REVIEW ARTICLE

INTESTINAL RESEARCH

Does fecal calprotectin equally and accurately measure disease activity in small bowel and large bowel Crohn's disease?: a systematic review

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Fecal calprotectin (FC) is a highly sensitive disease activity biomarker in inflammatory bowel disease. However, there are conflicting reports on whether the diagnostic accuracy in Crohn's disease is influenced by disease location. The aim of this study was to undertake a systematic review of the published literature. Relevant databases were searched from inception to November 8, 2016 for cohort and case control studies which had data on FC in patients with isolated small bowel (SB) and large bowel (LB) Crohn's disease. Reference standards for disease activity were endoscopy, magnetic resonance imaging, computed tomography or a combination of these. The QUADAS-2 research tool was used to assess the risk of bias. There were 5,619 records identified at initial search. The 2,098 duplicates were removed and 3,521 records screened. Sixty-one full text articles were assessed for eligibility and 16 studies were included in the final review with sensitivities and specificities per disease location available from 8 studies. Sensitivities of FC at SB and LB locations ranged from 42.9% to 100% and 66.7% to 100% respectively while corresponding specificities were 50% to 100% and 28.6% to 100% respectively. The sensitivities and specificities of FC to accurately measure disease activity in Crohn's disease at different disease locations are diverse and no firm conclusion can be made. Better studies need to be undertaken to categorically answer the effect of disease location on the diagnostic accuracy of FC. **(Intest Res 2019;17:160-170)**

Key Words: Crohn disease; Disease activity; Fecal calprotectin

INTRODUCTION

Crohn's disease (CD) is a chronic disorder characterized by transmural inflammation and patchy distribution in the GI

tract. The importance of assessing ongoing GI mucosal inflammation in this condition lies in the fact that it helps predict course of disease,[1-7] response to therapy,[1] advent of complications,[7] need for hospitalization and surgery.[4] To this effect, various studies have shown mucosal healing to be the best predictor of positive long-term outcomes.[3-6] Endoscopy is currently regarded as the gold standard test for assessment of mucosal healing.[8] However, it is expensive, invasive, associated with patient discomfort and has an associated small risk of serious complications, thus making it an unfeasible modality for frequent monitoring. Biochemical markers like CRP are inexpensive but have moderate diagnostic accuracy with a specificity of 0.92 (95% CI, 0.72–0.96) but a sensitivity of only

0.49 (95% CI, 0.34–0.64),[9] hence limiting its use as a disease biomarker.

Since the acutely inflamed intestinal mucosa is deemed to be neutrophil–rich, fecal tests based on neutrophil-derived markers are a realistic option for assessing mucosal inflammation. Among the various fecal markers of intestinal inflammation; fecal calprotectin (FC) is the one most commonly used in clinical practice.[10] FC has a sensitivity of 87% and specificity of 67% when used to detect endoscopic activity in symptomatic CD.[9] It accurately predicts the response to therapy as well as 1-year risk of relapse.[11-13] There are though conflicting reports on whether the diagnostic accuracy in CD is influenced by disease location. FC has been shown to have a lower specificity in CD than in UC and this might be driven through the different disease locations.[14-16] Some studies report that the FC level is lower in small bowel (SB) disease location compared to large bowel (LB) location,[17,18] while others did not observe any difference.[14,19] We feel this is an important matter that could potentially either change practice or serve as a basis for downstream research. We thus aimed to undertake a systematic review of published literature and discuss the effect of disease location on the sensitivity and specificity of FC to accurately measure disease activity in CD.

METHODS

1. Criteria for Inclusion and Exclusion

Case control and cohort studies that provided data on FC separately by SB and LB locations were selected. Only those studies which had clearly mentioned the use of endoscopy, MRI, CT or a combination of these modalities as reference standard to assess disease activity were included.[8,20] The subjects included both adult and pediatric patients who had been diagnosed with CD on the basis of their clinical symptoms and supporting investigations (endoscopy, biopsies, imaging, blood and stool tests). We also included studies in which healthy volunteers and subjects with IBS were recruited as controls. We excluded studies focusing only on SB-CD and studies where the reference standard for activity used was based on clinical or biochemical criteria. We also excluded studies specifically dealing with postoperative CD as it would not have been possible to define the disease location as SB or LB if the recurrence was limited to the anastomosis.

2. Search Strategy

Our search included Medline, Embase, Web of Science and Cochrane Library from inception up to November 8, 2016 with the help of a senior librarian to obtain the appropriate studies. There were no language or publication restrictions applied while searching. Details of the search strategy are provided in the Supplementary Material 1.

Conference proceedings from Digestive Diseases Week, United European Gastroenterology Week, European Crohn's and Colitis Organisation (ECCO) and British Society of Gastroenterology annual meetings over the past 12 years (2005–2016) were also searched for relevant additional studies. We performed a manual search from references in the included studies and pertinent review articles. We also searched the Grey Literature Database OpenGrey to check for eligible studies.

3. Selection

The selected studies were initially screened for eligibility by 3 authors (E.G.S., R.W., and A.A.T.). The abstracts were reviewed and those eligible were included for full text review. The full manuscripts were independently assessed (E.G.S. and G.W.M.) as per the inclusion criteria. If there were any disagreements, these were resolved by discussion and consensus with the other authors (S.S., R.W., and A.A.T.). Studies published only in abstract format were included as long as inclusion criteria were satisfied.

4. Data Extraction

Two authors (E.G.S. and G.W.M.) independently completed the data extraction forms for studies in the final selection list. The following data was collated: general information (journal, year, author, title), publication type (full paper or abstract), location, number of centers involved, study design (prospective/cross-sectional), total number of CD subjects and stratification based on disease location, age group (adult/pediatric/both), follow up period in months, FC levels with cutoff, clinical disease activity index, relevant reference standard (with appropriate disease activity score if provided), number of true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) and miscellaneous details. If any of the selected studies had missing data or needed clarification, multiple attempts through electronic mail were made to contact the authors to furnish the same.

5. Risk of Bias

To assess the risk of bias, QUADAS-2 was used (Supplementary Material 2). This is a research tool to check the quality of systematic reviews of diagnostic accuracy studies.[21] This was

assessed independently by 2 authors (E.G.S. and G.W.M.) while any disagreement was resolved by consensus with co-authors (S.S., R.W., and A.A.T.).

6. Data Synthesis

Sensitivity and specificity in the SB and LB locations were separately derived by calculation from the information provided (i.e., TP, TN, FP, and FN) or as reported in the published literature.

RESULTS

The electronic data base search on November 8, 2016 identified 5,619 results. After the removal of 2,098 duplicates, 3,521 records were screened for inclusion. From the latter, 61 studies were deemed to be relevant and subjected to full text review. Thereafter, 45 studies[12,13,15,22-63] were excluded either because the numerical data on FC at SB and LB locations were not separately available or because the reference standards used did not conform to inclusion criteria. Finally, 16 studies were included in the qualitative review (Fig. 1) involving 328 patients with SB-CD and 332 patients with LB disease location.
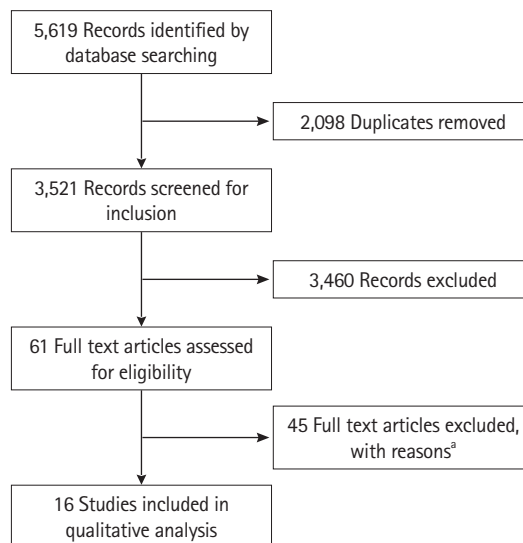

Fig. 1. PRISMA flow diagram. [a]Sixteen studies, numerical data not available for fecal calprotectin (FC) at large bowel and small bowel locations separately; 16 studies, reference standards for assessment of disease activity were different from those mentioned in inclusion criteria; 13 studies, both numerical data for FC at the 2 locations were not separately available and reference standards used for assessment of disease activity were different from those mentioned in inclusion criteria. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Study Characteristics

Study	Design	Patient spectrum	SB Crohn's	LB Crohn's	Reference standard/ scoring system used
af Björkesten[14]	Prospective	Anti-TNF treated luminal Crohn's	33	50	SES-CD
Faubion[65]	Cross-sectional	Crohn's cohort on follow-up	22	12	ICO-CTE score
Gecse[17]	Cross-sectional	Crohn's undergoing ileocolonoscopy	9	20	SES-CD
Jensen[19]	Cross-sectional	Suspected Crohn's under evaluation	13	16	Endoscopy/capsule/surgery
Jones[64]	Cross-sectional	Crohn's undergoing ileocolonoscopy	53	40	SES-CD
Lobatón[67]	Cross-sectional	Crohn's undergoing ileocolonoscopy	26	45	CDEIS
Makanyanga[68]	Cross-sectional	Crohn's cohort on follow-up	18	15	MEGS
Maltz[69]	Cross-sectional	Crohn's cohort on follow-up	9	18	Endoscopy
Schoepfer[70]	Cross-sectional	Crohn's undergoing ileocolonoscopy	35	20	SES-CD
Sipponen[71]	Cross-sectional	Crohn's undergoing ileocolonoscopy	16	17	SES-CD
Sipponen[18]	Cross-sectional	Crohn's undergoing ileocolonoscopy	19	14	CDEIS
Stawczyk-Eder[72]	Cross-sectional	Hospitalized Crohn's	44	22	SES-CD
Zittan[73]	Cross-sectional	Crohn's cohort on follow-up	14	23	SES-CD, MaRIA
Moniuszko[74]	Cross-sectional	Hospitalized Crohn's	NA	NA	SES-CD, CT enteroclysis
Goutorbe[75]	Cross-sectional	Crohn's undergoing ileocolonoscopy	13	12	CDEIS
Lin[76]	Prospective	Crohn's cohort on follow-up	4	8	CDEIS

SB, small bowel; LB, large bowel; SES-CD, Simple Endoscopic Score for Crohn's Disease; ICO-CTE, ileocolonoscopy and CT enterography; CDEIS, Crohn's Disease Endoscopic Index of Severity; MEGS, MRI enterography global score; MaRIA, magnetic resonance index of activity; NA, not available.

1. Study Demographics

Fourteen relevant cross-sectional[17,19,64-75] and 2 prospective studies[14,76] were published between 2008 and 2016 (Table 1). Four of the 16 studies were published as conference abstracts[65,69,73,74] although 1 of these was subsequently published as a full text article.[66] Almost all the studies were single/dual-center based other than the studies by Faubion et al.[66] and Lin et al.[76] which were multi-center. All the studies were performed in Europe and North America apart from a single study originating from Asia.[76] The majority of the studies involved adult subjects. The study by Jones et al.[64] included 23 subjects who were less than 16 years while the youngest subject in the study by Jensen et al.[19] was 16 years. With regard to the reference standards utilized; 11 studies used endoscopy, 2 used endoscopy and CT in combination while there was one each for MRI alone, endoscopy and MRI in combination and a composite assessment of endoscopy/capsule endoscopy/surgery (Table 1).

2. Risk of Bias Assessment

With regard to QUADAS-2 risk assessments of the selected studies (Table 2), only a single study[75] scored low in all 4 domains of risk of bias and the domain of concern for applicabil-

ity. There were again just 3 studies[64,71,76] by which scored low in 3 domains of risk of bias. Most studies had an unclear risk of bias in patient selection. With respect to the index test, there were 3 studies that had high risk[67,68,72] while one[69] was unclear. The studies were almost evenly distributed between low and unclear risk with regard to the reference standard. Eight studies had either high or unclear risk of bias under subject flow and selection.[18,64,66-68,70,73,74] There were just 6 studies[64,67,70,72,75,76] which had low concern for applicability under subject selection.

3. Sensitivity and Specificity of FC by Location

The data on the effect of disease location on FC is heterogeneous (Table 3). Some studies[17,18,67,69] showed that the FC was significantly higher in LB vs. SB location while others[14,19,68,70,74-76] did not corroborate this finding, though absolute values have limited value.

The studies by Jones et al.,[64] Sipponen et al.,[71] and Zittan et al.[73] showed that FC significantly correlated with the reference standard only at the LB location but not at the SB location while the other 2 studies[67,72] showed that FC correlated with the reference standard at both the locations (Table 4). The reference standard used in these studies was endoscopy with the scor-

Table 2. QUADAS-2 Risk Assessment for the Selected Studies

Study	Risk of bias				Applicability concerns		
	Subject selection	Index test	Reference standard	Flow and timing	Subject selection	Index test	Reference standard
af Björkesten[14]	Low	Low	Low	Low	High	NC	NC
Faubion[66]	Unclear	Low	Unclear	Unclear	High	NC	NC
Gecse[17]	High	Low	Unclear	Low	Unclear	NC	NC
Jensen[19]	Unclear	Low	Unclear	High	High	NC	NC
Jones[64]	Unclear	Low	Low	Low	Low	NC	NC
Lobatón[67]	Low	High	Low	High	Low	NC	NC
Makanyanga[68]	Unclear	High	Low	Unclear	High	NC	NC
Maltz[69]	Unclear	Unclear	Unclear	Low	Unclear	NC	NC
Schoepfer[70]	High	Low	Low	Unclear	Low	NC	NC
Sipponen[71]	Unclear	Low	Low	Low	Unclear	NC	NC
Sipponen[18]	Unclear	Low	Unclear	Unclear	Unclear	NC	NC
Stawczyk-Eder[72]	Unclear	High	Low	Low	Low	NC	NC
Zittan[73]	Unclear	Low	Unclear	Unclear	Unclear	NC	NC
Moniuszko[74]	Unclear	Low	Unclear	Unclear	Unclear	NC	NC
Goutorbe[75]	Low	Low	Low	Low	Low	NC	NC
Lin[76]	Unclear	Low	Low	Low	Low	NC	NC

NC, not a concern.

Table 3. Comparison of Mean or Median Levels in the 2 Locations

Study	SB Crohn's	LB Crohn's	Reference standard/ scoring system used	Key result	Inference
af Björkesten[14]	33	50	SES-CD	Median FC level in SB: 86 µg/g LB: 158 µg/g (NS)	No difference between both locations
Gecse[17]	9	20	SES-CD	Mean FC level in SB: 297±81 µg/g LB: 1,523±97 µg/g (P<0.0001)	Higher in LB location
Jensen[19]	13	16	Endoscopy/capsule/surgery	Median FC level in SB: 890 mg/kg LB: 830 mg/kg (NS)	No difference between both locations
Lobatón[67]	26	45	CDEIS	Median FC level in SB: 420.5 µg/g LB: 1,297 µg/g (P=0.013)	Higher in LB location
Makanyanga[68]	18	15	MEGS	Mean FC level in SB: 319.1 µg/g LB: 342 µg/g (NS)	No difference between both locations
Maltz[69]	9	18	Endoscopy	Median FC level in SB: 442 µg/g LB: 66 µg/g (P<0.002)	Higher in LB location
Schoepfer[70]	35	20	SES-CD	Mean FC level in SB: 287±279 µg/g LB: 401±312 µg/g (NS)	No difference between both locations
Sipponen[18]	19	14	CDEIS	Median FC level in SB: 180 µg/g LB: 1,383 µg/g (P=0.017)	Higher in LB location
Moniuszko[74]	NA	NA	SES-CD, CT enteroclysis	Median FC level in SB: 195 µg/g LB: 401 µg/g (NS)	No difference between both locations
Goutorbe[75]	13	12	CDEIS	Median FC level in SB: 841 µg/g LB: 1,575.5 µg/g (NS)	No difference between both locations
Lin[76]	4	8	CDEIS	Median FC level in SB: 2,693 µg/g LB: 176 µg/g (NS)	No difference between both locations

SB, small bowel; LB, large bowel; SES-CD, Simple Endoscopic Score for Crohn's Disease; FC, fecal calprotectin; CDEIS, Crohn's Disease Endoscopic Index of Severity; MEGS, MRI enterography global score; NA, not available.

Table 4. Correlation between Fecal Calprotectin and Reference Standard at Respective Locations

Study	SB Crohn's	LB Crohn's	Reference standard/ scoring system used	Key result	Comment
Jones[64]	53	40	SES-CD	Correlation in SB: -0.01 (NS) LB: 0.8 (P<0.05)	Correlation noted only at LB location
Lobatón[67]	26	45	CDEIS	Correlation in SB: 0.437 (P=0.016) LB: 0.725 (P<0.01)	-
Sipponen[71]	16	17	SES-CD	Correlation in SB: 0.317 (NS) LB: 0.642 (P<0.01)	Correlation noted only at LB location
Stawczyk-Eder[72]	44	22	SES-CD	Correlation with SES-CD in SB: 0.78 (P<0.0001) LB: 0.78 (P<0.0002)	-
Zittan[73]	14	23	SES-CD, MaRIA	Correlation in SB: 0.4 (P=NS) LB: 0.61 (P<0.0001)	Correlation noted only at LB location

SB, small bowel; LB, large bowel; SES-CD, Simple Endoscopic Score for Crohn's Disease; CDEIS, Crohn's Disease Endoscopic Index of Severity; MaRIA, magnetic resonance index of activity.

Table 5. Diagnostic Accuracy of Fecal Calprotectin in CD at SB versus LB Location

Study	Sensitivity		Specificity		FC cutoff (μg/g)
	SB (95% CI)	LB (95% CI)	SB (95% CI)	LB (95% CI)	
Jensen[19,a]	92	94	NA	NA	50
Lobatón[67,a]	63	79	100	100	272
Zittan[79,a]	75	100	50	67	100
af Björkesten[14]	60.0 (32.9–82.5)	78.9 (53.9–93.0)	100.0 (62.9–100.0)	75.0 (35.6–95.5)	100
Faubion[66]	76.9 (46.0–93.8)	80.0 (29.9–98.9)	75.0 (35.6–95.5)	28.6 (5.1–69.7)	100
Gecse[17]	42.9 (11.8–79.8)	100.0 (78.1–100.0)	NA	100.0 (5.5–100.0)	200
Goutorbe[75]	100 (51.7–100)	100.0 (62.9–100.0)	50.0 (13.9–86.0)	33.3 (1.8–87.5)	200
Moniuszko[74]	100 (31.0–100)	66.7 (30.9–91.0)	100.0 (31.0–100.0)	50.0 (2.7–97.3)	238

All unit of data is percent.
[a]Raw data and associated CI are not available.
SB, small bowel; LB, large bowel; FC, fecal calprotectin; NA, not available.

ing system being either Simple Endoscopic Score for Crohn's Disease (SES-CD),[64,71-73] Crohn's Disease Endoscopic Index of Severity (CDEIS)[67] although in the study by Zittan et al.,[73] MR enterography score (MaRIA, magnetic resonance index of activity) was also used in the SB location.

The sensitivity and specificity data were available for 8 studies in total (Table 5). Sensitivities were available in the published literature for just 2 studies[19,67] while in 1 study,[73] these were retrospectively provided by the author. For the remaining 5 studies,[14,17,66,74,75] the relevant authors provided the raw data on the number of TP, TN, FP, and FN, from which the sensitivity and specificity values were retrospectively calculated.

Including data from all the 8 studies, the sensitivity and specificity of FC in the SB ranged from 42.9% to 100% and from 50% to 100% respectively. The sensitivity and specificity of FC in the LB ranged from 66.7% to 100% and from 28.6% to 100% respectively.

DISCUSSION

A variety of clinical studies have indicated a wide range of sensitivities and specificities for FC in CD at different disease locations.[14,17-19] We have undertaken a systematic review to objectively appraise the literature. Overall, the sensitivity and specificity of FC in the SB ranged from 42.9% to 100% and 50% to 100% while those in the LB were from 66.7% to 100% and 28.6% to 100% respectively indicating that FC may be equally useful to measure disease activity in CD at these 2 locations but no firm conclusion can be made from the published literature. The QUADAS-2 tool indicated that the quality of the selected studies was modest.

The data represented here is heterogeneous with varying gold-standards. There are only 5 studies in the published literature with the primary aim of investigating the effect of disease location on the sensitivity and specificity of FC.[17,19,72-74] In the remaining eleven studies, this information was expressed as a sub-analysis. Moreover, apart from the published data, raw data to calculate sensitivity and specificity was only available in 5 small studies. These data did not pertain to all the cohorts published but only relevant to smaller sub-groups.[14,17,65,74,75] One might speculate that LB disease location is within reach of colonoscopy and hence is more commonly validated with a gold-standard investigation. As for SB disease location, unless the disease is in the terminal ileum this might not be as accurately located though the sensitivities and specificities of MRI to measure disease activity is widely published.[77] A possible reason for the effect of disease location on the specificity of FC might be that other common disease of the colon such as diverticulitis, microscopic colitis or infectious enteritides might raise FC other than LB-CD. The same might not be said for SB inflammation in cohort studies undertaken in the Western Hemisphere where CD is the commonest cause for ileal inflammation. Effectively, this systematic analysis highlights the need of properly designed prospective studies to answer this important question.

Despite endoscopy being the gold standard for assessment of disease activity, we also included studies where radiological tests such as CT or MRI were utilized as reference standards to evaluate the SB activity as these have been supported by the ECCO guidelines.[8,20] However, the lack of a uniform gold standard was a limiting factor. This heterogeneity multiplied by the inter-observer variability for the various investigative

modalities used, limited the validity of the reported sensitivities and specificities. The limitations of CT and MRI may include decreased sensitivity to detect early disease that may otherwise be detected on endoscopy. Even in those studies that have used endoscopy as the reference standard, various scoring systems such as the SES-CD and the CDEIS scores were utilized. These scoring systems themselves have limitations such as the endoscopic evaluation being confined to the terminal ileum or colon subject to the reach of the colonoscope and inter-observer variability. Capsule endoscopy is a non-invasive way to evaluate the entire SB. However, its disadvantages include lack of utility when there is a SB stricture as well as subjective nature of reporting.

There are certain limitations in the published literature that need to be highlighted. The FC cutoffs used in all the reported studies are different. The cutoff values can influence the test accuracy and there are different cutoff values for FC depending on the intent of use. The current National Institute for Health and Care Excellence (NICE) guideline[78] indicates that an FC value < 50 μg/g suggest no significant GI mucosal inflammation, with a value of > 250 μg/g corresponds well with endoscopic and histology activity.[9,79] The cutoff values used in the studies presented in this systematic review were not uniform. Most of the studies used cutoff of 100 μg/g with just 3 studies using a cutoff value of 50 μg/g. The diagnostic test used to determine the FC levels were not uniform. Most studies used ELISA test while some used the rapid test (Quantum Blue). Stool collection time was not standardized across the studies described in this systematic review. There was a paucity of detail regarding processing of the stool samples across the studies. These factors could also contribute to differences of FC across the studies.

Our systematic review included both pediatric and adult studies though most of the data was from the adult population and the pediatric population appeared under-represented. The specificity of FC appears to improve with patient age. van Rheenen et al.,[80] in their meta-analysis of 13 studies, obtained a pooled sensitivity of 93% and specificity of 96% in adults and 92% and 76% in children respectively. The larger share of irritable bowel disease with absence of alarm symptoms was thought to overestimate the specificity in the adults subjects compared to children. Henderson et al.[54] undertook a meta-analysis of 8 studies and concluded that the sensitivity and specificity of FC in IBD in the pediatric cohort were 97.8% and 68.2%. Factors that could contribute to the difference in specificity of FC in adult versus pediatric populations include the

variation in the disease prevalence and spectrum, variation in the FC threshold to trigger endoscopic evaluation, parental expectation and concerns about missed diagnosis.[54] The pediatric cohort in this systematic review was too small to be able to make any firm conclusions.

We observed that most of the studies originated from the Western Hemisphere except for the study from Taiwan,[76] perhaps indicating that these findings may not be reflective of the situation in the general population worldwide. It would be difficult to get homogenous world-wide data on the accuracy of FC in SB and LB locations due to differences in incidence and prevalence of IBD across regions.[81]

This systematic review has some major strengths. We had undertaken a comprehensive search including important online databases (MEDLINE, Embase, Web of Science, and Cochrane Library). We had no language or publication restrictions. Moreover, relevant conference proceedings were searched since 2005 to ensure no publication bias was introduced within our search. We excluded studies that were merely restricted to SB-CD since we also needed information from the LB in order to compare. We excluded those studies solely describing postoperative cohorts to exclude the effect of non-IBD related anastomotic ulceration on the analysis. Moreover, since the raw figures (i.e., TP, TN, FP, and FN in both SB and LB locations) of the selected studies were not provided in the original published manuscripts, electronic communication with relevant study authors was undertaken as part of our data extraction process for this systematic review.

The range of sensitivities and specificities for FC by disease location are variable and incomparable. As the gold standard comparators used in various studies are heterogeneous it has not been possible to pool the data and calculate common variables for FC. Prospective cohort studies with common comparators and similar quantification methodologies for FC are needed to answer this question; in order to better understand the right place for FC as a disease monitoring tool.

FINANCIAL SUPPORT

CONFLICT OF INTEREST

AUTHOR CONTRIBUTION

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See "Does fecal calprotectin equally and accurately measure disease activity in small bowel and large bowel Crohn's disease? - a systematic review" on page 160-170.

Supplementary Material 1

Search strategies:
A. MEDLINE - Search strategy

1. exp Leukocyte L1 Antigen Complex/
2. (calprotectin* or calgranulin*).mp.
3. (S100A8* or S100A9*).mp.
4. "Leukocyte L1 Antigen Complex".mp.
5. (leu#ocyt* adj3 "L1" adj3 antigen* adj3 complex*).mp.
6. 1 or 2 or 3 or 4 or 5
7. exp Biological Markers/
8. (((bio* or lab* or progno* or predict* or fecal* or faecal* or feces* or faeces*) adj2 marker*) or biomarker* or (biologic* adj marker*) or marker* or surrogat*).mp.
9. 7 or 8
10. exp Crohn Disease/
11. crohn*.mp.
12. exp Inflammatory Bowel Diseases/
13. (ibd* or (inflam* adj3 bowel*)).mp.
14. exp Colitis, Ulcerative/
15. (ulcer* adj3 colitis*).mp.
16. 10 or 11 or 12 or 13 or 14 or 15
17. (fecal* or faecal* or feces* or faeces* or excret* or stool*).mp.
18. 6 and 16
19. 9 and 16 and 17
20. 18 or 19

B. Embase - Search strategy

1. exp calgranulin/
2. (calprotectin* or calgranulin*).mp.
3. "Leukocyte L1 Antigen Complex".mp.
4. (leu#ocyt* adj3 "L1" adj3 antigen* adj3 complex*).mp.
5. (S100A8* or S100A9*).mp.
6. 1 or 2 or 3 or 4 or 5
7. exp biological marker/
8. (((bio* or lab* or progno* or predict* or fecal* or faecal* or feces* or faeces*) adj2 marker*) or biomarker* or (biologic* adj marker*) or surrogat*).mp.
9. 7 or 8
10. exp Crohn disease/
11. exp ulcerative colitis/
12. exp inflammatory bowel disease/
13. crohn*.mp.
14. (ibd* or (inflam* adj3 bowel*)).mp.
15. (ulcer* adj3 colitis*).mp.
16. 10 or 11 or 12 or 13 or 14 or 15

17. (faecal* or fecal* or feces* or faeces* or stool* or excre*).mp.
18. 6 and 16
19. 9 and 16 and 17
20. 18 or 19

C. Cochrane Library (Central) - Search strategy

1. "Inflammatory bowel disease" or "ulcerative colitis" or "Crohn's disease"
2. "disease activity"
3. "calprotectin"
4. (1 OR 2) AND 3

D. Web of Science - Search strategy

1. "Inflammatory bowel disease" or "ulcerative colitis" or "Crohn's disease"
2. "calprotectin" or "calgranulin"
3. 1 AND 2

Supplementary Material 2

The following criteria were assessed in QUADAS-2:
1. Was a consecutive or random sample of subjects enrolled?
2. Was a case-control design avoided?
3. Did the study avoid inappropriate exclusions?
4. Could the selection of subjects have introduced bias?
5. Is there concern that the included subjects do not match the review question?
6. Were the index test results interpreted without knowledge of the results of the reference standard?
7. If a threshold was used, was it pre-specified?
8. Could the conduct or interpretation of the index test have introduced bias?
9. Is there concern that the index test, its conduct, or interpretation differ from the review question?
10. Is the reference standard likely to correctly classify the target condition?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Could the reference standard, its conduct, or its interpretation have introduced bias?
13. Is there concern that the target condition as defined by the reference standard does not match the review question?
14. Was there an appropriate interval between index test(s) and reference standard?
15. Did all subjects receive a reference standard?
16. Did subjects receive the same reference standard?
17. Were all subjects included in the analysis?
18. Could the subject flow have introduced bias?

We modified the application of the QUADAS-2 as previously shown.[1] With regard to question 5, "low concern" was scored if the subjects clearly had established CD and "high concern" if the study sample had subjects presenting for the first time with CD. Question 6 was not scored as fecal calprotectin is an objective test based on laboratory result which is not affected by blinding the index test interpreter to the reference standard. The applicability of the index test (question 9) was not a concern for this review despite the variations in the way the index test was performed and interpreted. For question 10, "yes" was scored for all the studies since endoscopy is considered the gold standard for diagnosis of CD while MRI or CT are considered useful in assessment for CD in the small bowel in the most recent European guidelines.[2,3] Since the gold standards used for assessment of CD were endoscopy, MRI or CT; question 13 (applicability of reference standard) was considered not of concern.

The responses for the signalling questions were "yes," "no" or "unclear" and the risk of bias was marked as "low," "high" or "unclear." If all the signalling questions for a particular domain were "yes," this would indicate a "low" risk of bias while presence of any "no" would raise the concern for bias. When the information was insufficient, "unclear" has been marked.

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