complete colonoscopy with random colonic biopsies from 2011 were included in the derivation cohort. The mean age of these individuals was 53.6 years (range 17 to 91 years) and 303 (63.7%) were female. Of the included subjects, 85 (17.9%) patients were diagnosed with MC on histological grounds: 67 with collagenous colitis, and 18 with lymphocytic colitis. The remaining 391 patients had a macroscopically normal colonoscopy and normal random colonic biopsies. Demographic data for the 476 patients in the derivation cohort are provided in Table 1.

Odds ratios for the association of each item in the diagnostic scoring system with the presence of MC, along with 95% CIs, for the derivation cohort are presented in Table 2. There was no significant association between presence of celiac disease or nocturnal diarrhea and MC, and these items did not contribute to the total score. Each of the remaining item scores ranged from -8 to +13. These were summed to obtain the total score for each patient, which ranged from -8 to +38. The ROC curve for this diagnostic scoring system in predicting the presence of MC demonstrated an optimal cut-off point of ≥+8 (Figure 1a), with an area under the curve of 0.79. At this threshold the diagnostic scoring system correctly identified 80 (94.1%) of 85 MC patients, and would have avoided unnecessary random colonic biopsies in 190 (48.6%) of 391 patients without MC. Sensitivity, specificity, PPV, and NPV, along with 95% CIs, at this threshold are provided in Table 3.

The total cost of performing random colonic biopsies with histopathological interpretation in these 476 patients was £20,468, or £240.80 per case of MC

diagnosed. Applying the diagnostic scoring system at this threshold would have reduced the total cost of random colonic biopsies and histopathological interpretation to £12,083, with a cost per case of MC diagnosed of £151.04, a saving of £89.76 per case diagnosed.

Given that a missed diagnosis of MC may be problematic for patients, we assessed the performance of a lower threshold score of ≥+4 to predict MC, in order to maximize sensitivity. At this cut-off the diagnostic scoring system correctly identified 84 (98.8%) of 85 patients with MC, and would have avoided unnecessary biopsies in 145 (37.1%) of 391 patients without MC. The sensitivity, specificity, PPV, and NPV and their 95% CIs at this threshold are also provided in Table 3.

Validation cohort

In the validation cohort we selected 460 (20.5%) of 2246 patients with chronic diarrhea undergoing complete colonoscopy with random colonic biopsies from 2012. There were 74 (16.1%) patients with confirmed MC, and 386 with a macroscopically normal colonoscopy with no evidence of MC on random colonic biopsies. The mean age of these 286 individuals was 52.9 years (range 17 to 98 years), and 275 (59.8%) were female. Among the 74 patients with MC, there were 47 with collagenous colitis, and 27 with lymphocytic colitis. Demographic data for the 460 patients in the validation cohort are provided in Table 1.

In the validation cohort, a score of ≥+8 performed similarly, with an area under the ROC curve of 0.76 (Figure 1b). At this cut-off, the diagnostic scoring system correctly identified 67 (90.5%) of 74 MC patients and would have avoided the need for random colonic biopsies in 175 (45.3%) of 386 patients without MC. The sensitivity, specificity, PPV, and NPV, along with 95% CIs, at this threshold are

provided in Table 3. The total cost of performing random colonic biopsies with histopathological interpretation in these 460 patients was £19,780, or £267.30 per case of MC diagnosed. Applying the diagnostic scoring system at this threshold would have reduced the total cost of random colonic biopsies and histopathological interpretation to £11,954, with a cost per case of MC diagnosed of £178.42.

When a cut-off of ≥+4 was used to predict presence of MC, the diagnostic scoring system correctly identified 70 (94.6%) of 74 patients with MC, and would have obviated the need for random colonic biopsies in 126 (32.6%) of 386 patients without MC. Sensitivity, specificity, PPV, and NPV at this threshold are provided in Table 3.

DISCUSSION

This study was designed to derive and validate a novel diagnostic scoring system to distinguish patients with MC from those with functional bowel disease based on clinical data, which can easily be collected and implemented when taking a history from the patient. In our derivation cohort, factors associated with MC included female gender, age 50 years and above, NSAID or PPI use, presence of weight loss, and absence of abdominal pain. When these were combined in our diagnostic scoring system this was highly accurate in predicting patients found to have MC on random colonic biopsies in the derivation cohort, with a sensitivity of 94% when a cut off ≥+8 was used, and 99% using a cut off of ≥+4. Applying the diagnostic scoring system would have obviated the need for random colonic biopsies in 37% to 49% of patients without MC depending on the cut off used, and reduced the total costs associated with excluding MC by >£8,000. The scoring system performed similarly in the validation cohort, with a sensitivity of 90% with a cut off of ≥+8, avoiding the need for biopsies in 44% of patients, and leading to a reduction in costs of >£7,000.

Strengths of this study include the large sample size and standardized approach to obtaining biopsy specimens. In addition, rather than just examining the association between various demographic and symptom data and the presence of MC, as others have done previously, we have used the significant associations we observed in order to derive a diagnostic scoring system that predicts the presence of MC, and then validated it by testing its performance in an entirely separate cohort of patients. As the performance of the scoring system was comparable in the two cohorts, this suggests that it will perform similarly in other secondary care centers. This should mean that the results of our study are applicable to other Gastroenterologists consulting with chronic diarrhea patients in usual clinical practice.

Using a retrospective approach has important limitations. We were reliant on the responsible physician recording the data of interest at the time of their initial consultation with the patient, rather than prospective standardized data collection using a questionnaire. This also means that we were unable to study the relationship between the timing of initiation of medications, or the exact duration of symptoms, and the presence of MC. In addition, the fact that we did not include all patients with a macroscopically normal colonoscopy, and without MC after random colonic biopsies, in our analyses may mean that the performance of the scoring system has been overestimated, because the arbitrary size of this group could theoretically result in an artificially lower false positive rate, leading to a higher specificity and positive predictive value than would be observed if the scoring system were to be applied in real time in usual clinical practice.

Our study compares the characteristics of a relatively large number of cases of MC with chronic diarrhea patients with a macroscopically normal colonoscopy and normal biopsies, and who are therefore likely to have functional bowel disease, in a UK population. There has been a previous retrospective analysis from Ireland but this only assessed patients with histologically-confirmed MC. (23) Like similar studies from other parts of the world, we have identified positive associations between MC and female gender, age ≥50 years, and PPI or NSAID use. (14-16) However, we could not demonstrate associations with celiac disease or nocturnal diarrhea, although this may be due to the fact that testing for celiac disease was not mandated as part of our study design, as well as being a relatively common finding in those without MC, and presence or absence of nocturnal diarrhea was not recorded in all patients. We observed a higher proportion of MC patients to have collagenous colitis, compared with lymphocytic colitis, in contrast to other investigators. (1, 3)

Two recent prospective studies have confirmed that increasing age is associated with MC, with those ≥50 years being significantly more likely to be found to have MC, (14, 16) but one of these did not demonstrate a significant association between female gender and MC. (16) However 70% of their control group met diagnostic criteria for irritable bowel syndrome, which is commoner in women. (24) These authors also reported that absence of abdominal pain and the presence of weight loss were more likely in those with MC. (16) A prospective case control study from 2013 showed a positive association between lansoprazole use and MC, (15) and Macaigne et al. also demonstrated a strong association between newly started medications, including PPIs, and MC. (16) Other drugs including selective serotonin re-uptake inhibitors, statins, and angiotensin converting enzyme inhibitors have also been implicated. (25)

There have been no previous attempts in the literature, to our knowledge, to derive a diagnostic scoring system to distinguish MC from functional bowel disease. Our findings are therefore novel and may be clinically useful. Applying the scoring system in real time has the potential to lead to a considerable decrease in the number of chronic diarrhea patients requiring random colonic biopsy, reducing both the duration of the colonoscopy, and costs to the health service. The actual cost savings in the real world are likely to be higher than those observed in our study, due to the arbitrary size of our group of patients without MC. The optimal cut off used to make this decision, based on the ROC curve analysis, was a score of ≥+8, but if a missed diagnosis of MC is deemed unacceptable then a score of ≥+4 or more may be preferable in order to maximize sensitivity. In clinical practice, if symptoms persisted despite the use of anti-diarrheal agents in a patient labeled as low-risk of MC by the diagnostic scoring system, and in whom random colonic biopsies had not been

obtained, there would then be the option of performing a flexible sigmoidoscopy and obtaining left-sided colonic biopsies, which has been shown to detect up to 98% of MC cases by other investigators. (26) The cost of this extra procedure would, however, reduce the overall cost savings of implementing our proposed model.

The results of our study need to be replicated in other centers, and using a prospective design, with patients recruited as part of routine clinical practice. In the interim, however, these data provide confirmation of previously reported associations between increasing age, female gender, PPI or NSAID use, presence of weight loss, and absence of abdominal pain and MC in a UK population. By combining these risk factors we have created an effective diagnostic scoring system, which can be applied in the outpatient clinic and/or endoscopy room in order to identify those at high risk for MC, and who will therefore require random colonic biopsies for confirmation of the diagnosis, as well as those in whom functional bowel disease is likely, in which case biopsies can be avoided, shortening the procedure time and potentially leading to reduced costs of excluding MC in this group of patients.

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Table 1: Demographic Characteristics of Chronic Diarrhea Patients with MC, and Chronic Diarrhea Patients without MC in the Derivation and Validation Cohorts.

	Derivation cohort (n = 476)		Validation cohort (n = 460)	
	Chronic diarrhea patients with MC (n = 85)	**Chronic diarrhea patients without MC (n = 391)**	**Chronic diarrhea patients with MC (n = 74)**	**Chronic diarrhea patients without MC (n = 386)**
Mean age (SD)	65.8 (14.2)	51.0 (17.2)	65.6 (12.2)	50.4 (16.3)
Age ≥50 years (%)	76 (89.4%)	214 (54.7%)	65 (87.8%)	208 (53.9%)
Female gender (%)	64 (75.3%)	239 (61.1%)	51 (68.9%)	224 (58.0%)
Current PPI use (%)	34 (40.0%)	98 (25.1%)	35 (47.3%)	101 (26.2%)
Current NSAID use (%)	14 (16.5%)	16 (4.1%)	12 (16.2%)	28 (7.3%)
Celiac disease (%)	6 (7.1%)	12 (3.1%)	2 (2.7%)	8 (2.1%)

Table 2: Item Scores within the Diagnostic Scoring System.

Item	Odds ratio	95% CI	Regression coefficient	Used within the Scoring System	Item score
Female gender	1.94	1.14 – 3.30	0.662	Yes	+4
Age ≥50 years	6.98	3.40 – 14.3	1.944	Yes	+13
Current PPI use	2.47	1.46 – 4.16	0.903	Yes	+6
Current NSAID use	5.28	2.44 – 11.4	1.664	Yes	+11
Weight loss present	1.89	1.11 – 3.24	0.639	Yes	+4
Abdominal pain present	0.28	0.16 – 0.47	-1.283	Yes	-8
Celiac disease present	2.35	0.85 – 6.51	0.854	No	N/A
Nocturnal diarrhea present	1.17	0.54 – 2.53	0.155	No	N/A

Table 3: Sensitivity, Specificity, Positive, and Negative Predictive Values of the Diagnostic Scoring System in Chronic Diarrhea Patients in the Derivation and Validation Cohorts.

		No. with MC with a score above the cut-off	No. without MC with a score above the cut-off	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Derivation cohort	**Score of ≥+8**	80 / 85	201 / 391	94.1% (86.8% - 98.1%)	48.6% (43.5% - 53.7%)	28.5% (23.5% - 34.0%)	97.4% (94.1% - 98.9%)
	Score of ≥+4	84 / 85	246 / 391	98.8% (93.6% - 99.8%)	37.1% (32.4% - 42.0%)	25.5% (21.1% - 30.4%)	99.3% (96.2% - 99.9%)
Validation cohort	**Score of ≥+8**	67 / 74	211 / 386	90.5% (81.7% - 95.3%)	45.3% (40.3% - 50.5%)	24.1% (19.2% - 29.6%)	96.2% (92.2% - 98.4%)
	Score of ≥+4	70 / 74	260 / 386	94.6% (86.9% - 97.9%)	32.6% (28.0% - 37.6%)	21.2% (16.9% - 26.0%)	96.9% (92.3% - 99.2%)

Figure 1a: ROC curve for the Diagnostic Scoring System in Predicting MC in the Derivation Cohort.

Figure 1b: ROC curve for the Diagnostic Scoring System in Predicting MC in the Validation Cohort.