Journal of Crohn's and Colitis Advance Access published May 18, 2015

*Journal of Crohn's and Colitis*, 2015, 1–6
doi:10.1093/ecco-jcc/jjv067
Original Article

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# Development of Red Flags Index for Early Referral of Adults with Symptoms and Signs Suggestive of Crohn's Disease: An IOIBD Initiative

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## Abstract

**Background and Aims:** Diagnostic delay is frequent in patients with Crohn's disease (CD). We developed a tool to predict early diagnosis.

**Methods:** A systematic literature review and 12 CD specialists identified 'Red Flags', i.e. symptoms or signs suggestive of CD. A 21-item questionnaire was administered to 36 healthy subjects, 80 patients with irritable bowel syndrome (non-CD group) and 85 patients with recently diagnosed (<18 months) CD. Patients with CD were asked to recall symptoms and signs they experienced during the 12 months before diagnosis. Multiple logistic regression analyses selected and weighted independent items to construct the Red Flags index. A receiver operating characteristic curve was used to assess the threshold that discriminated CD from non-CD. Association with the Red Flags index relative to this threshold was expressed as the odds ratios (OR).

**Results:** Two hundred and one subjects, CD and non-CD, answered the questionnaire. The multivariate analysis identified eight items independently associated with a diagnosis of CD. A minimum Red Flags index value of 8 was highly predictive of CD diagnosis with sensitivity and specificity bootstrap estimates of 0.94 (95% confidence interval 0.88–0.99) and 0.94 (0.90–0.97),

respectively. Positive and negative likelihood ratios were 15.1 (9.3–33.6) and 0.066 (0.013–0.125), respectively. The association between CD diagnosis and a Red Flags index value of ≥8 corresponds to an OR of 290 ($p < 0.0001$).

**Conclusions:** The Red Flags index using early symptoms and signs has high predictive value for the diagnosis of CD. These results need prospective validation prior to introduction into clinical practice.

**Keywords:** Crohn's disease, Red Flags, diagnostic delay

## 1. 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 compared with ulcerative colitis (median 9 vs 4 months, $p < 0.001$). Seventy-five percent of patients with CD were diagnosed within 24 months, compared with 12 months for patients with ulcerative colitis.[1] In France, a prospective study of 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 after noticing first symptoms. Almost 20% had to wait >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] Radiological evidence of disease complications at the time of diagnosis is present in >50% of patients and is 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 of ≥25 months).[1]

In other chronic inflammatory diseases, such as rheumatoid arthritis and multiple system atrophy (MSA), diagnostic delay presents a similar challenge.[6–9] Studies in 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 >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 of 57 patients with MSA compared with 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]

As is the case with 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.

## 2. 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 USA provided their clinical experience. Second, a multicentre, controlled, cross-sectional study of consecutive patients from three European IBD centres was performed.

### 2.1. 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 16 relevant studies.[12–26] 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.

### 2.2. 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 as patients with an established diagnosis of IBS and healthy subjects selected from staff members or relatives with no 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 shortly before. Answers (yes/no) were recorded. All data were collated for the final analysis.

### 2.3. 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[27] (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.

In the cross-sectional study, the frequency of each item was analysed in the CD and non-CD (IBS and healthy subjects combined) cohorts. Differences were analysed by Fisher's exact 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 by 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. Receiver operating characteristic (ROC) analysis was then used to determine, from the value closest to the upper left corner of the ROC plot, the cut-off (threshold) for a positive Red Flags index value related to a diagnosis of CD in the study population.[29] The association between the Red Flags index relative to the cut-off value and CD diagnosis was expressed as 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.[30] One thousand different samples of 201 patients were derived from the original sample by 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 in each bootstrapped sample. Each characteristic was finally described as an estimate with the 95% confidence interval (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).

## 3. Results

The literature search and the opinions of the 12 CD specialists identified 21 questions (Table 1).

In the cross-sectional study, the distribution of the study population according to patient groups (CD, IBS, healthy subjects) for each 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), and 16 were significantly different from the IBS population (Supplementary Table 2). One item (presence of abdominal pain 30–45 minutes after meals, predominantly after vegetables) was more frequent in the non-CD cohort than in CD subjects, and thus in the final analysis it was reversed to 'no abdominal pain 30–45 minutes after meals, predominantly after vegetables' for consistency with the rest of items. Multivariate analysis identified eight independent items (Table 2) significantly related to a diagnosis of CD, items that were included in the Red Flags index. Because the item 'rectal urgency' was negatively associated with CD (coefficient −2), this item was reversed to 'no rectal urgency' in order not to have negative scores in the final index. In the multivariate analysis, ROC analysis set a Red Flags score ≥8 as a threshold that discriminated patients with CD from the non-CD population (Figure 2). Subjects having a Red Flags score ≥8 were significantly more likely to have CD than to belong to the non-CD population (OR 290, 95% CI 77–1086, $p < 0.0001$). Sensitivity and

**Table 1**. Association between a positive answer to a question and Crohn's disease diagnosis.

| Question | Crohn's disease (%, $n$ = 85) | Non-Crohn's disease (%, $n$ = 116) | OR (95% CI) | $p$ value |
|---|---|---|---|---|
| Non-healing or complex perianal fistula or abscess or perianal lesions (apart from haemorrhoids)[a] | 31 | 1 | 50.7 (6.7–382.7) | <0.0001 |
| Mild fever in the last 3 months[b] | 52 | 3 | 40.4 (11.9–137.3) | <0.0001 |
| Weight loss (≥5% of usual body weight) in the last 3 months[a] | 76 | 8 | 38.6 (16.6–90.0) | <0.0001 |
| Chronic or recurrent anaemia[a] | 51 | 4 | 22.7 (8.4–61.3) | <0.0001 |
| Chronic diarrhoea (>3 bowel movements, >4 weeks duration)[a] | 76 | 16 | 17.7 (8.7–36.0) | <0.0001 |
| Nocturnal diarrhoea[b] | 59 | 8 | 17.0 (7.6–38.0) | <0.0001 |
| Chronic abdominal pain (>3 months)[a] | 87 | 34 | 12.8 (6.1–26.8) | <0.0001 |
| Anal pain[b] | 42 | 7 | 9.9 (4.3–22.9) | <0.0001 |
| Rectal bleeding[a] | 44 | 11 | 6.1 (3.0–12.5) | <0.0001 |
| Presence of any concomitant or previous extraintestinal manifestations [a] | 34 | 9 | 5.5 (2.5–12.1) | <0.0001 |
| Presence of rectal urgency[b] | 33 | 9 | 4.7 (2.2–10.1) | <0.0001 |
| Failure to thrive[a, c] | 22 | 1 | 33.1 (4.3–253.0) | <0.0001 |
| First-degree relative with confirmed inflammatory bowel disease [a] | 18 | 2 | 12.2 (2.7–55.0) | <0.0001 |
| Smoking history: regular smoker or stopped recently[b] | 22 | 6 | 4.5 (1.8–11.2) | 0.001 |
| Onset of rectal bleeding within 5 years of stopping smoking[b] | 6 | 1 | 7.2 (0.8–62.7) | 0.08 |
| No abdominal pain 30–45 min after meals, predominantly after vegetables[b, d] | 84 | 74 | 1.8 (0.9–3.6) | 0.12 |
| Any relative with autoimmune disease[a] | 6 | 7 | 0.8 (0.3–2.7) | 1.0 |
| Continuous abdominal pain[b] | 14 | 15 | 1.0 (0.4–2.1) | 1.0 |
| Ashkenazi Jewish ethnicity[a] | 2 | 3 | 0.9 (0.1–5.6) | 1.0 |
| Abdominal pain and diarrhoea associated with NSAID intake[a] | 0 | 4 | NE | 0.07 |
| History of *Campylobacter* infection[a] | 0 | 1 | NE | 1.0 |

NSAID, non-steroidal anti-inflammatory drug; NE, could not be estimated.

[a]Derived from the literature search.

[b]Derived from specialist opinion.

[c]Defined as a delayed growth curve.

[d]The question was reversed from 'presence of abdominal pain 30–45 minutes after meals, predominantly after vegetables' for consistency.

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 (95% CI 9.3–33.6) and 0.066 (95% CI 0.013–0.125), and positive and negative predictive values were 0.91 (95% CI 0.87–0.97) and 0.96 (95% CI 0.91–0.99) respectively, all indicating good discrimination between groups.

## 4. 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 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 before starting any diagnostic workup. 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] although in recent cohorts the median time from symptoms to diagnosis has been shorter than 1 year.[18,26] Functional gut disorders like IBS often mimic early manifestations of CD,[12] thereby delaying referral to IBD specialists. This delay can subvert early therapeutic intervention and consequently can be associated with a worse outcome. Data from randomized controlled trials with anti-tumour necrosis factor (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% of patients treated with certolizumab within 1 year of CD diagnosis responded to therapy, compared with 57.3% patients treated ≥5 years after diagnosis ($p < 0.05$).[31] In the EXTEND trial, numerically higher rates of deep remission (combined clinical control and endoscopic mucosal healing) were observed in patients with early CD.[32] Peyrin-Biroulet et al.[33] showed that early intervention with immunomodulators and anti-TNF therapy for non-stricturing, non-penetrating CD was associated with a lower risk of surgery.

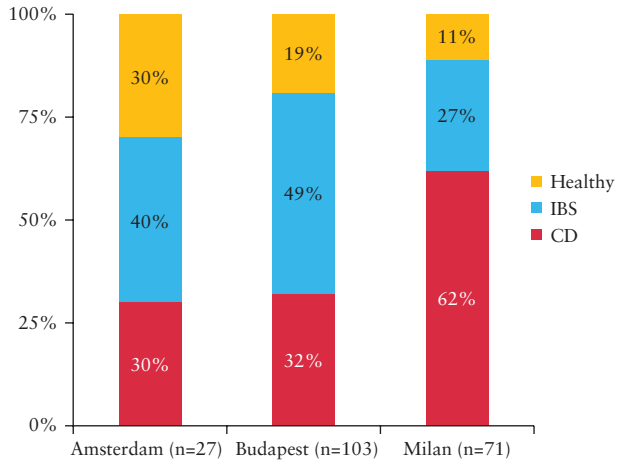


**Figure 1.** Distribution of the study population according to diagnosis at each centre.

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 with 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 CD correctly with high accuracy in the majority of patients. 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, including only items independently associated with 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 multicentre cohort of patients with IBD, showing that score-based systems are useful in correctly classifying IBD.[34] Ours is the first tool designed to enable early and timely diagnosis of CD in patients presenting with abdominal 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 and central nervous system diseases.[6–9] The tools increase the appropriateness of 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.[35] This indicates that a Red Flags tool can be accurate in the 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 to and confounding with those of

**Table 2.** Items independently associated with Crohn's disease diagnosis derived from logistic regression with backward selection using the likelihood ratio test.

| Item | Coefficient | SE | *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 |
| First-degree relative with confirmed inflammatory bowel disease | 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 |
| Nocturnal diarrhoea | 2.541 | 0.813 | 0.0008 | 3 |
| Mild fever in the last 3 months | 2.169 | 0.882 | 0.0083 | 2 |
| No abdominal pain 30–45 min after meals, predominantly after vegetables | 1.581 | 0.750 | 0.0243 | 2 |
| No rectal urgency[a] | 1.569 | 0.831 | 0.0486 | 2 |

[a]Reversed from 'presence of rectal urgency' to obtain a positive rounded coefficient.

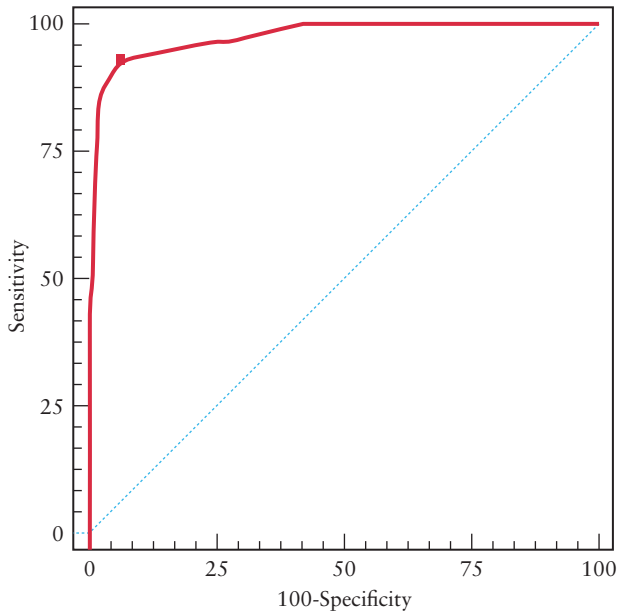


**Figure 2.** The receiver operating characteristic curve analysis showed that a Red Flags index ≥8 (black square) was associated with Crohn's disease (area under the curve 0.97, 95% CI 0.94–0.99).

CD. We were able to identify 16 symptoms and signs that were more typical of CD than of IBS, and vice versa.

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, for whom data were collected at or shortly before the time of the visit. This may have introduced recall bias in the CD population. Second, the proportions of 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. Also, the distribution according to localization ((according to the Montreal Classification) only 5% of CD subjects with L3) and behaviour of disease (50% of B2 and B3 subjects) in the CD cohort might seem to be not representative of the real distribution at diagnosis of CD in the target population. This may be relevant, especially considering that the sample size calculation was estimated using the rule of thumb of at least 5 times the number of variables[27] rather than the 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 proportions of CD, IBS and healthy subjects in our sample may be closer to those in the target population than might be expected; in addition, disease location and behaviour would not impact significantly on the usefulness of the tool as all items included in the Red Flags index are not specific to the CD phenotype. Third, we did not analyse the different patterns occurring in IBS (like diarrhoea-prevalent, constipation-prevalent or mixed pattern) compared with the CD population. Fourth, we included some items that were found to be independently associated with CD (such as absence of rectal urgency or abdominal pain 30–45 min after meals, especially vegetables), although they are usually thought not to be specific for CD, since they are also common in the general population. Fifth, the validity and 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, when 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.

## Funding

This work was supported by an International Organization for Inflammatory Bowel Disease research grant.

## Acknowledgments

The following colleagues contributed to the enrolment and data collection in phase 2: Beatrice Salvioli, MD, PhD, Daniela Gilardi, PharmD and Marina Alfieri, BSc, Humanitas Research Hospital, Rozzano, Milan, Italy; Petra A. Golovics, MD and Barbara D. Lovasz, MD, 1st Department of Medicine, Semmelweis University; Tim Hoogendoorn, RN, Maria de Jong, RN and Suzan Stolte, RN, IBD Center, AMC, Amsterdam, The Netherlands, for which we are most grateful.

## Disclosures

None of the authors has any relevant disclosures.

## Conference presentation

European Crohn's Colitis Organization Congress, Copenhagen 2014; Digestive Disease Week, Chicago, 2014.

## Author contributions

SD, GF and LP-B conceived and designed the study; all authors equally contributed to study phase 1; SD, GF, PLL and GD'H enrolled the subjects in phase 2 and collected the data; GF and J-YM analysed and interpreted the data and performed the statistical analysis; GF, J-YM and SD drafted the manuscript; SD supervised the study, obtained funding and critically revised the manuscript; all authors reviewed and accepted the final version of the manuscript.

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