DEVELOPMENT OF A RED FLAGS INDEX FOR SUSPECTED CROHN'S DISEASE: AN IOIBD INITIATIVE

Short title: Red Flags in Crohn's disease

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ABSTRACT

Background and aims: Diagnostic delay is frequent in patients with Crohn's disease (CD). We developed a tool to reduce diagnostic delay.

Methods: Twelve CD specialists indentified "Red Flag" symptoms or signs suggestive of CD through a systematic literature review and their experience. A pilot questionnaire containing 21 items was administered to 36 healthy subjects and 80 patients with irritable bowel syndrome (non-CD group), and 85 patients with recently diagnosed CD (<18 months). Patients with CD were asked to recall the symptoms or signs that they experienced during the 12 months before their diagnosis. The frequency of items in the CD and non-CD groups was compared with the χ^2 test. Simple and multiple logistic regression analyses weighted items, and a ROC curve assessed the threshold that discriminated CD from non CD. Logistic regression quantified the predictive value of items and of the score through odds-ratios (OR).

Results: Two hundred one patients and controls answered 21 pilot items. Fourteen items were more frequent in CD than controls. These 14 items underwent multivariate analysis which identified 8 final items associated with a diagnosis of CD. ROC curve analysis identified a minimum Red Flag score of 8 as predictive for CD (sensitivity 0.93, specificity 0.98). Positive and negative likelihood ratios were 15.1 and 0.066. Logistic regression confirmed that a score ≥8 discriminated CD from non-CD (OR 290, 95% CI: 77-1086, p<0.0001).

Conclusions: A Red Flag score has a high predictive value for the diagnosis of CD. These results need validation prior to introduction into clinical practice.

Keywords: Crohn's disease, red flags, diagnostic delay

INTRODUCTION

Delay in the diagnosis of inflammatory bowel disease (IBD) is a problem for both patients and physicians. This is particularly true for Crohn's disease (CD), because the initial signs and symptoms can be non-specific, and overlap with symptoms of irritable bowel syndrome (IBS). In a Swiss IBD cohort, diagnostic delay occurred more commonly in patients with CD as compared with ulcerative colitis (UC) (median 9 versus 4 months, p<0.001). Seventy-five percent of patients with CD were diagnosed within 24 months, as compared to 12 months for patients with UC[1]. In France, a prospective study on a cohort of 364 patients reported a median diagnostic delay of 5 months. A long diagnostic delay (>12 months) was associated with the presence of disease complications at the time of diagnosis in 28 patients (8.6%), suggesting that a delay in diagnosis beyond 12 months may result in missing the therapeutic window to intervene before disease complications occur[2]. Results from a European online survey conducted among IBD patients across 25 national IBD associations[3] showed similar results. Among 4670 patients who completed the survey, only 54% reported a final diagnosis within 12 months from noticing first symptoms. Almost 20% had to wait over 5 years, and 67% had an emergency department visit at least once before diagnosis[3].

In population-based cohorts, approximately 20-30% of patients with CD already have disease complications (stricture, abscess and/or fistula) at the time of diagnosis.[4] Radiologic evidence of disease complications at the time of diagnosis are present in more than 50% of patients, and are associated with worse outcomes including hospitalization and need for surgery.[5] In a Swiss IBD cohort, diagnostic delay was associated with the occurrence of stricture (odds ratio (OR) 1.76, p=0.011 for delay of ≥25 months) and surgical resection (OR 1.76, p=0.014 for delay of 10-24 months and OR 2.03, P=0.003 for delay ≥25 months).[1]

In other chronic inflammatory diseases such as rheumatoid arthritis or multiple system atrophy (MSA), diagnostic delay presents a similar challenge[6-9]. Studies from rheumatology show that a tool for early referral of children and adolescents with signs or symptoms suggestive of chronic arthropathy to paediatric rheumatology centres correctly classified over 90% of subjects in a cohort of 129 children (48 with juvenile idiopathic arthritis, 39 with musculoskeletal pain, and 42 controls)[7]. Similarly, a study on 57 patients with MSA compared to 116 patients with Parkinson's disease as a control group, showed that two or more signs and symptoms in a 'Red Flags' tool had 98% specificity and 84% sensitivity for a diagnosis of MSA, on average 15 months earlier than usual[6].

Similar to rheumatoid arthritis, initiating effective treatment early in the course of CD may be the best way to modify the disease course.[10, 11] However, a tool for early referral of adults with symptoms and signs suggestive of CD is lacking. We developed a 'Red Flags' instrument to detect signs and symptoms that necessitate evaluation for CD.

MATERIALS AND METHODS

The study consisted of two sequential steps. First, a systematic literature review of signs and symptoms suggestive of early CD was conducted, and 12 CD specialists from Europe and the United States provided their clinical experience. Second, a multicenter, controlled, cross-sectional study of consecutive patients from three European IBD centres was performed.

Phase 1

A systematic literature review including the terms ("early Crohn" OR "early symptoms" OR "early signs" OR "diagnosis" OR "incidence" OR "red flags") AND ("Crohn's disease" OR "inflammatory bowel disease") was conducted to identify clinical signs and symptoms of suspected CD. This search identified 15 relevant studies[12-25]. In addition, 12 CD specialists independently provided their own list of signs and symptoms suggestive of CD, based on their experience and knowledge by responding to the question "What are the 6 to 20 questions you ask a patient strongly suspected of having CD?" The final list included 21 questions from both sources. The specialists were then asked to rank all the items for their relevance for a diagnosis of early CD.

Phase 2

Three tertiary referral IBD Centres (Humanitas Research Hospital, Rozzano, Milan, Italy; Semmelweis University, Budapest, Hungary; Amsterdam Medical Center, Amsterdam, The Netherlands) conducted the second phase. The study was approved by the Ethics Committee at each centre. Between January and June 2013, a questionnaire with the 21 previously selected questions was administered by the investigator to all consecutive outpatients with a diagnosis of CD <18 months before the date of the visit, as well patients with an established diagnosis of IBS, and healthy subjects selected from staff members or relatives without any gastrointestinal symptoms. All patients with CD were asked to recall the symptoms and signs that they had experienced during the 12 months previous to the date of diagnosis. Patients with IBS and healthy subjects were asked about symptoms and signs present at the time of the visit or soon before. Answers (yes/no) were recorded. All data were collated for the final analysis.

Statistical methods

Due to the lack of any previous studies on this topic in CD, the minimum sample size was based on a rule of thumb that the sample size should be at least 5 times the number of variables[26] (i.e. at least 105 subjects in

total). The total of 201 subjects and the distribution in the three study groups were a consequence of active recruitment of consecutive patients seen in the three centres during the 6-month study period.

Based on the rankings by the 12 CD specialists, the median of the rank of each item was used as a weighted coefficient to define the specialist 'Red Flags' index. The specialist 'Red Flags' index in a patient was calculated by summing the median ranks of all items that were present in that patient. The cut-off value to define a diagnosis of CD was determined from the value closest to the upper left corner of the ROC plot[27] The association between the specialist 'Red Flags' index relative to the cut-off value, was expressed through the odds ratio.

In the cross-sectional study, the frequency of each item was analyzed in the CD and non-CD (IBS and healthy subjects combined) cohorts. Differences were analyzed by χ^2 test. All items with a p value <0.25 in this analysis were then included in a multivariate logistic regression analysis. Independent Items significantly associated with diagnosis of CD were determined through backward selection, using the likelihood ratio test[28]. Statistical significance was defined as $p<0.05$. The 'Red Flags' index value for each patient was calculated by summing the rounded coefficients of all independent items that were present in that patient. ROC analysis was then used to set a cut-off (threshold) for a positive 'Red Flags' index value related to a diagnosis of CD in the study population. The association between the "Red Flags" index relative to the cut-off value and CD diagnosis was expressed through the odds ratio.

Unbiased estimates of the characteristics of the "Red Flags" index relative to the cut-off value in relation to CD diagnosis were obtained by a bootstrap method[29]. One thousand different samples of 201 patients were derived from the original sample through re-sampling with replacement. The sensitivity and specificity, positive and negative likelihood ratios, positive and negative predictive values were then obtained for each bootstrap sample. In parallel, both positive and negative likelihood ratios and the positive and negative predictive values for a diagnosis of CD were estimated. Each characteristic was finally described as an estimate with 95 % confidence interval (95% CI), provided by their distribution among the 1000 bootstrap samples.

Statistical significance was defined as $p<0.05$. All statistical analyses were performed using SPSS® software (SPSS Inc. Chicago, IL, USA).

RESULTS

The literature search and the opinions of the 12 CD specialists identified 21 questions included in the specialists' 'Red Flags' index (Table 1).

In the cross-sectional study, the distribution of the study population according to patient groups (CD, IBS, healthy subjects) per centre is shown in Figure 1. Baseline characteristics of patients with CD are summarized in Supplementary Table 1. From the questionnaire of 21 items, 14 were significantly more frequent in the CD than in the non-CD population (Table 1). Multivariate analysis identified 8 independent items (Table 2) significantly related to a diagnosis of CD, items that were included in the enquiry 'Red Flags' index. ROC analysis set a enquiry 'Red Flags' score ≥8 as a threshold that discriminated patients with CD compared to the non-CD (Figure 2). Subjects having a enquiry 'Red Flags' score ≥8 were significantly more likely to suffer from CD than to belong to the non-CD population (OR 290, 95% CI: 77-1086, $p<0.0001$). Sensitivity and specificity estimates derived from bootstrapping were 0.94 (95% CI: 0.88-0.99) and 0.94 (95% CI: 0.90-0.97), respectively. Positive and negative likelihood ratios were 15.1 (CI 95%, 9.3-33.6) and 0.066 (CI 95%, 0.013-0.125), and positive and negative predictive values were 0.91 (CI 95%, 0.87-0.97) and 0.96 (CI 95% 0.91-0.99) respectively, all indicating good discrimination between groups.

DISCUSSION

We have developed a simple, easy-to-use tool, the 'Red Flags Index for Suspected Crohn's Disease' that reliably discriminates functional gut disorders or normality from early CD. The tool is intended to help clinicians in primary or secondary care, and potentially patients, to reliably identify symptoms and signs that might lead to the diagnosis of CD. The hope is that this Red Flags index will reduce the time to diagnosis and enable intervention at a time when the course of the disease may be changed.

Crohn's disease is frequently diagnosed after a long delay, with a median time from symptoms to diagnosis of 1-2 years.[1, 3] Functional gut disorders like IBS often mimic early manifestations of CD[12], thereby delaying referral to IBD specialists. This delay can delay early therapeutic intervention and consequently can be associated with a worse outcome. Data from randomized controlled trials with anti-TNF therapy show that administering effective therapy in selected patients early in the course of CD is associated with significantly better control of the disease. In the PRECiSE 2 trial, 89.5% patients treated with certolizumab within 1 year of CD diagnosis responded to therapy, compared to 57.3% patients treated ≥ 5 years after diagnosis ($p<0.05$).[30] In the EXTEND trial, numerically higher rates of deep remission (combined clinical control and endoscopic mucosal healing) were observed in patients with early CD.[31] Peyrin-Biroulet et al. showed that early intervention with immunomodulators and anti-TNF therapy for non-stricturing, non-penetrating CD was associated with a lower risk of surgery[32].

Because CD can present with different clinical features, we tried in this study to identify the most common early symptoms, signs and characteristics of CD, combining a systematic literature search and specialist opinion. Using this strategy, 21 items were identified and evaluated in a cohort of patients with recently (< 18 months) diagnosed CD and non-CD controls (IBS and healthy subjects), in order to investigate the frequency of such clinical features, especially in the differential diagnosis between CD and IBS. The questionnaire was able to identify correctly CD in the majority of patients with high accuracy. Since the 21-item questionnaire was thought too complex to administer routinely, we used multivariate logistic regression of individual items to reduce it to the minimum number of items that could maintain accurate discrimination of CD from non-CD. Bootstrap analysis confirmed the good performance of the tool.

A scoring system to discriminate ulcerative colitis from colonic CD has already been developed, using a multicenter cohort of patients with IBD, showing that score-based systems are useful in correctly classifying IBD[33]. Ours is the first tool designed to enable early and timely diagnosis of CD in patients presenting with bowel

symptoms. Studies from other chronic and relatively uncommon diseases demonstrate that questionnaire-based tools are able to discriminate between diseases with similar clinical features (e.g. joint pain or headache), including juvenile chronic arthropathy, multiple system atrophy, or central nervous system diseases[6-9]. The tools increase appropriate diagnostic workups in selected patients and can avoid unnecessary, high-cost examinations in low-risk patients. For instance, the RADAR study compared two referral strategies (primary care referral vs. diagnosis based on predetermined 'Red Flags' combination of items) and demonstrated good performance with good concordance in identifying axial spondyloarthritis[34]. This indicates that a 'Red Flags' tool can be accurate in presence of different levels of expertise. In our study, we chose IBS as the best comparator, because the symptoms, age of onset, and chronic pattern of symptoms can be very similar and confounding to those of CD. We were able to identify 15 symptoms and signs that were more typical of CD than in IBS, and vice versa (Supplementary Table 2).

There are some limitations in this study. First, patients with CD were asked to recall retrospectively their symptoms up to the time before diagnosis, when completing the questionnaire, in contrast to those with IBS and healthy controls where data were collected at the time of the visit or soon before. This may have introduced recall bias in the CD population. Second, the proportion between CD, IBS and healthy subjects enrolled in the study may not be representative of the incidence and prevalence of these conditions in the general population. This may be relevant, especially considering that the sample size calculation was estimated on the rule of thumb of at least 5 times the number of variables[26] and not on expected differences to be found between the CD and control groups. On the other hand, if we consider that the 'Red Flags Index' may be helpful mainly in people with clinical symptoms or signs suggestive of gastrointestinal disorders (principally IBS), or in healthy subjects at risk of CD because of smoking habit or family history, the proportion of CD, IBS, and healthy subjects in our sample may be closer to the target population than might be expected. Third, we included some items that were significantly less frequent in CD than in the non-CD population (such as absence of rectal urgency or abdominal cramps 30-45 minutes after meals, especially vegetables), although they are usually thought not to be specific for CD, since they are common in the general population. Fourth, the validity and the performance of the 'Red Flags Index' need to be established by a prospective validation study involving subjects evaluated by general practitioners for intestinal symptoms.

We have developed an easy-to-calculate index that may be helpful in identifying patients with symptoms suggestive of CD who should be referred to a specialist for further evaluation. If prospective validation of the 'Red Flags Index' confirms the initial performance characteristics of the tool, we can expect to identify patients early in

their disease course and prior to the development of disease complications, where there is a therapeutic window of opportunity for effective therapeutic intervention. This early diagnosis and intervention may in turn reduce the risk of disease complications and surgery.

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TABLE 1: ASSOCIATION BETWEEN A POSITIVE ANSWER TO A QUESTION AND CD DIAGNOSIS, AND THE MEDIAN RANK OF THE ITEMS ACCORDING TO THE SPECIALISTS' OPINION.

Questions	Median specialists' rank	CD (%, n=85)	Non-CD (%, n=116)	OR (95% CI)	p value
Non-healing or complex perianal fistula or abscess or perianal lesions (apart from haemorrhoids)[a]	4	31	1	5.5 (2.5-12.1)	***<0.0001***
Mild fever in the last 3 months[b]	3	52	3	17.0 (7.6-38.0)	***<0.0001***
Weight loss (≥5% of usual body weight) in the last 3 months[a]	3	76	8	50.7 (6.7-382.7)	***<0.0001***
Chronic or recurrent anaemia[a]	3	51	4	12.8 (6.1-26.8)	***<0.0001***
Nocturnal diarrhoea[b]	3	59	8	38.6 (16.6-90.0)	***<0.0001***
Chronic abdominal pain (> 3 months)[a]	3	87	34	22.7 (8.4-61.3)	***<0.0001***
Anal pain[b]	3	42	7	6.1 (3.0-12.5)	***<0.0001***
Rectal bleeding[a]	3	44	11	9.9 (4.3-22.9)	***<0.0001***
Presence of any concomitant or previous EIM[a]	3	34	9	12.2 (2.7-55.0)	***<0.0001***
First-degree relative with confirmed IBD[a]	2	18	2	4.5 (1.8-11.2)	***0.0007***
Chronic diarrhoea (>3 bowel movements, > 4 weeks duration)[a]	2	76	16	40.4 (11.9-137.3)	***<0.0001***
Absence of rectal urgency[b]	2	33	9	4.7 (2.2-10.1)	***0.0001***
Failure to thrive[a]	2	22	1	17.6 (8.7-36.0)	***0.0001***
Smoking history: regular smoker or stopped recently[b]	2	22	6	33.1 (4.3-253.0)	***0.0007***
Onset of rectal bleeding within 5 years of stopping smoking[b]	2	6	1	0.9 (0.1-5.6)	*0.91*
No abdominal pain 30-45 minutes after meals, predominantly after vegetables[b]	2	84	74	7.2 (0.8-62.7)	*0.07*
Any relative with autoimmune disease[a]	1	6	7	1.8 (0.9-3.6)	*0.11*
Continuous abdominal pain[b]	1	14	15	NE	*0.98*

Ashkenazi Jewish ethnicity[a]	1	2	3	NE	*0.98*
Abdominal pain and diarrhoea associated with NSAID intake[a]	1	0	4	0.8 (0.3-2.7)	*0.77*
History of *Campylobacter* infection[a]	1	0	1	1.0 (0.4-2.1)	*0.91*

CD= Crohn's disease; OR=Odds ratio; EIM=extraintestinal manifestations; IBD=inflammatory bowel disease; NSAID=Non steroidal anti-inflammatory drugs; NE=could not be estimated

[1] Derived from the literature search; [b] Derived from specialist opinion

TABLE 2: ITEMS INDEPENDENTLY ASSOCIATED WITH CD DIAGNOSIS DERIVED FROM LOGISTIC REGRESSION WITH BACKWARD SELECTION USING THE LIKELIHOOD RATIO TEST.

Item	Coefficient	S.E.	p value	Rounded coefficient
Non-healing or complex perianal fistula or abscess or perianal lesions (apart from haemorrhoids)	4.648	1.822	0.0009	5
Nocturnal diarrhoea	2.541	0.813	0.0008	3
First-degree relative with confirmed IBD	4.282	1.174	0.0002	4
Weight loss (5% of usual body weight) in the last 3 months	3.303	0.721	<0.0001	3
Chronic abdominal pain (>3 months)	2.928	0.750	<0.0001	3
Mild fever in the last 3 months	2.169	0.882	0.0083	2
No abdominal pain 30-45 minutes after meals, predominantly after vegetables	1.581	0.750	0.0243	2
No rectal urgency	1.569	0.831	0.0486	2

Figure 1 Distribution of the study population according to diagnosis per centre

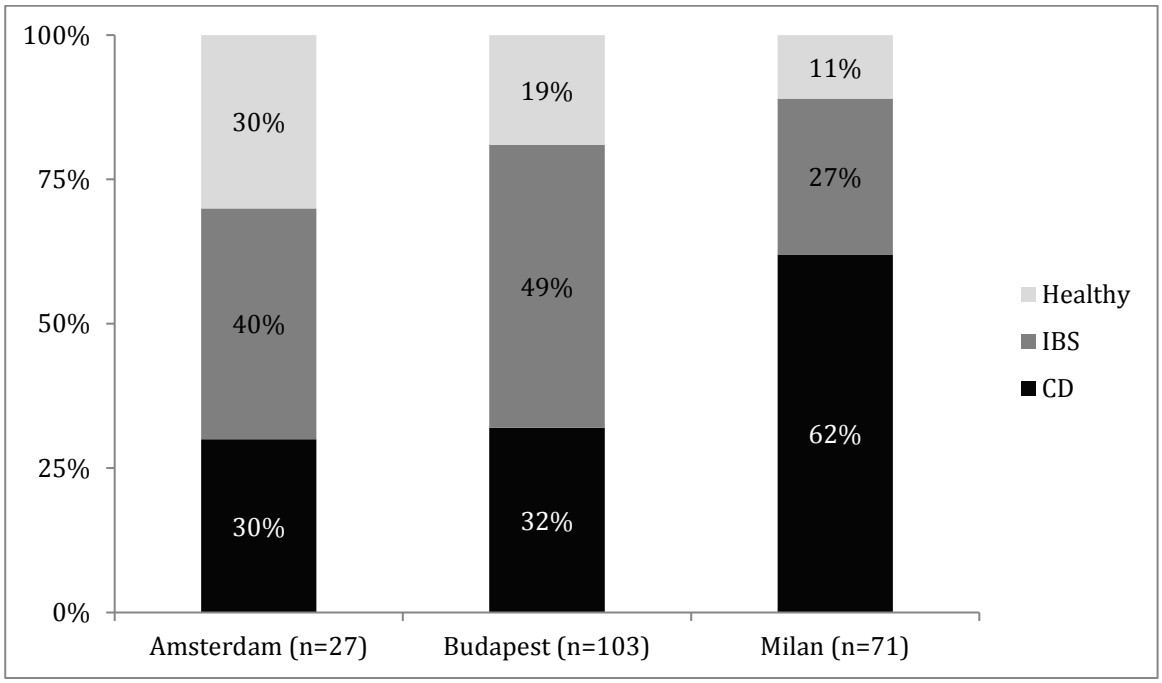
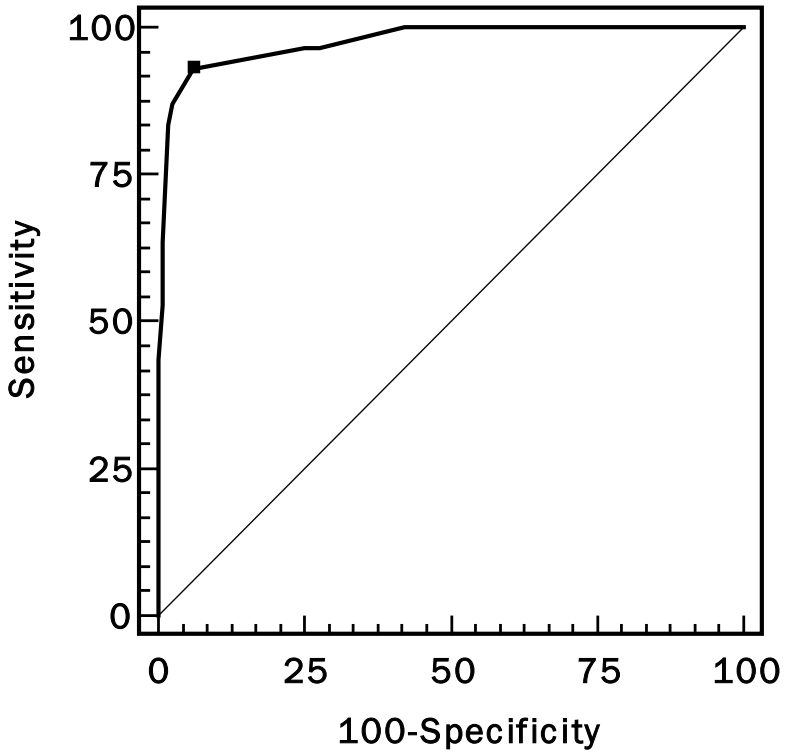


Figure 2 The ROC curve analysis identified a Red Flags Index ≥8 (black square) to be associated with Crohn's disease (area under the curve 0.97, 95% confidence interval : 0.94-0.99)



SUPPLEMENTARY TABLE 1. BASELINE CHARACTERISTICS OF CD SUBJECTS (N=85)

Median age (range)	31 (18-68)
Males	34 (40%)
Months from diagnosis (median)	11 (0-18)
Localization	
Ileal	47 (55.3%)
Colonic	34 (40%)
Ileo-colonic	4 (4.7%)
Isolated upper	0 (0%)
Behaviour	
Non-stricturing, non-penetrating	39 (45.8%)
Stricturing	23 (27.1%)
Penetrating	23 (27.1%)

SUPPLEMENTARY TABLE 2. ASSOCIATION BETWEEN A POSITIVE ANSWER TO A QUESTION AND CD DIAGNOSIS COMPARED TO IBS DIAGNOSIS

Questions	CD (%, n=85)	IBS (%, n=80)	p value
Weight loss (≥5% of usual body weight) in the last 3 months	76	11	<0.0001
Chronic diarrhoea (>3 bowel movements, > 4 weeks duration)	76	23	<0.0001
Nocturnal diarrhoea	59	10	<0.0001
Chronic abdominal pain (> 3 months)	87	50	<0.0001
Mild fever in the last 3 months	52	4	<0.0001
Chronic or recurrent anaemia	51	6	<0.0001
Rectal bleeding	44	14	<0.0001
Non-healing or complex perianal fistula or abscess or perianal lesions (apart from haemorrhoids)	31	1	<0.0001
Anal pain	42	10	0.0001
Failure to thrive	22	1	0.0001
Presence of any concomitant or previous EIM	34	11	0.001
First-degree relative with confirmed IBD	18	3	0.003
Absence of rectal urgency	33	14	0.006
Smoking history: regular smoker or stopped recently	22	6	0.006
No abdominal pain 30-45 minutes after meals, predominantly after vegetables	84	65	0.01
Abdominal pain and diarrhoea associated with NSAID intake	0	6	0.06
Onset of rectal bleeding within 5 years of stopping smoking	6	1	0.24
Continuous abdominal pain	14	21	0.31
History of *Campylobacter* infection	0	0	0.75
Any relative with autoimmune disease	6	4	0.78
Ashkenazi Jewish ethnicity	2	4	0.94

CD= Crohn's disease; OR=Odds ratio; EIM=extraintestinal manifestations; IBD=inflammatory bowel disease; NSAID=Non steroidal anti-inflammatory drugs; NE=could not be estimated

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