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TITLE PAGE

Title: Lack of Utility of Symptoms and Signs at First Presentation as Predictors of Inflammatory Bowel Disease in Secondary Care.

Short running head: Symptoms and Signs at First Presentation in Predicting IBD.

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Abbreviations:

BMI	body mass index
CI	confidence interval
CD	Crohn's disease
GI	gastrointestinal
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified
IBS	irritable bowel syndrome
LR	likelihood ratio
PR	per rectum

SD	standard deviation
UC	ulcerative colitis

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ABSTRACT

Objectives: There are few data concerning the utility of symptoms and signs at first presentation in predicting a diagnosis of ulcerative colitis (UC) or Crohn's disease (CD). We conducted a study to examine this issue in secondary care.

Methods: We collected complete symptom, colonoscopy, and histology data prospectively from 1981 consecutive adult patients with lower gastrointestinal symptoms at two hospitals in Hamilton, Ontario. Assessors were blinded to symptom status. The reference standard used to define the presence of UC or CD was according to accepted histological criteria. Patients without UC or CD served as controls. Sensitivity, specificity, and positive and negative likelihood ratios (LRs) were calculated for individual items from the clinical history, as well as combinations of these.

Results: In identifying 302 patients with IBD, positive LRs for individual items ranged from 1.18 (incomplete emptying) to 2.30 (>4 stools per day), and negative LRs from 0.70 (bloody stools) to 0.96 (incomplete emptying). Combinations of items had a high specificity, but at the expense of sensitivity. Items that were independent predictors of IBD after logistic regression analysis were family history of IBD, younger age, more than 4 stools ≥75% time, urgency most of the time, and anemia.

Conclusions: Individual items from the clinical history are not helpful in predicting a diagnosis of UC or CD. However, this may be because some items lacked sufficient detail. Combinations of symptoms and computer models had a high specificity, but overall were only modestly useful diagnostically. Future studies should evaluate biological markers in combination with symptoms to improve accuracy.

What is current knowledge?

There may be a considerable delay between onset of symptoms and a diagnosis of inflammatory bowel disease (IBD) being secured.

This delay may mean that there is increased digestive damage due to a failure to institute appropriate therapy.

The utility of symptoms and signs in predicting a diagnosis of IBD is unclear.

What is new here?

Individual symptoms and signs are not helpful in predicting a diagnosis of IBD.

Combinations of symptoms and signs, and computer models exhibited greater specificity, but poor sensitivity.

Future studies should evaluate biological markers in combination with symptoms to improve the accuracy of diagnosing IBD, in order to develop referral criteria that identify patients with a high likelihood of IBD who warrant urgent investigation.

INTRODUCTION

The inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), are a group of disorders of the gastrointestinal (GI) tract of unknown etiology. The population prevalence of UC and CD are between 150 and 250 per 100,000 people. [1-6] Patients present with symptoms such as abdominal pain, change in bowel habit, and rectal bleeding. [7, 8] However, these symptoms are common in patients who do not have IBD, such as irritable bowel syndrome (IBS) or hemorrhoids. [9, 10] As not all people who experience these symptoms will consult a doctor or be referred for investigation, there is therefore the potential for a diagnosis of IBD to be missed or delayed, due to confusion with non-organic lower GI conditions such as IBS. [11, 12]

Data from population-based cohorts suggest that there may be a considerable lag time between onset of symptoms and a diagnosis of IBD being secured. [13, 14] Delays in diagnosis theoretically mean that there is the possibility of worsening disease activity and increased digestive damage due to a failure to institute appropriate therapy that may alter the natural history of the disease in a timely manner. This is supported by recent evidence suggesting that the length of diagnostic delay correlates with stricture development and need for intestinal surgery. [15]

This delay in diagnosis may be avoided if doctors were more aware of which symptoms or signs were likely to be predictive of a diagnosis of IBD. However, there have been few studies to our knowledge, to date examining this issue. We have therefore conducted a study to assess the utility of individual symptoms and signs at first presentation, as well as combinations of these, in predicting a histologically confirmed diagnosis of UC or CD among a large cohort of unselected patients newly

referred from primary care to secondary care for the assessment and investigation of lower GI symptoms.

METHODS

Participants and Setting

We recruited consecutive unselected patients, aged ≥16 years, newly referred from primary care during a 4-year period for consideration of investigation of GI symptoms to the outpatient clinics of two hospitals in Hamilton, Ontario. The McMaster University Medical Center and St. Joseph's Healthcare provide secondary care services to a local population of 520,000. All new patients were potentially eligible, unless they could not understand written English, and were provided with a study information sheet at their initial clinic visit. As this was a questionnaire study, patients who agreed to participate were asked to provide written informed consent at that visit. The study was approved by the Hamilton Health Sciences and McMaster University research ethics board in January 2008, and recruitment continued through to December 2012. We have previously validated the Rome III criteria for IBS and functional dyspepsia, and described the overlap between the functional bowel disorders, using this dataset. [16-18]

Data Collection and Synthesis

Demographic and Symptom Data

All demographic and symptom data were collected prospectively at the initial clinic visit, and hence prior to referral for colonoscopy. We recorded age, gender, ethnicity, marital status, educational level, lifestyle (tobacco and alcohol use), height (in metres), and weight (in kilograms), which were used to calculate body mass index (BMI). Symptom data were collected using the Rome III diagnostic questionnaire for

the adult functional GI disorders. This is a 93-item instrument, which has been validated previously. [19] We used the symptoms and signs from this questionnaire that may be the presenting features of IBD. These included: presence of lower abdominal pain; presence of a feeling of incomplete emptying after a bowel movement; passage of ≥4 stools per day; presence of loose, mushy, or watery stools; presence of urgency; passage of mucus per rectum (PR); passage of blood in the stools; presence of anal pain; whether the patient had been told by their doctor that they were anemic; or weight loss of >5kg over the last year. We also recorded whether there was a family history of CD or UC. As these were all newly referred patients in whom a final diagnosis had not been reached, we did not use disease specific IBD questionnaires such as the Mayo score or the Crohn's disease activity index. All questionnaire data were entered into a database by a trained researcher who was not involved with the clinical care of the patient, thus ensuring assessors were blinded to symptom status.

Colonoscopic and Histopathological Data

All included patients underwent complete colonoscopy to the cecum or terminal ileum, as part of routine clinical practice, using Pentax colonoscopes (Pentax Canada, Inc) and following standard bowel preparation, using either polyethylene glycol or sodium picosulfate (depending on patient and physician preference). The responsible physician performing colonoscopic examinations was blinded to the questionnaire data for each patient. Findings were recorded using the endoPRO reporting system (Pentax Canada, Inc). These reports were accessed by the study investigators in order to record the ultimate colonoscopic diagnosis for each included patient.

Biopsy specimens were obtained at the discretion of the responsible physician performing the colonoscopy. These specimens were interpreted by experienced GI histopathologists, who were also blinded to the questionnaire data of the patient. Histolopathological findings were recorded using the MEDITECH Healthcare Reporting System (Medical Information Technology Inc, Westwood, MA), and this was accessed by the study investigators in order to record the ultimate histopathological diagnosis.

The reference standard to define patients with IBD was those who exhibited findings consistent with either CD or UC after histopathological examination of their biopsy specimens, according to accepted criteria. [20] Patients with lower GI symptoms with normal colonoscopy and normal histology, or those with any other organic lower GI disease at either colonoscopy (including colorectal carcinoma, stricture, evidence of radiation-induced colorectal disease, colorectal adenoma, or hemorrhoids), or on examination of biopsy specimens (colonic or rectal adenocarcinoma, microscopic colitis, ischemic colitis, radiation enteropathy, or neuroendocrine tumor) served as controls without IBD.

Statistical Analysis

In order to assess whether those who underwent colonoscopy were representative of all patients seen in the two GI outpatient clinics demographic data were compared between those undergoing colonoscopy who completed the symptom questionnaire, and those who completed the symptom questionnaire but did not undergo colonoscopy, using a χ^2 test for categorical data, and an independent samples t-test for continuous data, with a mean and standard deviation (SD). Due to multiple comparisons a 2-tailed P value of <0.01 was considered statistically significant for

these analyses. These statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc, Chicago, IL, USA).

The aim of the study was to describe the performance of individual items from the clinical history, as well as combinations of these, in predicting the presence of true IBD, UC, or CD versus the reference standard. The sensitivity, specificity, and positive and negative likelihood ratios (LRs), and their 95% confidence intervals (CIs), were calculated for each of these using a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA). The positive LR can be calculated from the formula: positive LR = sensitivity / (1-specificity), while the negative LR is derived from the formula: negative LR = (1-sensitivity) / specificity. As a guide, positive LRs above 10 are very useful in ruling in a disease, and negative LRs below 0.1 are very useful in ruling out a disease. [21] These calculations were checked using Meta-DiSc® version 1.4 (Universidad Complutense, Madrid, Spain). We performed these analyses for UC and CD separately, using both those with normal colonoscopy and histology and those with other organic lower GI disease as controls in order to best reflect the heterogeneous nature of patients consulting with lower GI symptoms in usual clinical practice.

Logistic regression models were conducted for all IBD patients, as well as UC and CD separately to evaluate symptoms that independently predicted disease and interaction terms were included for all significant symptom predictors in the model in order to assess whether there were statistically significant interactions between symptoms. The proportion of the variation in the data explained by the model was calculated using the Nagelkerke R^2 statistic. These analyses were performed using SPSS for Windows version 21.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

There were a total of 4224 consecutive patients who gave informed consent and were recruited in to the study between January 2008 and December 2012 (Figure 1). The mean age of recruited subjects was 47.6 years (range 16 to 93 years) and 2617 (62.0%) were female. In total, 1981 (46.9%) of these 4224 patients underwent complete colonoscopic evaluation for their lower GI symptoms. The remaining patients were consulting with upper GI symptoms, or colonoscopy was deemed unnecessary in reaching a diagnosis by the responsible physician. Demographic data of the patients who had complete colonoscopy, compared with the 2243 subjects who did not, have been described previously. [16] Briefly, those undergoing colonoscopy were slightly older (48.9 years vs. 46.1 years), of higher BMI (27.3kg/m^2 vs. 26.7kg/m^2), and were more likely to be White Caucasian (90.8% vs. 85.5%), but there were no other significant differences.

Of those colonoscoped, 1289 (65.1%) had colonic or rectal biopsies taken, and 302 (15.2%) were found to have IBD, 104 (5.2%) with UC, 147 (7.4%) with CD, and 51 (2.6%) with IBD-U. Baseline demographic data of those with IBD, as well as the 1679 patients without IBD are provided in Table 1. The 1679 patients without IBD included 897 (53.4%) with both a normal colonoscopy and normal colonic biopsies, 468 (27.9%) with adenomatous or hyperplastic polyps, 162 (9.6%) with hemorrhoids, 49 (2.9%) with colorectal cancer, 33 (2.0%) with microscopic colitis, 15 (0.9%) with angiodysplasia, and 10 (0.6%) with radiation enteropathy.

Performance of Symptoms and Signs at First Presentation in Predicting IBD

The performance of individual items, as well as combinations of these, in predicting a diagnosis of IBD (UC, CD, and IBD-U combined) is summarized in

Table 2. Positive LRs for individual items ranged from 1.18 for the presence of a feeling of incomplete emptying after a bowel movement at least most of the time, to 2.30 for more than 4 stools per day at least most of the time. Negative LRs were of similar utility, ranging from 0.70 for presence of blood in the stools to 0.96 for the presence of a feeling of incomplete emptying after a bowel movement at least most of the time.

When symptoms and signs were combined the positive LRs improved (Table 2). A combination of having been told by a doctor they were anemic, weight loss of >5kg in the last year, and more than 4 stools per day yielded a positive LR of 8.77, presence of more than 4 stools per day, blood in the stools, and mucus PR a positive LR of 5.56, and having been told by a doctor they were anemic and more than 4 stools per day gave a positive LR of 5.53. However, negative LRs were poor, ranging from 0.85 to 0.96, because of their low sensitivity, as few patients with IBD reported these symptom combinations. When we repeated the above analyses with controls split into two groups, those with an organic lower GI disease, and those with no lower GI organic disease, the results were remarkably similar (data not shown).

After logistic regression using all factors described in Table 2, family history of IBD, younger age, urgency at least most of the time, more than 4 stools ≥ 75% time, urgency most of the time, and having been told by a doctor they were anemic were independent predictors of IBD (Supplementary Table 1). None of the interaction terms were statistically significant and the model explained only 30% of the variation in the data. Overall the model had a sensitivity of 56% (95% CI 49% to 62%), a specificity of 92% (95% CI 90% to 94%), a positive LR of 6.9 (95% CI 5.2 to 9.1), a negative LR of 0.48 (95% CI 0.41 to 0.55), and a diagnostic odds ratio of 14.3 (95% CI 9.6 to 21.4).

Performance of Symptoms and Signs at First Presentation in Predicting UC

The performance of individual items from the clinical history, as well as combinations of these, in predicting UC versus the reference standard is provided in Table 3. Individual items performed only modestly in predicting the presence of UC, with positive LRs ranging between 1.15 for presence of lower abdominal pain at least once a week, and 2.85 for passage of mucus PR at least most of the time, and negative LRs of between 0.53 for absence of blood in the stools, and 0.94 for presence of a feeling of incomplete emptying after a bowel movement at least most of the time.

Combinations of items were slightly more promising (Table 3). Having been told by a doctor they were anemic, weight loss of >5kg in the last year, and more than 4 stools per day yielded a positive LR of 14.6, having been told by a doctor they were anemic and more than 4 stools per day gave a positive LR of 7.87, and presence of more than 4 stools per day, blood in the stools, and mucus PR a positive LR of 7.38. Positive LRs were high because few people without UC reported these combinations, meaning that specificity ranged from 97.9% to 99.5%. However, in all instances the negative LRs for these combinations were poor, ranging between 0.85 and 0.93, because the number of people with UC reporting all of the required items was small, meaning that the sensitivities were low for all of these, ranging between 7.9% and 16.7%. We repeated all the above analyses with controls split into two groups, those with an organic lower GI disease, and those with no lower GI organic disease, but the results were remarkably similar (data not shown).

A logistic regression model of all factors described in Table 3 found that family history of UC, more than 4 stools ≥ 75% time, urgency most of the time, having been told by a doctor they were anemic, and blood in the stools were independent predictors of UC (Supplementary Table 2). None of the interaction terms

were statistically significant and the model explained only 18% of the variation in the data. Overall the model had a sensitivity of 11% (95% CI 5% to 19%), a specificity of 98% (95% CI 97% to 99%), a positive LR of 6.2 (95% CI 2.7 to 13.7), a negative LR of 0.91 (95% CI 0.83 to 0.96), and a diagnostic odds ratio of 6.8 (95% CI 2.8 to 16.4).

Performance of Symptoms and Signs at First Presentation in Predicting CD

The performance of individual items, as well as combinations of these, in predicting a diagnosis of CD is summarized in Table 4. Positive LRs for individual items were again modest at best, ranging from 1.02 for the presence of a feeling of incomplete emptying after a bowel movement at least most of the time, to 2.18 for either a family history of CD or more than 4 stools per day at least most of the time. Negative LRs were of similar utility, ranging from 0.70 for loose stools at least 75% of the time to 1.00 for the presence of a feeling of incomplete emptying after a bowel movement at least most of the time.

Combinations of items performed better, although not as well as in UC. Having been told by a doctor they were anemic, weight loss of >5kg in the last year, and more than 4 stools per day yielded a positive LR of 6.46, presence of more than 4 stools per day, blood in the stools, and mucus PR yielded a positive LR of 5.67, and having been told by a doctor they were anemic and more than 4 stools per day gave a positive LR of 5.46. However, in all instances negative LRs were suboptimal ranging from 0.90 to 0.97 due to the low sensitivity of these combinations. Again, when we repeated all the above analyses with controls split into two groups, those with an organic lower GI disease, and those with no lower GI organic disease, the observed LRs were broadly comparable (data not shown).

A logistic regression model of all factors described in Table 4 found that family history of CD, loose stools ≥ 75% time, and having been told by a doctor they were anemic were independent predictors of CD (Supplementary Table 3). None of the interaction terms were statistically significant and the model explained only 15% of the variation in the data. Overall the model had a sensitivity of 9.1% (95% CI 4.8% to 15.3%), a specificity of 98.6% (95% CI 97.3% to 99.4%), a positive LR of 6.5 (95% 2.9 to 14.8), a negative LR of 0.92 (95% CI 0.86 to 0.96), and a diagnostic odds ratio of 7.1 (95% CI 2.7 to 19.4).

DISCUSSION

We have examined the utility of individual symptoms and signs at first presentation, as well as combinations of these, in predicting a diagnosis of UC or CD versus an accepted reference standard in a cohort of almost 2000 unselected new referrals to secondary care with lower GI symptoms who underwent complete colonoscopy. The prevalence of IBD in our cohort, after investigation, was 15%. The study has demonstrated that individual items perform modestly at best in predicting a diagnosis of IBD, with positive LRs ranging from 1.18 to 2.30, and negative LRs from 0.70 to 0.96. Combinations of items were an improvement in terms of positive LRs, which in some cases were above 5, but negative LRs were poor in all instances due to the low sensitivities of these combinations, which were below 10% in some cases because few patients with IBD reported all of these. The performance of these items was not enhanced when they were used to distinguish between those with IBD and only those without organic lower GI disease at colonoscopy.

Strengths of this study include the large sample size, with over 1900 individuals undergoing colonoscopy and providing complete symptom data, meaning that this is one of the largest studies to examine the utility of symptoms and signs at first presentation in predicting a diagnosis of UC or CD conducted, to our knowledge, to date. The study was designed to adhere closely to the STARD guidelines for the reporting of studies of diagnostic accuracy, with consecutive patients recruited, assessors blinded, and an accepted reference standard used. We also performed subgroup analyses, with only those with no evidence of organic lower GI disease as the comparator group. Finally, the majority of patients we recruited were unselected referrals to secondary care, and we used a heterogeneous group of patients with either no organic lower GI disease or an organic lower GI disease other than IBD as controls

without IBD, meaning that the results are likely to be generalizable to Gastroenterologists consulting with individuals with lower GI symptoms, in whom IBD may be suspected, in usual clinical practice.

Weaknesses of the study include the fact that we did not perform colonoscopy in all individuals with lower GI symptoms as part of the study design. This means that in some individuals who were not subject to colonoscopy a diagnosis of IBD may have been missed. If these patients also endorsed the items from the clinical history that we studied, then the accuracy of these may have been underestimated. In addition, those who did undergo colonoscopy and provide complete symptom data were not entirely representative of the entire study population, with an over representation of White Caucasians, older individuals, and patients with a higher BMI. [16] However, in most cases the absolute differences in demographic data between those undergoing colonoscopy and providing complete symptom data and those who did not undergo colonoscopy were small. Finally, the questions that were contained within the questionnaire perhaps lacked sufficient detail, in some instances, to be able to differentiate between IBD and other organic lower GI disease. An example would be passage of blood in the stools, where some physicians consulting with a patient with this symptom would enquire about exact color, and whether the blood was mixed in with the stools, in the toilet bowl, or on the toilet paper.

In addition, as the study was conducted in usual clinical practice, terminal ileal intubation was not mandated, nor did we perform small bowel investigations in all individuals, meaning that isolated CD in the proximal or distal ileum may have been misclassified as the absence of IBD in some instances. However, the majority of CD patients will have either a colonic or ileocolonic distribution at diagnosis, [22] so it is likely that the number of individuals misclassified will be small. The questionnaire we

utilized did not assess the presence of other symptoms or signs from the clinical history and examination that may be useful in predicting a diagnosis of IBD, such as nocturnal diarrhea, presence of an abdominal mass, or fever. Finally, as this study was conducted within usual clinical practice, we did not mandate a minimum level of blood work, such as complete blood count or C-reactive protein, or measurement of fecal calprotectin levels. It may be that combining these, or other, biomarkers with items from the clinical history would have provided a greater ability to discriminate between patients with and without IBD.

Our finding that items from the clinical history performed only modestly in predicting a diagnosis of IBD, CD or UC is not surprising. We have previously studied the utility of symptoms and signs in discriminating between functional and organic lower GI disease, [23, 24] including colorectal cancer and IBS, and in most cases these have been disappointing. One method that can be utilized when clinical features are suboptimal in predicting the disease of interest is to concentrate on those symptoms or signs that have a high specificity, as this can be used to rule the disease of interest in. [25] Applying this approach to our data would suggest that specificity can be increased by using more than one item in almost any combination, or using data derived from computer models. However all approaches that lead to specificities >98% have sensitivities <15% and this is unlikely to be diagnostically useful.

Other investigators have demonstrated that a delay in confirming a diagnosis of IBD is associated with increased need for surgery, poorer treatment outcomes, reduced quality of life, and extension of disease. [15, 26, 27] Given the modest positive LRs of most of the symptoms we examined, an alternative approach to expedite a diagnosis is to use the presence of these symptoms as potential indicators of IBD, which then mandate further urgent work-up in the form of measurement of

inflammatory markers in stool and blood, rather than immediate referral for colonoscopy. Of the available markers, fecal calprotectin performs better than blood C-reactive protein or erythrocyte sedimentation rate in screening for IBD. [28-30]

The findings of the current study demonstrate that symptoms and signs at first presentation are not helpful in predicting a diagnosis of IBD as an entity, or either CD or UC separately. Future studies should evaluate biological markers in combination with symptoms to improve the accuracy of diagnosing IBD. This may enable the development of referral criteria to better identify patients with a high likelihood of IBD who warrant urgent investigation.

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CONFLICTS OF INTEREST/STUDY SUPPORT

Guarantor of the article: ACF is guarantor.

Specific author contributions: ACF, PM, PB, DGM, CB, MIP-S, and WR conceived and drafted the study. ACF, CB, and MIP-S collected all data. ACF analyzed and interpreted the data. PM and WR provided statistical advice and support. ACF drafted the manuscript. All authors have approved the final draft of the manuscript.

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REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;**142**:46-54.

2. Loftus CG, Loftus Jr EV, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. Inflamm Bowel Dis 2007;**13**:254-261.

3. Loftus Jr EV, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. Gastroenterology 1999;**116**:1161-1168.

4. Loftus Jr EV, Silverstein MD, Sandborn WJ, Tremaine WJ, Harmsen WS, Zinsmeister AR. Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. Gut 2000;**46**:336-343.

5. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol 2007;**5**:1424-1429.

6. Langholz E, Munkholm P, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of ulcerative colitis in Copenhagen county from 1962 to 1987. Scand J Gastroenterol 1991;**26**:1247-1256.

7. Ford AC, Khan KJ, Talley NJ, Moayyedi P. 5-aminosalicylates prevent relapse of Crohn's disease after surgically induced remission: systematic review and meta-analysis. Am J Gastroenterol 2011;**106**:413-420.

8. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet 2012;**380**:1590-605.

9. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol 2012;**10**:712-721.

10. Eslick GD, Kalantar JS, Talley NJ. Rectal bleeding: epidemiology, associated risk factors, and health care seeking behaviour: a population-based study. Colorectal Dis 2009;**11**:921-6.

11. Barratt SM, Leeds JS, Robinson K, Lobo AJ, McAlindon ME, Sanders DS. Prodromal irritable bowel syndrome may be responsible for delays in diagnosis in patients presenting with unrecognized Crohn's disease and celiac disease, but not ulcerative colitis. Dig Dis Sci 2011;**56**:3270-5.

12. Burgmann T, Clara I, Graff L, et al. The Manitoba Inflammatory Bowel Disease Cohort Study: prolonged symptoms before diagnosis--how much is irritable bowel syndrome? Clin Gastroenterol Hepatol 2006;**4**:614-20.

13. Vavricka SR, Spigaglia SM, Rogler G, et al. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. Inflamm Bowel Dis 2012;**18**:496-505.

14. Romberg-Camps MJ, Hesselink-van de Kruijs MA, Schouten LJ, et al. Inflammatory Bowel Disease in South Limburg (the Netherlands) 1991-2002: Incidence, diagnostic delay, and seasonal variations in onset of symptoms. J Crohns Colitis 2009;**3**:115-24.

15. Schoepfer AM, Dehlavi MA, Fournier N, et al. Diagnostic delay in Crohn's disease is associated with a complicated disease course and increased operation rate. Am J Gastroenterol 2013;**108**:1744-53.

16. Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. Gastroenterology 2013;**145**:1262-1270.

17. Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. The Rome III criteria for the diagnosis of functional dyspepsia in secondary care are not superior to previous definitions. Gastroenterology 2014;**146**:932-40.

18. Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Characteristics of functional bowel disorder patients: A cross-sectional survey using the Rome III criteria. Aliment Pharmacol Ther 2014;**39**:312-21.

19. Whitehead WE, and the Validation Working Team Committee in association with the Rome Questionnaire C. Development and validation of the Rome III diagnostic questionnaire. In: Drossman DA, editor.Rome III: The functional gastrointestinal disorders, 3rd edition.Virginia: Degnon Associates Inc 2006:835-853.

20. Magro F, Langner C, Driessen A, et al. European consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis 2013;**7**:827-51.

21. Moayyedi P, Axon AT. The usefulness of the likelihood ratio in the diagnosis of dyspepsia and gastroesophageal reflux disease. Am J Gastroenterol 1999;**94**:3122-5.

22. Lakatos L, Kiss LS, David G, et al. Incidence, disease phenotype at diagnosis, and early disease course in inflammatory bowel diseases in Western Hungary, 2002-2006. Inflamm Bowel Dis 2011;**17**:2558-65.

23. Ford AC, Veldhuyzen Van Zanten SJO, Rodgers CC, Talley NJ, Vakil NB, Moayyedi P. Diagnostic utility of alarm features for colorectal cancer: Systematic review and meta-analysis. Gut 2008;**57**:1545-1553.

24. Ford AC, Talley NJ, Veldhuyzen Van Zanten SJ, Vakil NB, Simel DL, Moayyedi P. Will the history and physical examination help establish that irritable bowel syndrome is causing this patient's lower gastrointestinal tract symptoms? JAMA: The Journal of the American Medical Association 2008;**300**:1793-1805.

25. Haynes RB, Sackett DL, Guyatt GH, Tugwell P. Evaluating diagnostic tests. Clinical epidemiology: How to do clinical practice research.Lippincott, Williams and Wilkins 2006:273-322.

26. Pellino G, Sciaudone G, Selvaggi F, Riegler G. Delayed diagnosis is influenced by the clinical pattern of Crohn's disease and affects treatment outcomes

and quality of life in the long term: a cross-sectional study of 361 patients in Southern Italy. Eur J Gastroenterol Hepatol 2015;**27**(2):175-81.

27. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, et al. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol 2009;**104**(8):2080-8.

28. Langhorst J, Elsenbruch S, Koelzer J, Rueffer A, Michalsen A, Dobos GJ. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. Am J Gastroenterol 2008;**103**(1):162-9.

29. Henderson P, Casey A, Lawrence SJ, et al. The diagnostic accuracy of fecal calprotectin during the investigation of suspected pediatric inflammatory bowel disease. Am J Gastroenterol 2012;**107**(6):941-9.

30. Schoepfer AM, Trummler M, Seeholzer P, Seibold-Schmid B, Seibold F. Discriminating IBD from IBS: comparison of the test performance of fecal markers, blood leukocytes, CRP, and IBD antibodies. Inflamm Bowel Dis 2008;**14**(1):32-9.

TABLES

Table 1. Demographics and Baseline Characteristics of Patients with IBD Compared with Patients without IBD.

	Patients with IBD (n = 302)	**Patients without IBD (n = 1679)**
Mean age (SD)	37.1 (14.9)	51.5 (16.5)
Mean BMI (SD)	26.0 (6.2)	27.5 (5.9)
Female gender (%)	175 (57.9)	1076 (64.1)
Tobacco user (%)	63 (20.9)	346 (20.6)
Alcohol user (%)	171 (56.6)	994 (59.2)
Marital status (%)		
Married or co-habiting	164 (54.3)	1048 (62.4)
Divorced or separated	22 (7.3)	205 (12.2)
Never married	110 (36.4)	319 (19.0)
Widowed	2 (0.7)	88 (5.2)
Educational level (%)		
Elementary	9 (3.0)	86 (5.1)
High school	85 (28.1)	487 (29.0)
College or technical school	87 (28.8)	504 (30.0)
University	92 (30.5)	412 (24.5)
Postgraduate	24 (7.9)	158 (9.4)
Ethnicity (%)		
White Caucasian	271 (89.7)	1516 (90.3)
South Asian	5 (1.7)	17 (1.0)
Middle-Eastern	3 (1.0)	18 (1.1)
First Nations	1 (0.3)	20 (1.2)
African	5 (1.7)	16 (1.0)
South-East Asian	3 (1.0)	11 (0.7)
Latin-American	2 (0.7)	11 (0.7)

Table 2. Sensitivity, Specificity, and Positive and Negative Likelihood Ratios for Various Items from the Clinical History in Predicting a Diagnosis of IBD.

	No. with IBD reporting	No. without IBD reporting	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Family history of UC or CD	93 / 278	272 / 1461	33.5% (27.9% - 39.3%)	81.4% (79.3% - 83.4%)	1.80 (1.47 - 2.18)	0.82 (0.74 - 0.89)
Lower abdominal pain ≥once a week	169 / 299	745 / 1622	56.5% (50.7% - 62.2%)	54.1% (51.6% - 56.5%)	1.23 (1.09 - 1.37)	0.80 (0.70 – 0.92)
Presence of a feeling of incomplete emptying after a bowel movement ≥most of the time	59 / 300	277 / 1661	19.7% (15.3% - 24.6%)	83.3% (81.4% - 85.1%)	1.18 (0.91 - 1.51)	0.96 (0.90 - 1.02)
≥4 stools per day ≥most of the time	86 / 298	208 / 1655	28.9% (23.8% - 34.4%)	87.4% (85.7% - 89.0%)	2.30 (1.84 - 2.85)	0.81 (0.75 - 0.87)
Loose, mushy, or watery stools ≥75% of the time	134 / 299	401 / 1645	44.8% (39.1% - 50.6%)	75.6% (73.5% - 77.7%)	1.84 (1.57 - 2.13)	0.73 (0.65 - 0.81)
Urgency ≥most of the time	83 / 298	235 / 1655	27.9% (22.8% - 33.3%)	85.8% (84.3% - 87.5%)	1.96 (1.57 - 2.43)	0.84 (0.78 - 0.90)

Mucus PR ≥most of the time	46 / 296	115 / 1591	15.5% (11.6% - 20.2%)	92.8% (91.4% - 94.0%)	2.15 (1.56 – 2.94)	0.91 (0.86 - 0.95)
Blood in the stools	157 / 298	539 / 1649	52.7% (46.8% - 58.5%)	67.3% (65.0% - 69.6%)	1.61 (1.41 – 1.82)	0.70 (0.62 - 0.79)
Aching in the back passage ≥once a week	85 / 296	355 / 1619	28.7% (23.6% - 34.2%)	78.1% (76.0% - 80.1%)	1.31 (1.07 - 1.59)	0.91 (0.84 - 0.98)
Weight loss >5kg in the last year	77 / 288	259 / 1604	26.7% (21.7% - 32.2%)	83.9% (82.0% - 85.6%)	1.66 (1.32 - 2.06)	0.87 (0.81 - 0.93)
Told by the doctor you are anemic	106 / 294	374 / 1614	36.1% (30.6% - 41.8%)	76.8% (74.7% - 78.9%)	1.56 (1.30 – 1.85)	0.83 (0.76 - 0.91)
≥4 stools per day ≥most of the time and blood in the stools	59 / 299	88 / 1656	19.7% (15.4% - 24.7%)	94.7% (93.5% - 95.7%)	3.71 (2.73 - 5.02)	0.85 (0.80 - 0.89)
≥4 stools per day ≥most of the time and blood in the stools and mucus PR ≥most of the time	22 / 298	22 / 1656	7.4% (4.7% - 11.0%)	98.7% (98.0% - 99.2%)	5.56 (3.13 - 9.81)	0.94 (0.90 - 0.96)
≥4 stools per day ≥most of the time and mucus PR ≥most of the time	29 / 297	45 / 1654	9.8% (6.6% - 13.7%)	97.3% (96.4% - 98.0%)	3.60 (2.29 - 5.59)	0.93 (0.89 - 0.96)

Blood in the stools and mucus PR ≥most of the time	37 / 298	60 / 1630	12.4% (8.9%- 16.7%)	96.3% (95.3% - 97.2%)	3.37 (2.28 - 4.96)	0.91 (0.86 - 0.94)
Weight loss >5kg in the last year and ≥4 stools per day ≥most of the time	32 / 292	47 / 1652	11.0% (7.6% - 15.1%)	97.2% (96.2% - 97.9%)	3.85 (2.50 - 5.89)	0.92 (0.87 - 0.95)
Told by the doctor you are anemic and ≥4 stools per day ≥most of the time	35 / 299	35 / 1653	11.7% (8.3% - 15.9%)	97.9% (97.1% - 98.5%)	5.53 (3.52 - 8.63)	0.90 (0.86 - 0.94)
Told by the doctor you are anemic and weight loss >5kg in the last year	33 / 293	61 / 1628	11.3% (7.9% - 15.5%)	96.3% (95.2% - 97.1%)	3.01 (2.00 - 4.48)	0.92 (0.88 - 0.96)
Told by the doctor you are anemic and weight loss >5kg in the last year and ≥4 stools per day ≥most of the time	14 / 295	9 / 1663	4.7% (2.6% - 7.8%)	99.5% (99.0% - 99.8%)	8.77 (3.91 - 19.6)	0.96 (0.93 - 0.98)

Table 3. Sensitivity, Specificity, and Positive and Negative Likelihood Ratios for Various Items from the Clinical History in Predicting a Diagnosis of UC.

	No. with UC reporting	No. without IBD reporting	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Family history of UC	26 / 97	152 / 1431	26.8% (18.3% - 36.8%)	89.4% (87.7% - 90.9%)	2.52 (1.74 - 3.56)	0.82 (0.71 - 0.91)
Family history of UC or CD	32 / 97	272 / 1461	33.0% (23.8% - 43.3%)	81.4% (79.3% - 83.4%)	1.77 (1.29 - 2.35)	0.82 (0.70 - 0.93)
Lower abdominal pain ≥once a week	54 / 102	745 / 1622	52.9% (42.8% - 62.9%)	54.1% (51.6% - 56.5%)	1.15 (0.94 - 1.37)	0.87 (0.69 - 1.05)
Presence of a feeling of incomplete emptying after a bowel movement ≥most of the time	22 / 103	277 / 1661	21.4% (13.9% - 30.5%)	83.3% (81.4% - 85.1%)	1.28 (0.86 - 1.84)	0.94 (0.84 - 1.03)
≥4 stools per day ≥most of the time	35 / 103	208 / 1655	34.0% (24.9% - 44.0%)	87.4% (85.7% - 89.0%)	2.70 (1.98 - 3.58)	0.76 (0.64 - 0.85)
Loose, mushy, or watery stools ≥75% of the time	44 / 102	401 / 1645	43.1% (33.4% - 53.3%)	75.6% (73.5% - 77.7%)	1.77 (1.37 - 2.21)	0.75 (0.62 - 0.88)

Urgency ≥most of the time	35 / 101	235 / 1655	34.7% (25.5% - 44.8%)	85.8% (84.3% - 87.5%)	2.44 (1.80 - 3.22)	0.76 (0.65 - 0.86)
Mucus PR ≥most of the time	21 / 102	115 / 1591	20.6% (13.2% - 29.7%)	92.8% (91.4% - 94.0%)	2.85 (1.85 - 4.25)	0.86 (0.76 - 0.93)
Blood in the stools	66 / 103	539 / 1649	64.1% (54.0% - 73.3%)	67.3% (65.0% - 69.6%)	1.96 (1.64 - 2.27)	0.53 (0.41 - 0.68)
Aching in the back passage ≥once a week	33 / 101	355 / 1619	32.7% (23.7% - 42.7%)	78.1% (76.0% - 80.1%)	1.49 (1.09 - 1.96)	0.86 (0.74 - 0.97)
Weight loss >5kg in the last year	28 / 100	259 / 1604	28.0% (19.5% - 37.8%)	83.9% (82.0% - 85.6%)	1.73 (1.23 - 2.37)	0.86 (0.74 - 0.95)
Told by the doctor you are anemic	37 / 102	374 / 1614	36.3% (27.0% - 46.4%)	76.8% (74.7% - 78.9%)	1.57 (1.18 - 2.02)	0.83 (0.70 - 0.95)
≥4 stools per day ≥most of the time and blood in the stools	30 / 103	88 / 1656	29.1% (20.6% - 38.9%)	94.7% (93.5% - 95.7%)	5.48 (3.77 - 7.77)	0.75 (0.65 - 0.83)
≥4 stools per day ≥most of the time and blood in the stools and mucus PR ≥most of the time	10 / 102	22 / 1656	9.8% (4.8% - 17.3%)	98.7% (98.0% - 99.2%)	7.38 (3.61 - 14.8)	0.91 (0.84 - 0.96)

≥4 stools per day ≥most of the time and mucus PR ≥most of the time	10 / 102	45 / 1654	9.8% (4.8% - 17.3%)	97.3% (96.4% - 98.0%)	3.60 (1.87 - 6.75)	0.93 (0.85 - 0.97)
Blood in the stools and mucus PR ≥most of the time	21 / 102	60 / 1630	20.6% (13.2%- 29.7%)	96.3% (95.3% - 97.2%)	5.59 (3.52 - 8.67)	0.82 (0.73 - 0.89)
Weight loss >5kg in the last year and ≥4 stools per day ≥most of the time	14 / 101	47 / 1652	13.9% (7.8% - 22.2%)	97.2% (96.2% - 97.9%)	4.87 (2.77 - 8.36)	0.89 (0.80 - 0.94)
Told by the doctor you are anemic and ≥4 stools per day ≥most of the time	17 / 102	35 / 1653	16.7% (10.0% - 25.3%)	97.9% (97.1% - 98.5%)	7.87 (4.55 - 13.3)	0.85 (0.77 - 0.91)
Told by the doctor you are anemic and weight loss >5kg in the last year	10 / 100	61 / 1628	10.0% (4.9% - 17.6%)	96.3% (95.2% - 97.1%)	2.67 (1.41 - 4.91)	0.94 (0.86 - 0.98)
Told by the doctor you are anemic and weight loss >5kg in the last year and ≥4 stools per day ≥most of the time	8 / 101	9 / 1663	7.9% (3.5% - 15.0%)	99.5% (99.0% - 99.8%)	14.6 (5.90 - 35.7)	0.93 (0.86 - 0.96)

Table 4. Sensitivity, Specificity, and Positive and Negative Likelihood Ratios for Various Items from the Clinical History in Predicting a Diagnosis of CD.

	No. with CD reporting	No. without IBD reporting	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Family history of CD	36 / 135	177 / 1445	26.7% (19.4% - 35.0%)	87.8% (86.0% - 89.4%)	2.18 (1.58 - 2.93)	0.84 (0.74 - 0.91)
Family history of CD or UC	50 / 137	272 / 1461	36.5% (28.4% - 45.2%)	81.4% (79.3% - 83.4%)	1.96 (1.52 - 2.48)	0.78 (0.68 - 0.88)
Lower abdominal pain ≥once a week	78 / 146	745 / 1622	53.4% (45.0% - 61.7%)	54.1% (51.6% - 56.5%)	1.16 (0.98 - 1.35)	0.86 (0.71 - 1.02)
Presence of a feeling of incomplete emptying after a bowel movement ≥most of the time	25 / 147	277 / 1661	17.0% (11.3% - 24.1%)	83.3% (81.4% - 85.1%)	1.02 (0.70 - 1.46)	1.00 (0.91 - 1.06)
≥4 stools per day ≥most of the time	40 / 146	208 / 1655	27.4% (20.4% - 35.4%)	87.4% (85.7% - 89.0%)	2.18 (1.61 - 2.89)	0.83 (0.74 - 0.91)
Loose, mushy, or watery stools ≥75% of the time	69 / 147	401 / 1645	46.9% (38.7% - 55.3%)	75.6% (73.5% - 77.7%)	1.93 (1.57 - 2.31)	0.70 (0.59 - 0.81)

Urgency ≥most of the time	35 / 147	235 / 1655	23.8% (17.2% - 31.5%)	85.8% (84.0% - 87.5%)	1.68 (1.22 - 2.26)	0.90 (0.80 - 0.96)
Mucus PR ≥most of the time	21 / 145	115 / 1591	14.5% (9.2% - 21.3%)	92.8% (91.4% - 94.0%)	2.00 (1.29 - 3.04)	0.92 (0.85 - 0.98)
Blood in the stools	64 / 146	539 / 1649	43.8% (35.6% - 52.3%)	67.3% (65.0% - 69.6%)	1.34 (1.09 - 1.61)	0.83 (0.71 - 0.95)
Aching in the back passage ≥once a week	38 / 145	355 / 1619	26.2% (19.3% - 34.2%)	78.1% (76.0% - 80.1%)	1.20 (0.89 - 1.57)	0.95 (0.84 - 1.03)
Weight loss >5kg in the last year	33 / 138	259 / 1604	23.9% (17.1% - 31.9%)	83.9% (82.0% - 85.6%)	1.48 (1.07 - 2.01)	0.91 (0.81 - 0.99)
Told by the doctor you are anemic	62 / 143	374 / 1614	43.4% (35.1% - 51.9%)	76.8% (74.7% - 78.9%)	1.87 (1.51 - 2.28)	0.74 (0.63 - 0.84)
≥4 stools per day ≥most of the time and blood in the stools	23 / 147	88 / 1656	15.7% (10.2% - 22.6%)	94.7% (93.5% - 95.7%)	2.94 (1.91 - 4.45)	0.89 (0.82 - 0.94)
≥4 stools per day ≥most of the time and blood in the stools and mucus PR ≥most of the time	11 / 146	22 / 1656	7.5% (3.8% - 13.1%)	98.7% (98.0% - 99.3%)	5.67 (2.83 - 11.2)	0.94 (0.88 - 0.97)

≥4 stools per day ≥most of the time and mucus PR ≥most of the time	18 / 146	45 / 1654	12.3% (7.5% - 18.8%)	97.3% (96.4% - 98.0%)	4.53 (2.69 - 7.51)	0.90 (0.84 - 0.95)
Blood in the stools and mucus PR ≥most of the time	12 / 146	60 / 1630	8.2% (4.3% - 13.9%)	96.3% (95.3% - 97.2%)	2.23 (1.23 - 3.97)	0.95 (0.89 - 0.99)
Weight loss >5kg in the last year and ≥4 stools per day ≥most of the time	13 / 140	47 / 1652	9.3% (5.0% - 15.4%)	97.2% (96.2% - 97.9%)	3.26 (1.81 - 5.77)	0.93 (0.87 - 0.97)
Told by the doctor you are anemic and ≥4 stools per day ≥most of the time	17 / 147	35 / 1653	11.6% (6.9% - 17.9%)	97.9% (97.1% - 98.5%)	5.46 (3.14 - 9.37)	0.90 (0.84 - 0.95)
Told by the doctor you are anemic and weight loss >5kg in the last year	18 / 142	61 / 1628	12.7% (7.7% - 19.3%)	96.3% (95.2% - 97.1%)	3.38 (2.05 - 5.48)	0.91 (0.84 - 0.96)
Told by the doctor you are anemic and weight loss >5kg in the last year and ≥4 stools per day ≥most of the time	5 / 143	9 / 1663	3.5% (1.1% - 8.0%)	99.5% (99.0% - 99.8%)	6.46 (2.29 - 18.0)	0.97 (0.93 - 0.99)

FIGURE LEGENDS

Figure 1. Flow of Study Participants.