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**Are faecal markers good indicators of mucosal healing in inflammatory bowel disease?**

Boon GJAM *et al.* Faecal markers and mucosal healing in IBD

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**Abstract**

The inflammatory bowel diseases (IBD), including Crohn’s disease and ulcerative colitis, are chronic diseases characterised by inflammation of the gastrointestinal tract. It is increasingly clear that clinical manifestations (such as abdominal pain or diarrhoea), corresponding clinical indices and biochemical assessment are not fully representative of the degree of intestinal inflammation. Mucosal healing may be a more reliable indicator of mucosal inflammation and response to therapy. The gold standard for assessing disease severity in individuals with IBD is colonoscopy with mucosal biopsies and histological examination. Non-invasive alternatives to endoscopy would be of great benefit to both patients and health care professionals. This review gives an overview of the current understanding of the potential role of faecal biomarkers in the assessment of mucosal healing and whether they could be an appropriate surrogate to endoscopy in IBD patients. The available studies show that faecal markers, such as calprotectin and lactoferrin, are promising non-invasive indicators of mucosal healing. However, due to wide variability in study design, especially with regard to the definition of mucosal healing and evaluation of marker cut offs, the available data do not yet indicate the optimal roles of these markers.

**Key words:** Crohn’s disease; Ulcerative colitis; Mucosal healing; Faecal calprotectin; Faecal lactoferrin; Inflammatory bowel disease

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**Core tip:** With regard to mucosal inflammation and response to therapy in Crohn’s disease and ulcerative colitis patients, mucosal healing may be a more reliable target for treatment than clinical and biochemical assessment. The available studies in this review show that faecal biomarkers are promising non-invasive indicators of mucosal healing and they could be an appropriate surrogate to endoscopy (the gold standard) in inflammatory bowel diseases patients. However, due to a wide variability in the use of clinical indices and marker cut offs, it’s difficult to compare their performances. Moreover, a clear definition of mucosal healing is needed.

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**INTRODUCTION**

The inflammatory bowel diseases (IBD), Crohn’s disease (CD) and ulcerative colitis (UC), are chronic diseases characterised by inflammatory changes in the gastrointestinal tract, which can present at any age and are defined according to disease location, extent and histological findings[1]. IBD features chronic inflammatory changes, with a relapsing/remitting course. Symptoms of active disease typically include abdominal pain, diarrhoea, haematochezia and nutritional compromise. Although predominantly involving the gastrointestinal tract, extra-intestinal manifestations such as skin lesions, joint changes and hepatobiliary disease, may be seen in both CD and UC.

Historically, the treatment goal of IBD has been symptom palliation with clinical remission or response used as the primary outcomes in clinical trials and for registration by regulatory bodies such as the FDA. Clinical disease indices such as the Simple Clinical Colitis Activity Index (SCCAI) are examples of indices used in this way, while composite indices such as the Crohn’s disease activity index (CDAI) use a combination of clinical and laboratory data[2,3].{Winship, 1979 #426} While this approach has many merits, emerging data suggest that other goals may be associated with an improved prognosis.

Mucosal healing (MH) is associated with improved outcomes in clinical trials and has been suggested as the gold standard for remission as it is a direct measure of inflammation of the target organ[4]. In clinical trials of biological drugs, MH has been associated with a lower risk of hospitalisation and colectomy[5], improved symptom control and reduced corticosteroid use[6], and a reduced risk of clinical and surgical relapse following ileocolic resection in patients with CD[7].{Rutgeerts, 1990 #12913}{Rutgeerts, 1990 #12913} Despite much discussion concerning MH as a treatment goal, there is not yet a clear consensus on its definition[8]. In addition to MH, the concept of deep remission (encompassing both clinical remission and mucosal healing) has been developed although is yet to be formally tested in clinical trials[9].

Recently a working group of the International Organisation for the study of Inflammatory Bowel Diseases (IOIBD) published a detailed description of potential targets for the management of IBD. The process leading to a “treat to target” approach in IBD has mirrored that seen in other diseases where tight disease control has led to improved patient outcomes[10]. For both CD and UC, a key target identified is mucosal healing, in addition to the absence of clinical symptoms. While biochemical markers of inflammation in blood (*e.g.*, C-reactive protein (CRP)) and stool (*e.g*., faecal calprotectin (FC)) were thought to be adjuvant targets, it was concluded that insufficient data exist for them to be used as treatment targets in their own right. At present, the assessment of MH requires ileocolonoscopy[11]. While ileocolonoscopy is the gold standard in assessing the severity and extent of mucosal inflammation and healing in individuals with IBD[12], it is invasive, expensive and, therefore, not appropriate for repeated regular assessment of disease activity.

Faecal tests of inflammation have significant promise as non-invasive biomarkers that may reflect intestinal inflammation. These proteins can be measured easily in a single stool sample and efficiently quantified by enzyme-linked immunosorbent assay (ELISA). Furthermore, a number of these proteins can be measured using point of care devices facilitating rapid clinical decision-making based on the current inflammatory burden[13]. Recent studies have considered the potential of those non‑invasive markers as ways to assist in the diagnosis of IBD and as indicators of the response to therapy[14]. However, for faecal biomarkers to have a key role in the management of IBD in the treat to target era, it is essential that there are robust, accurate and validated data to support specific cut-off values to aid clinical decision making.

This review aims to examine studies that assess mucosal healing by non-invasive faecal tests. The role of several faecal markers will be discussed with comparison to endoscopic assessment.

**MATERIALS AND METHODS**

Bibliographical searches were performed in MEDLINE electronic database up to February 2015, using the following terms: “inflammatory bowel disease”, “Crohn´s disease”, “ulcerative colitis”, “faecal markers”, “calprotectin”, “lactoferrin”, “S100A12”, “endoscop\*”, “mucosal healing”, “remission”. In addition, relevant references from these studies were also included.

Studies included in this review assessed mucosal inflammation by endoscopic and/or histological means and compared these findings to faecal marker concentrations in IBD patient cohorts. Articles had to be published between 1990 and February 2014 and written in English. Papers excluded from the review were those where the faecal biomarker concentration was compared between patients with IBD and controls or other disease groups (*e.g.*, irritable bowel syndrome), those where serum biomarkers were used, those with a heterogeneous study population and those only assessing post-operative disease. No specific funding was obtained for this study.

**RESULTS**

***Research design***

Thirty-six studies published between 1990 and 2014 were included[15-49] Summaries of the studies are shown in Tables 1 - 6. Studies comprised variable numbers of study participants, considered CD (15 to 164 participants)[15-26,28,38,41-43,45,46,50,51] or UC (12 to 152 participants)[16,22,23,26,28,35-37,39,42,45-48,50,52] separately or as a combined group (11 to 252 participants)[22,23,28-34,40,42,44,50]. Eight reports included paediatric patients[16,31,34,35,38,43,44,50].

Several indices were used to document mucosal inflammation, encompassing eleven endoscopic and eight histologic grading systems. Some of these systems have been validated (*e.g.,* CDEIS and SES-CD), whilst others utilised grading systems that have not been widely validated. The majority of the available reports focused on faecal calprotectin (33 studies)[15-37,42-44,50], whilst others assessed faecal lactoferrin (13 studies)[17-20,22-24,26,28,30,32,38] and one study assessed S100A12[42]. In addition, studies utilised different faecal biomarker concentration cut offs for the assessment of markers and scoring systems.

Across all of the biomarkers, there is a wide range of correlation describing the association between faecal markers and endoscopic disease activity (*r*-values ranging from 0.32 to 0.87, *P*‑values ranging from < 0.0001 to 0.7815). Correlation coefficients are described in almost all studies and are used more commonly than outcome measures such as sensitivity, specificity, PPV and/or NPV. Overall, the studies that have evaluated faecal calprotectin (FC) and/or faecal lactoferrin (FL) and their relationship with endoscopic disease activity show inconsistent results (Tables 1 and 2). Fewer studies have studied the correlation between FC and FL with histologic severity (Tables 4 and 5).

***Faecal calprotectin and endoscopic severity***

Of the 28 studies investigating the ability of FC to determine endoscopic disease activity in patients with IBD(Table 1), 17 specifically included patients with CD. Two reports demonstrate high sensitivity and specificity[15,21]. However, the number of patients in these studies was relatively low (*n* = 64 and 122, respectively). In a cohort of 64 CD patients, Schoepfer and colleagues used a FC cut off concentration of 70 µg/g to demonstrate a sensitivity and specificity of 89% and 72% for the identification of MH, respectively[21]. On the other hand, in a cohort of 122 CD patients, Björkesten et al. found a sensitivity of 84% and a specificity of 74% with a FC cut off of 94 µg/g[15]. While these values are comparable, the studies used different SES-CD scores to reflect endoscopic remission (SES-CD ≤ 3 and ≤ 2 respectively). Reanalysis using a SES‑CD score of 0 (absence of ulcers) in Björkesten’s study reduced the ability of FC to detect remission. In both studies only FC was capable of discriminating between various degrees of disease activity in contrast to other indicators such as CRP and the CDAI.

Where calculated, PPV and NPV are variable between the studies of FC in CD patients. Much of this variability appears to be secondary to differences in the cut off concentrations for the faecal biomarkers and the cut off endoscopic scores used to define MH.

Thirteen studies described the use of FC concentration and its correlation with mucosal inflammation and healing in UC patients(Table 1). For all of these studies there was a statistically significant association between FC concentration and mucosal inflammation. However, only seven of these studies reported sensitivity, specificity, PPV and NPV for their studies with respect to a specific FC cut off concentration[16,23,27,45-48]. The largest study, which included 115 patients with UC, demonstrated a sensitivity of 93%, specificity of 71%, PPV of 91% and NPV of 81% using a FC cut off of 50 µg/g[27]. Re‑evaluation of this data using a higher cut off of 100ug/g resulted in values of 86%, 88%, 96% and 65%, respectively. The correlation coefficient of *r* = 0.83 for UC was higher than found in CD patients (*r* = 0.75). Again, FC was the only marker that was able to discriminate inactive from mild, moderate and highly active disease. A further study evaluating patients with UC using the Mayo Endoscopic Subscore and FC with a cut off of 48 µg/g, determined a sensitivity of 81.5% and specificity of 72.3%[23]. In contrast, an earlier study from the same region reported specificity of only 34% (for FC with cut off of 10 μg/g), or 62% using a cut off of 20 µg/g[37]. Four more recent studies have been more thorough in describing the association between FC concentration and endoscopic remission[45-48], although in relatively modest numbers of patients (38-62 patients only). Kristensen *et al*[48] analysed both Mayo 0 and Mayo 0 and 1 combined for two different commercial FC assays. Not surprisingly, specificity and PPV were greater when using the Mayo 0 score with both FC assays. On the other hand, in a study of 39 adults with UC, D’Haens *et al*[47] used Mayo 0 and a FC cut off of < 250 μg/g leading to 100% specificity and NPV, but just 50% PPV. Therefore, this would suggest that while a FC concentration of greater than 250 μg/g is highly predictive of the presence of mucosal inflammation in UC, this concentration is no better than flipping a coin for determining whether a patient has mucosal healing.

***Faecal calprotectin and histological assessment***

FC has been compared with histological activity in only 11 studies (Table 4). A study of 61 CD patients showed a significant correlation between FC concentration (*r* = 0.563, *P* < 0.01) and colonic or ileocolonic disease, but not with ileal disease[18]. This is consistent with an earlier study published by the same group[19], which demonstrated a significant association between FC concentration and pretreatment colonic disease (*r* = 0.522, *P* = 0.046) although only 15 patients were included.

For UC, the patient groups are small in all of the studies and there are mixed results regarding the correlation between FC concentration and histological appearance. Furthermore, few studies report a FC cut off concentration that optimally reflects MH.

***Paediatric studies evaluating faecal calprotectin***

Only one of eight paediatric studies documented sensitivity, specificity, PPV and NPV in addition to correlation coefficients[16]. Although the sensitivity was high in both CD (94.7%) and UC patients (94.1%), when utilising a cut off of 100 µg/g, the specificity was only 50%. Using a cut off of 150 µg/g, the specificity for active UC increased to 87.5%. Furthermore, Aomatsu *et al*[16] demonstrated that FC correlates closely with the SES‑CD and Matt’s grading (*r* = 0.760 and 0.838, respectively) – the strongest correlations identified amongst these studies.

Fagerberg *et al*[43] studied a paediatric group with predominantly colonic CD. Experienced gastrointestinal histopathologists divided the patients into two groups (inflamed and non-inflamed), based upon conventional criteria for IBD. Using a FC cut off of 50 µg/g resulted in sensitivity 95%, specificity 93%, PPV 95% and NPV 93%. In 2007 Fagerberg *et al*[31] evaluated a mixed group of children with CD and UC. Using a cut off of 85.7 µg/g for FC, the authors demonstrated a sensitivity 93%, specificity 82%, PPV 93% and NPV 82% for the identification of mucosal healing.

It is difficult to directly compare paediatric and adult studies of faecal biomarkers due to the heterogeneity of the study designs, particularly with respect to the use of different endoscopic indices and the definition of MH.

***Faecal lactoferrin and endoscopic severity***

Ten of twelve studies focusing on FL included just patients with CD (Table 2). For example, Langhorst *et al*[20] used the SES-CD to demonstrate a sensitivity of 81.8% and specificity of 60% for FL (*r* = 0.35, *P* < 0.05)[23]. In another study using the same cut off concentration (< 7.25 µg/g), a sensitivity of 71% and a specificity 83% were demonstrated with a PPV of 89% and NPV of 60%. A PPV of 100% has been shown in a further report including just 15 patients: however the NPV in this series was only 58%[19].

In a group of patients with UC, Langhorst *et al*[28] used the Mayo Endoscopic Subscore (without a given cut off concentration for FL), leading to specificity and sensitivity of 92.6% and 66.7%, respectively, with a correlation of *r* = 0.56, *P* < 0.001[23]. A different cohort using the same index showed a lower correlation coefficient for FL (*r* = 0.354, *P* = 0.023)[28].

***Faecal lactoferrin and histological assessment***

Four studies have evaluated correlations between FL and histologic severity[18,19,28,30]. Sipponen *et al*[18] described a significant correlation between FL and colonic or ileocolonic CD (r=0.543), but not for ileal disease (*r* = 0.291)[18]. Subsequently, the same authors divided patients into subgroups of pretreatment colonic, post-treatment colonic and ileal disease[19]. This report did not find a significant correlation between FL and mucosal histology. An additional study performed by D’Inca *et al*[28] with only 15 participants demonstrated moderate sensitivity (77%), specificity (80%) and PPV (95%), which was comparable to the performance of FC in the same group of patients.

Only one study has measured FL and histologic severity in patients with UC. A sensitivity of 75%, a specificity of 60%, a PPV of 87% and a significant correlation (*r* = 0.544) was ascertained in this report[28].

***Paediatric studies evaluating faecal lactoferrin***

Only one study has assessed FL in children with CD[38]. Using an unvalidated endoscopic grading system, the patients were divided into active and inactive groups. A cut off of 7.25 µg/g demonstrated a sensitivity of 100% and a specificity of 43%, whereas a cut off of 60 µg/g resulted in a lower sensitivity (84%) but higher specificity (74%). Again, it is hard to compare these outcomes to the adult studies evaluating FL due to marked variability in study design.

***Other faecal markers***

Although the majority of studies included in this review have evaluated FC and FL, other faecal markers have also been assessed including α1‑antitrypsin, polymorphonuclear elastase, lysozyme, faecal haemoglobin (FHb), haemoglobin-haptoglobin complex (Hb-Hp), neopterin and S100A12 (Tables 3 and 6).

Cellier *et al*[41] compared faecal α1-antitrypsin to CDEIS in 121 CD patients and found no correlation (*r* = 0.26). In contrast, Moran *et al*[68] demonstrated in 28 IBD patients a significant correlation between faecal α1‑antitrypsin and an alternative endoscopic index (*r* = 0.83, *P* = 0.001)[68].

Faecal polymorphonuclear elastase (PMN-e) is significantly correlated with endoscopic severity in CD (*r* = 0.32) and UC patients (*r* = 0.36)[23]. Similar results for a mixed group of patients were found by Silberer *et al*[32].

Nakarai *et al*[39] assessed faecal haemoglobin concentrations in 152 UC patients and compared this with the Mayo Endoscopic Score (threshold of mucosal healing). FHb showed sensitivity 94%, specificity 74%, PPV 40%, and NPV 98%.

Of the studies included in this review, only Kaiser *et al*[42] investigated the faecal marker S100A12. The specificity for both CD and UC subgroups was 100%, whereas the sensitivity was 81% in CD and 91% in UC.

**DISCUSSION**

Faecal biomarkers such as FC and FL offer tremendous promise as non-invasive markers of mucosal inflammation. As therapeutic targets move from symptom control to mucosal healing, it is imperative that non-invasive markers of inflammation are firstly validated and then become available for routine clinical use. This could allow more regular assessment of inflammation with subsequent timely clinical decisions and possibly lead to a reduced requirement for follow-up endoscopies. Sensitive and specific biomarkers are essential if a true treat-to-target approach is to be adopted.

At best the currently available studies show a mixed picture with few findings strongly replicated across multiple studies. This variability is reflected in diverse study designs with a wide range of endoscopic and other indices employed. Even within studies using the same indices, variable scores have been used to define MH or remission. Additionally, a wide range of cut off concentrations for faecal biomarkers have been used, leading to difficulty in the interpretation of individual results. Until a clear target for treatment is defined, it is difficult to resolve many of the differences between these studies.

Correlation coefficients are a useful means of comparing the association between two sets of continuous data (such as faecal biomarker concentration and mucosal inflammation). However, once such correlations have been shown to be significant, it is essential that accurate cut-off concentrations are determined for biomarkers using categorical data for mucosal inflammation. This allows sensitivity, specificity, positive and negative predictive values (in addition to accuracy) to be determined. These parameters are clinically useful, whereas correlation coefficients provide limited clinical relevance. Unfortunately, few studies provided in depth statistical analysis including all the required parameters.

While there were a large number of studies that assessed the utility of faecal biomarkers in reflecting mucosal inflammation at a single point in time, few followed patients prospectively to determine the prognostic significance of elevated biomarkers. In clinical medicine, such prognostic data are essential in determining appropriate treatment escalation and de-escalation.

***Future studies***

We suggest a number of ways in which future studies may contribute to an improved understanding of the relationship between faecal biomarkers and mucosal inflammation and healing.

Firstly, treatment targets in IBD need to be defined and validated. This issue is much broader than the field of faecal biomarkers, but is a clinical and philosophical problem that needs to be urgently resolved. Once resolved, then studies can be performed using established and meaningful endoscopic or other endpoints against which faecal biomarkers can be measured. This includes the assessment of biomarkers against endoscopic and histologic indices, unless there appears to be lack of a validated grading system in IBD for the latter.

Secondly, studies should report their data in clinically meaningful ways including sensitivity, specificity, positive and negative predictive values and accuracy. This will allow comparison between the performances of individual biomarkers and may demonstrate specific advantages of one biomarker over another.

Thirdly, consideration should be made to combining non-endoscopic data to provide the best measure of mucosal inflammation. This could include combinations of clinical symptoms, serum and faecal biomarkers and is likely to be superior to one single parameter. Such analyses will require well‑powered studies to enable appropriate analyses.

Finally, the cost-effectiveness of biomarker-driven treatment algorithms needs to be compared with symptoms and endoscopy driven approaches. While biomarker assays are cheaper than endoscopy, the assay costs are still not inconsequential and cost effectiveness must be measured in future studies. These costs should include both direct and indirect costs (the latter are often missed in such analyses and the effect of absenteeism for clinical investigations for patients and their carers should be captured).

In conclusion,Surrogate markers for endoscopic severity in IBD patients are needed for many reasons. Mucosal healing is an important and meaningful objective in the management of this incurable disease. At present, faecal markers seem promising as tools to reflect mucosal healing in IBD, however further research is needed to elucidate their definitive role(s). The variability of study design and endpoints described in this review make it difficult to recommend the routine use of faecal biomarkers in all patients. Nor can one biomarker be suggested to be superior to another given the lack of robust comparative studies. Future research should focus on large studies with clinically meaningful endpoints.

**COMMENTS**

***Background***

With regard to disease severity in Crohn’s disease and ulcerative colitis patients, several endoscopic, clinical and histologic grading systems are being used. The gold standard for assessing mucosal inflammation and response to therapy in inflammatory bowel disease is endoscopy.

***Research frontiers***

Emerging data suggest that mucosal healing (MH) may be a more reliable target for treatment than clinical and biochemical assessment. MH is associated with improved outcomes in clinical trials. Faecal markers have shown to have multiple advantages in assessing MH and have been suggested as the gold standard for remission.

***Innovations and breakthroughs***

In addition to MH, the concept of deep remission (encompassing both clinical remission and MH) has been developed, although is yet to be formally tested in clinical trials. Recently a working group of the International Organisation for the study of Inflammatory Bowel Diseases published a detailed description of potential targets for the management of inflammatory bowel diseases (IBD). The process leading to a “treat to target” approach in IBD has mirrored that seen in other diseases where tight disease control has led to improved patient outcomes.

***Applications***

Current available studies show a mixed picture of the utility of faecal biomarkers due to a wide variability in study design and endpoints. According to these data, we cannot argue for the use or certain cut off values of these markers. If a true treat-to-target approach is to be adopted, accurate and validated data are needed in order to be able to recommend sensitive and specific biomarkers.

***Peer-review***

In the review, the authors aimed to review the available studies about fecal markers of mucosal healing in IBD. The manuscript is of great clinical importance.

**REFERENCES**

1 **Satsangi J**, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; **55**: 749-753 [PMID: 16698746 DOI: 10.1136/gut.2005.082909]

2 **Winship DH**, Summers RW, Singleton JW, Best WR, Becktel JM, Lenk LF, Kern F. National Cooperative Crohn's Disease Study: study design and conduct of the study. *Gastroenterology* 1979; **77**: 829-842 [PMID: 38175]

3 **Walmsley RS**, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. *Gut* 1998; **43**: 29-32 [PMID: 9771402 DOI: 10.1136/gut.43.1.29]

4 **Pineton de Chambrun G**, Peyrin-Biroulet L, Lémann M, Colombel JF. Clinical implications of mucosal healing for the management of IBD. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 15-29 [PMID: 19949430 DOI: 10.1038/nrgastro.2009.203]

5 **Lichtenstein GR**, Yan S, Bala M, Hanauer S. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. *Am J Gastroenterol* 2004; **99**: 91-96 [PMID: 14687148 DOI: 10.1046/j.1572-0241.2003.04010.x]

6 **Frøslie KF**, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422 [PMID: 17681162 DOI: 10.1053/j.gastro.2007.05.051]

7 **Rutgeerts P**, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**: 956-963 [PMID: 2394349]

8 **Neurath MF**, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012; **61**: 1619-1635 [PMID: 22842618 DOI: 10.1136/gutjnl-2012-302830]

9 **Hommes D**, Colombel JF, Emery P, Greco M, Sandborn WJ. Changing Crohn's disease management: need for new goals and indices to prevent disability and improve quality of life. *J Crohns Colitis* 2012; **6** Suppl 2: S224-S234 [PMID: 22463929 DOI: 10.1016/S1873-9946(12)60502-9]

10 **Smolen JS**, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M, van der Heijde D. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; **69**: 631-637 [PMID: 20215140 DOI: 10.1136/ard.2009.123919]

11 **Allen PB**, Peyrin-Biroulet L. Moving towards disease modification in inflammatory bowel disease therapy. *Curr Opin Gastroenterol* 2013; **29**: 397-404 [PMID: 23695427 DOI: 10.1097/MOG.0b013e3283622914]

12 **Schreyer AG**, Rath HC, Kikinis R, Völk M, Schölmerich J, Feuerbach S, Rogler G, Seitz J, Herfarth H. Comparison of magnetic resonance imaging colonography with conventional colonoscopy for the assessment of intestinal inflammation in patients with inflammatory bowel disease: a feasibility study. *Gut* 2005; **54**: 250-256 [PMID: 15647190 DOI: 10.1136/gut.2003.037390]

13 **Sydora MJ**, Sydora BC, Fedorak RN. Validation of a point-of-care desk top device to quantitate fecal calprotectin and distinguish inflammatory bowel disease from irritable bowel syndrome. *J Crohns Colitis* 2012; **6**: 207-214 [PMID: 22325175 DOI: 10.1016/j.crohns.2011.08.008]

14 **Turner D**, Leach ST, Mack D, Uusoue K, McLernon R, Hyams J, Leleiko N, Walters TD, Crandall W, Markowitz J, Otley AR, Griffiths AM, Day AS. Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe ulcerative colitis: a prospective multicentre comparison of predicting outcomes and monitoring response. *Gut* 2010; **59**: 1207-1212 [PMID: 20801771 DOI: 10.1136/gut.2010.211755]

15 **af Björkesten CG**, Nieminen U, Turunen U, Arkkila P, Sipponen T, Färkkilä M. Surrogate markers and clinical indices, alone or combined, as indicators for endoscopic remission in anti-TNF-treated luminal Crohn's disease. *Scand J Gastroenterol* 2012; **47**: 528-537 [PMID: 22356594 DOI: 10.3109/00365521.2012.660542]

16 **Aomatsu T**, Yoden A, Matsumoto K, Kimura E, Inoue K, Andoh A, Tamai H. Fecal calprotectin is a useful marker for disease activity in pediatric patients with inflammatory bowel disease. *Dig Dis Sci* 2011; **56**: 2372-2377 [PMID: 21394462 DOI: 10.1007/s10620-011-1633-y]

17 **Sipponen T**, Björkesten CG, Färkkilä M, Nuutinen H, Savilahti E, Kolho KL. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. *Scand J Gastroenterol* 2010; **45**: 325-331 [PMID: 20034360 DOI: 10.3109/00365520903483650]

18 **Sipponen T**, Kärkkäinen P, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. *Aliment Pharmacol Ther* 2008; **28**: 1221-1229 [PMID: 18752630 DOI: 10.1111/j.1365-2036.2008.03835.x]

19 **Sipponen T**, Savilahti E, Kärkkäinen P, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. *Inflamm Bowel Dis* 2008; **14**: 1392-1398 [PMID: 18484671 DOI: 10.1002/ibd.20490]

20 **Sipponen T**, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008; **14**: 40-46 [PMID: 18022866 DOI: 10.1002/ibd.20312]

21 **Schoepfer AM**, Beglinger C, Straumann A, Trummler M, Vavricka SR, Bruegger LE, Seibold F. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol* 2010; **105**: 162-169 [PMID: 19755969 DOI: 10.1038/ajg.2009.545]

22 **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**: 32-39 [PMID: 17924558 DOI: 10.1002/ibd.20275]

23 **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**: 162-169 [PMID: 17916108 DOI: 10.1111/j.1572-0241.2007.01556.x]

24 **Jones J**, Loftus EV, Panaccione R, Chen LS, Peterson S, McConnell J, Baudhuin L, Hanson K, Feagan BG, Harmsen SW, Zinsmeister AR, Helou E, Sandborn WJ. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2008; **6**: 1218-1224 [PMID: 18799360 DOI: 10.1016/j.cgh.2008.06.010]

25 **Denis MA**, Reenaers C, Fontaine F, Belaïche J, Louis E. Assessment of endoscopic activity index and biological inflammatory markers in clinically active Crohn's disease with normal C-reactive protein serum level. *Inflamm Bowel Dis* 2007; **13**: 1100-1105 [PMID: 17508418 DOI: 10.1002/ibd.20178]

26 **Schoepfer AM**, Trummler M, Seeholzer P, Criblez DH, Seibold F. Accuracy of four fecal assays in the diagnosis of colitis. *Dis Colon Rectum* 2007; **50**: 1697-1706 [PMID: 17762964 DOI: 10.1007/s10350-007-0303-9]

27 **Schoepfer AM**, Beglinger C, Straumann A, Trummler M, Renzulli P, Seibold F. Ulcerative colitis: correlation of the Rachmilewitz endoscopic activity index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009; **15**: 1851-1858 [PMID: 19462421 DOI: 10.1002/ibd.20986]

28 **D'Incà R**, Dal Pont E, Di Leo V, Ferronato A, Fries W, Vettorato MG, Martines D, Sturniolo GC. Calprotectin and lactoferrin in the assessment of intestinal inflammation and organic disease. *Int J Colorectal Dis* 2007; **22**: 429-437 [PMID: 16838143 DOI: 10.1007/s00384-006-0159-9]

29 **Molander P**, Sipponen T, Kemppainen H, Jussila A, Blomster T, Koskela R, Nissinen M, Rautiainen H, Kuisma J, Kolho KL, Färkkilä M. Achievement of deep remission during scheduled maintenance therapy with TNFα-blocking agents in IBD. *J Crohns Colitis* 2013; **7**: 730-735 [PMID: 23182163 DOI: 10.1016/j.crohns.2012.10.018]

30 **Vieira A**, Fang CB, Rolim EG, Klug WA, Steinwurz F, Rossini LG, Candelária PA. Inflammatory bowel disease activity assessed by fecal calprotectin and lactoferrin: correlation with laboratory parameters, clinical, endoscopic and histological indexes. *BMC Res Notes* 2009; **2**: 221 [PMID: 19874614 DOI: 10.1186/1756-0500-2-221]

31 **Fagerberg UL**, Lööf L, Lindholm J, Hansson LO, Finkel Y. Fecal calprotectin: a quantitative marker of colonic inflammation in children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **45**: 414-420 [PMID: 18030206 DOI: 10.1097/MPG.0b013e31810e75a9]

32 **Silberer H**, Küppers B, Mickisch O, Baniewicz W, Drescher M, Traber L, Kempf A, Schmidt-Gayk H. Fecal leukocyte proteins in inflammatory bowel disease and irritable bowel syndrome. *Clin Lab* 2005; **51**: 117-126 [PMID: 15819166]

33 **Røseth AG**, Aadland E, Grzyb K. Normalization of faecal calprotectin: a predictor of mucosal healing in patients with inflammatory bowel disease. *Scand J Gastroenterol* 2004; **39**: 1017-1020 [PMID: 15513345 DOI: 10.1080/00365520410007971]

34 **Bunn SK**, Bisset WM, Main MJ, Gray ES, Olson S, Golden BE. Fecal calprotectin: validation as a noninvasive measure of bowel inflammation in childhood inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2001; **33**: 14-22 [PMID: 11479402 DOI: 10.1097/00005176-200107000-00003]

35 **Komraus M**, Wos H, Wiecek S, Kajor M, Grzybowska-Chlebowczyk U. Usefulness of faecal calprotectin measurement in children with various types of inflammatory bowel disease. *Mediators Inflamm* 2012; **2012**: 608249 [PMID: 22665952 DOI: 10.1155/2012/608249]

36 **Hanai H**, Takeuchi K, Iida T, Kashiwagi N, Saniabadi AR, Matsushita I, Sato Y, Kasuga N, Nakamura T. Relationship between fecal calprotectin, intestinal inflammation, and peripheral blood neutrophils in patients with active ulcerative colitis. *Dig Dis Sci* 2004; **49**: 1438-1443 [PMID: 15481316 DOI: 10.1023/B: DDAS.0000042243.47279.87]

37 **Røseth AG**, Aadland E, Jahnsen J, Raknerud N. Assessment of disease activity in ulcerative colitis by faecal calprotectin, a novel granulocyte marker protein. *Digestion* 1997; **58**: 176-180 [PMID: 9144308 DOI: 10.1159/000201441]

38 **Pfefferkorn MD**, Boone JH, Nguyen JT, Juliar BE, Davis MA, Parker KK. Utility of fecal lactoferrin in identifying Crohn disease activity in children. *J Pediatr Gastroenterol Nutr* 2010; **51**: 425-428 [PMID: 20562721 DOI: 10.1097/MPG.0b013e3181d67e8f]

39 **Nakarai A**, Kato J, Hiraoka S, Kuriyama M, Akita M, Hirakawa T, Okada H, Yamamoto K. Evaluation of mucosal healing of ulcerative colitis by a quantitative fecal immunochemical test. *Am J Gastroenterol* 2013; **108**: 83-89 [PMID: 23007005 DOI: 10.1038/ajg.2012.315]

40 **Moran A**, Jones A, Asquith P. Laboratory markers of colonoscopic activity in ulcerative colitis and Crohn's colitis. *Scand J Gastroenterol* 1995; **30**: 356-360 [PMID: 7610352 DOI: 10.3109/00365529509093290]

41 **Cellier C**, Sahmoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, Florent C, Bouvry M, Mary JY, Modigliani R. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. *Gut* 1994; **35**: 231-235 [PMID: 7508411 DOI: 10.1136/gut.35.2.231]

42 **Kaiser T**, Langhorst J, Wittkowski H, Becker K, Friedrich AW, Rueffer A, Dobos GJ, Roth J, Foell D. Faecal S100A12 as a non-invasive marker distinguishing inflammatory bowel disease from irritable bowel syndrome. *Gut* 2007; **56**: 1706-1713 [PMID: 17675327 DOI: 10.1136/gut.2006.113431]

43 **Fagerberg UL**, Lööf L, Myrdal U, Hansson LO, Finkel Y. Colorectal inflammation is well predicted by fecal calprotectin in children with gastrointestinal symptoms. *J Pediatr Gastroenterol Nutr* 2005; **40**: 450-455 [PMID: 15795593 DOI: 10.1097/01.MPG.0000154657.08994.94]

44 **Kolho KL**, Raivio T, Lindahl H, Savilahti E. Fecal calprotectin remains high during glucocorticoid therapy in children with inflammatory bowel disease. *Scand J Gastroenterol* 2006; **41**: 720-725 [PMID: 16716972 DOI: 10.1080/00365520500419623]

45 **Nancey S**, Boschetti G, Moussata D, Cotte E, Peyras J, Cuerq C, Haybrard J, Charlois AL, Mialon A, Chauvenet M, Stroeymeyt K, Kaiserlian D, Drai J, Flourié B. Neopterin is a novel reliable fecal marker as accurate as calprotectin for predicting endoscopic disease activity in patients with inflammatory bowel diseases. *Inflamm Bowel Dis* 2013; **19**: 1043-1052 [PMID: 23511035 DOI: 10.1097/MIB.0b013e3182807577]

46 **Falvey JD**, Hoskin T, Meijer B, Ashcroft A, Walmsley R, Day AS, Gearry RB. Disease activity assessment in IBD: clinical indices and biomarkers fail to predict endoscopic remission. *Inflamm Bowel Dis* 2015; **21**: 824-831 [PMID: 25738372 DOI: 10.1097/MIB.0000000000000341]

47 **D'Haens G**, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, Geens P, Iwens D, Aerden I, Van Assche G, Van Olmen G, Rutgeerts P. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 2218-2224 [PMID: 22344983 DOI: 10.1002/ibd.22917]

48 **Kristensen V**, Klepp P, Cvancarova M, Røseth A, Skar V, Moum B. Prediction of endoscopic disease activity in ulcerative colitis by two different assays for fecal calprotectin. *J Crohns Colitis* 2015; **9**: 164-169 [PMID: 25518057 DOI: 10.1093/ecco-jcc/jju015]

49 **Lobatón T**, López-García A, Rodríguez-Moranta F, Ruiz A, Rodríguez L, Guardiola J. A new rapid test for fecal calprotectin predicts endoscopic remission and postoperative recurrence in Crohn's disease. *J Crohns Colitis* 2013; **7**: e641-e651 [PMID: 23810085 DOI: 10.1016/j.crohns.2013.05.005]

50 **Canani RB**, Terrin G, Rapacciuolo L, Miele E, Siani MC, Puzone C, Cosenza L, Staiano A, Troncone R. Faecal calprotectin as reliable non-invasive marker to assess the severity of mucosal inflammation in children with inflammatory bowel disease. *Dig Liver Dis* 2008; **40**: 547-553 [PMID: 18358796 DOI: 10.1016/j.dld.2008.01.017]

51 **Lobatón T**, Rodríguez-Moranta F, Lopez A, Sánchez E, Rodríguez-Alonso L, Guardiola J. A new rapid quantitative test for fecal calprotectin predicts endoscopic activity in ulcerative colitis. *Inflamm Bowel Dis* 2013; **19**: 1034-1042 [PMID: 23470502 DOI: 10.1097/MIB.0b013e3182802b6e]

52 **Schoepfer AM**, Safroneeva E, Vavricka SR, Peyrin-Biroulet L, Mottet C. Treatment of fibrostenotic and fistulizing Crohn's disease. *Digestion* 2012; **86** Suppl 1: 23-27 [PMID: 23051723 DOI: 10.1159/000341961]

53 **Bunn SK**, Bisset WM, Main MJ, Golden BE. Fecal calprotectin as a measure of disease activity in childhood inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2001; **32**: 171-177 [PMID: 11321388 DOI: 10.1097/00005176-200102000-00015]

54 **Daperno M**, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JY, Colombel JF, Rutgeerts P. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; **60**: 505-512 [PMID: 15472670 DOI: 10.1016/S0016-5107(04)01878-4]

55 **Mary JY**, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989; **30**: 983-989 [PMID: 2668130 DOI: 10.1136/gut.30.7.983]

56 **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317**: 1625-1629 [PMID: 3317057 DOI: 10.1056/NEJM198712243172603]

57 **Rachmilewitz D**. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989; **298**: 82-86 [PMID: 2563951 DOI: 10.1136/bmj.298.6666.82]

58 **Saverymuttu SH**, Camilleri M, Rees H, Lavender JP, Hodgson HJ, Chadwick VS. Indium 111-granulocyte scanning in the assessment of disease extent and disease activity in inflammatory bowel disease. A comparison with colonoscopy, histology, and fecal indium 111-granulocyte excretion. *Gastroenterology* 1986; **90**: 1121-1128 [PMID: 3956932]

59 **Stange EF**, Schreiber S, Fölsch UR, von Herbay A, Schölmerich J, Hoffmann J, Zeitz M, Fleig WE, Buhr HJ, Kroesen AJ, Moser G, Matthes H, Adler G, Reinshagen M, Stein J. [Diagnostics and treatment of Crohn's disease -- results of an evidence-based consensus conference of the German Society for Digestive and Metabolic Diseases]. *Z Gastroenterol* 2003; **41**: 19-20 [PMID: 12541167 DOI: 10.1055/s-2003-36661]

60 **Stange EF**, Riemann J, von Herbay A, Lochs H, Fleig WE, Schölmerich J, Kruis W, Porschen R, Bruch HP, Zeitz M, Schreiber S, Moser G, Matthes H, Selbmann HK, Goebell H, Caspary WF. [Diagnosis and therapy of ulcerative colitis--results of an evidence-based consensus conference of the German Society of Digestive and Metabolic Diseases]. *Z Gastroenterol* 2001; **39**: 19-20 [PMID: 11215358 DOI: 10.1055/s-2001-10692]

61 **Farup PG**, Hovde O, Halvorsen FA, Raknerud N, Brodin U. Mesalazine suppositories versus hydrocortisone foam in patients with distal ulcerative colitis. A comparison of the efficacy and practicality of two topical treatment regimens. *Scand J Gastroenterol* 1995; **30**: 164-170 [PMID: 7732340 DOI: 10.3109/00365529509093256]

62 **MATTS SG**. The value of rectal biopsy in the diagnosis of ulcerative colitis. *Q J Med* 1961; **30**: 393-407 [PMID: 14471445]

63 **Sandborn WJ**, Tremaine WJ, Schroeder KW, Steiner BL, Batts KP, Lawson GM. Cyclosporine enemas for treatment-resistant, mildly to moderately active, left-sided ulcerative colitis. *Am J Gastroenterol* 1993; **88**: 640-645 [PMID: 8480724]

64 **Farmer RG.** Endoscopy. In: J.E. B, editor. Bockus Gastroenterology. Philadelphia: Saunders; 1985. p. 1816-1817

65 **D'haens G**, Van Deventer S, Van Hogezand R, Chalmers D, Kothe C, Baert F, Braakman T, Schaible T, Geboes K, Rutgeerts P. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. *Gastroenterology* 1999; **116**: 1029-1034 [PMID: 10220494 DOI: 10.1016/S0016-5085(99)70005-3]

66 **Fazio VW**, Marchetti F, Church M, Goldblum JR, Lavery C, Hull TL, Milsom JW, Strong SA, Oakley JR, Secic M. Effect of resection margins on the recurrence of Crohn's disease in the small bowel. A randomized controlled trial. *Ann Surg* 1996; **224**: 563-71; discussion 571-3 [PMID: 8857860 DOI: 10.1097/00000658-199610000-00014]

67 **Florén CH**, Benoni C, Willén R. Histologic and colonoscopic assessment of disease extension in ulcerative colitis. *Scand J Gastroenterol* 1987; **22**: 459-462 [PMID: 3602926 DOI: 10.3109/00365528708991491]

68 **Moran A**, Lawson N, Morrow R, Jones A, Asquith P. Value of faecal alpha-1-antitrypsin, haemoglobin and a chemical occult blood test in the detection of gastrointestinal disease. *Clin Chim Acta* 1993; **217**: 153-161 [PMID: 8261624 DOI: 10.1016/0009-8981(93)90161-V]

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**Table 1 Studies investigating the correlation between faecal calprotectin concentrations and endoscopic activity in subjects with inflammatory bowel diseases**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Number of participants** | | | **Population** | **Endoscopic index used** | **Endoscopic index**  **cut off** | **Faecal calprotectin**  **cut off (μg/g)** | **Outcome measures** | | | | | | **Correlation** | | | |
| **CD** | | **UC** | **Sensitivity %** | | **Specificity %** | **PPV %** | | **NPV%** | ***r* value** | | ***P* value** | |
| **Crohn’s disease studies** | | | | | | | | | | | | | | | | | |
| Falvey *et al*[46] | 59 | |  | adults | SES-CD | ≤ 3 | 125 | 71 | | 71 | 85 | | 50 | 0.55 | | < 0.0001 | |
|  |  | |  |  |  |  | 200 | 60 | | 79 | 88 | | 45 |  | |  | |
| Lobaton *et al*[52] | 85 | |  | adults | CDEIS | < 3 | 274 ELISA | 77 | | 97 | 75 | | 98 | 0.784 | | < 0.001 | |
|  |  | |  |  |  | < 3 | 272 QPOC | 79 | | 97 | 76 | | 98 | 0.722 | | < 0.001 | |
|  |  | |  |  |  | 0 | 262 ELISA | 75 | | 76 |  | |  |  | |  | |
|  |  | |  |  |  | 0 | 200 QPOC | 75 | | 77 |  | |  |  | |  | |
| Nancey *et al*[45] | 78 | |  | adults | SES-CD | ≤ 2 | 250 | 71 | | 78 | 79 | | 71 | 0.53 | | < 0.0001 | |
|  |  | |  |  |  |  | 100 | 88 | | 38 | 62 | | 73 |  | |  | |
| D’Haens *et al*[51] | 87 | |  | adults | CDEIS | ≤ 3 | < 250 | 94.1 | | 62.2 | 48.5 | | 96.6 | 0.419 | | < 0.001 | |
|  |  | |  |  | SES-CD | 0 | < 250 | 51.6 | | 82.6 | 89.2 | | 38.0 | 0.490 | | < 0.001 | |
| Björkesten *et al*15] | 64 | |  | adults | SES-CD | ≤ 2 | < 100 | 81 | | 74 | - | | - | 0.56 | | < 0.001 | |
|  |  | |  |  |  |  | < 94 | 84 | | 74 | - | | - |  | |  | |
|  |  | |  |  | SES-CD | 0 | < 94 | 82 | | 78 | - | | - |  | |  | |
| Aomatsu *et al*[16] | 18 | |  | paediatrics | SES-CD | 0 | 100 | 94.7 | | 50.0 | 87.8 | | 71.4 | 0.760 | | < 0.01 | |
|  |  | |  |  |  |  | 150 | 94.7 | | 50.0 | 87.8 | | 71.4 |  | |  | |
| Sipponen *et al*[17] | 19 | |  | adults | SES-CD | ≤ 2 | < 100 | - | | 80 | - | | - | - | | - | |
| Schoepfer *et al*[21] | 122 | |  | adults | SES-CD | ≤ 3 | < 50 | 89 | | 58 | 89 | | 61 | 0.75 | | < 0.01 | |
|  |  | |  |  |  |  | < 70 | 89 | | 72 | 88 | | 76 |  | |  | |
| Langhorst *et al*[23] | 43 | |  | adults | SES-CD |  | > 6 | 100 | | 30 | 82.5 | | 100 | 0.35 | | < 0.05 | |
|  |  | |  |  |  |  | > 48 | 81.8 | | 80 | 93.1 | | 57.1 |  | |  | |
| Schoepfer *et al*[22] | 36 | |  | adults | SES-CD | ≤ 19 | 50 | - | | - | - | | - | - | | < 0.0001 | |
| Sipponen *et al*[18] | 61 | |  | adults | SES-CD (total) | ≤ 3 | < 100 | - | | - | - | | - | 0.662 | | < 0.001 | |
|  |  | |  |  | SES-CD (colon) | ≤ 3 | < 100 | - | | - | - | | - | 0.642 | | < 0.001 | |
|  |  | |  |  | SES-CD (ileal) | ≤ 3 | < 100 | - | | - | - | | - | 0.317 | | > 0.05 | |
| Sipponen *et al*[19] | 15 | |  | adults | CDEIS | ≤ 2 | < 200 | 87 | | 100 | 100 | | 70 | 0.831 | | < 0.001 | |
| Sipponen *et al*[20] | 77 | |  | adults | CDEIS | ≤ 2 | < 50 | 91 | | 44 | 76 | | 73 | 0.729 | | < 0.001 | |
|  |  | |  |  |  |  | < 100 | 81 | | 69 | 84 | | 66 |  | |  | |
|  |  | |  |  |  |  | < 200 | 70 | | 92 | 94 | | 61 |  | |  | |
| Jones *et al*[24] | 164 | |  | adults | SES-CD | ≤ 6 | ≤ 50 | - | | - | - | | - | 0.45 | | < 0.05 | |
| Denis *et al*[25] | 28 | |  | adults | CDEIS | ≤ 5 | < 50 | - | | - | - | | - | - | | 0.57 | |
| Schoepfer *et al*[26] | 24 | |  | adults | SES-CD | ≤ 19 | < 50 | - | | - | - | | - | - | | 0.0001 | |
| D' Inca *et al*[28] | 31 | |  | adults | SES-CD |  | > 80 | - | | - | - | | - | 0.48 | | 0.008 | |
| **Mixed inflammatory bowel disease population studies** | | | | | | | | | | | | | | | | | |
| Molander *et al*[29] | 183 | | 69 | mixed | SES-CD; Mayo | ≤ 2; ≤ 1 | <100 | - | | - | - | | 72 | - | | < 0.0001 | |
| Vieira *et al*[30] | 38 | | 40 | adults | CDEIS; Mayo | ≤ 2; ≤ 2 | >200.01 | 88.6 | | 97.1 | 97.5 | | 86.8 | - | | 0.000 | |
| Schoepfer *et al*[22] | 36 | | 28 | adults | SES-CD; Rachmilewitz | ≤ 19; ≤ 4 | 50 | - | | - | - | | - | - | | < 0.0001 | |
| Canani *et al*[50] | 26 | | 32 | paediatrics | Saverymuttu | ≤ 1 | 143 | - | | - | - | | - | 0.46 | | ≤ 0.05 | |
| Fagerberg *et al*[31] | 27 | | 10 | paediatrics | Saverymuttu |  | < 85.7 | - | | - | - | | - | 0.65 | | < 0.001 | |
| Silberer *et al*[32] | 21 | | 18 | adults | Stange |  | 18.6 | 61.5 | | 95 | - | | - | - | | < 0.0001 | |
| Roseth *et al*[33] | 17 | | 28 | adults | Farup |  | < 50 | 0 | | 100 | - | | 97.8 | - | | - | |
| Bunn *et al*[34] | 2 | | 9 | paediatrics | Saverymuttu |  |  | - | | - | - | | - | 0.65 | | < 0.05 | |
| **Ulcerative colitis studies** | | | | | | | | | | | | | | | | | |
| Falvey *et al*[46] | |  | 38 | adults | Baron | 0 | 125 | 74 | | 80 | 85 | | 67 | 0.55 | | < 0.0001 | |
|  | |  |  |  |  |  | 200 | 58 | | 95 | 95 | | 59 |  | |  | |
| Nancey *et al*[45] | |  | 55 | adults | Rachmilewitz | ≤ 2 | 250 | 91 | | 87 | 87 | | 91 | 0.75 | | < 0.0001 | |
|  | |  |  |  |  |  | 100 | 100 | | 53 | 85 | | 100 |  | |  | |
| Kristensen *et al*[48] | |  | 62 | adults | Mayo | 0 | 61 Cal | 84.1 | | 83.3 | 92.5 | | 68.2 |  | | < 0.001 | |
|  | |  |  |  |  | 0 | 96 BM | 90.9 | | 83.3 | 93.0 | | 78.9 |  | | < 0.001 | |
|  | |  |  |  |  | ≤ 1 | 110 Cal | 80.0 | | 66.6 | 69.2 | | 78.0 |  | |  | |
|  | |  |  |  |  | ≤ 1 | 259 BM | 83.3 | | 71.9 | 73.5 | | 82.1 |  | |  | |
| D’Haens *et al*[47] | |  | 39 | adults | Mayo | 0 | < 250 | 71 | | 100 | 100 | | 47.1 | 0.56 | | < 0.001 | |
| Komraus *et al*[35] | |  | 16 | paediatrics | Rachmilewitz |  | < 50 | - | | - | - | | - | 0.52 | | 0.0391 | |
| Aomatsu *et al*[16] | |  | 17 | paediatrics | Matts | ≤6 | 100 | 94.1 | | 50.0 | 88.9 | | 66.7 | 0.84 | | < 0.01 | |
|  | |  |  |  |  |  | 150 | 91.2 | | 87.5 | 96.9 | | 70.0 |  | |  | |
| Schoepfer *et al*[27] | |  | 115 | adults | Rachmilewitz | < 4 | < 50 | 93 | | 71 | 91 | | 81 | 0.83 | | < 0.001 | |
|  | |  |  |  |  |  | < 100 | 86 | | 88 | 96 | | 65 |  | |  | |
| Langhorst *et al*[23] | |  | 42 | adults | Mayo |  | > 6 | 100 | | 6.7 | 6.6 | | 100 | 0.49 | | < 0.001 | |
|  | |  |  |  |  |  | > 48 | 81.5 | | 72.3 | 84.6 | | 68.8 |  | |  | |
| Schoepfer *et al*[22] | |  | 28 | adults | Rachmilewitz | ≤ 4 | 50 | - | | - | - | | - | - | | 0.0025 | |
| Schoepfer *et al*[26] | |  | 12 | adults | Rachmilewitz | ≤ 1 | < 50 | - | - | | - | | - | - | | 0.0335 | |
| D' Inca *et al*[28] | |  | 46 | adults | Mayo |  | > 80 | - | | - | - | - | | | 0.511 | 0.001 | |
| Hanai *et al*[36] | |  | 31 | adults | Matts | ≤ 1 |  | - | | - | - | - | | | 0.81 | < 0.001 | |
| Roseth *et al*[37] | |  | 62 | adults | Sandborn | ≤ 1 | < 10 | - | | 34 | - | - | | | 0.57 | < 0.0001 | |
|  | |  |  |  |  |  | < 20 | - | | 62 | - | - | | |  |  |  |

CD: Crohn’s disease; UC: Ulcerative colitis; PPV: Positive predictive value; NPV: Negative predictive value; SES-CD: Simple endoscopic score for Crohn’s disease[54]; CDEIS: Crohn’s disease endoscopic index of severity[55]; ELISA: Enzyme linked immunosorbant assay; QPOC: Quantitative point of care test; Mayo: Mayo endoscopic sub-scoring of ulcerative colitis[56]; Rachmilewitz: Rachmilewitz endoscopic score[57]; Saverymuttu: Non-standard endoscopic scoring system[58]; Stange: Non-standard endoscopic scoring system[59,60]; Farup: Non-standard endoscopic scoring system[61]; Baron: Baron score; Matts: Matts score[62]; Sandborn: Non-standard endoscopic scoring system[63]; Cal: Calpro ELISA: Calpro Calprotectin ELISA, Calpro AS, Norway; BM: BM ELISA, EK-CAL, Bühlmann Laboratories AG, Switzerland; Farmer: Non-standard endoscopic scoring system[64];Faecal Hb: Faecal haemoglobin; PMN-e: Polymorhonuclear elastase; Hb-Hp: Haemoglobin; Haptoglobin complex; D’Haens: Non-standard histologic scoring system[65]; Fazio: Non-standard histologic scoring system[66]; Floren: Non-standard histologic scoring system[67].

**Table 2 Studies investigating the correlation between faecal lactoferrin concentrations and endoscopic activity in subjects with inflammatory bowel diseases**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Number of participants** | | **Population** | **Endoscopic index used** | **Endoscopic index**  **cut off** | **Faecal lactoferrin**  **cut off (μg/mL)** | | **Outcome measures** | | | | **Correlation** | |
| **CD** | **UC** | **Sensitivity %** | **Specificity %** | **PPV %** | **NPV %** | ***r* value** | ***P* value** |
| **Crohn’s disease studies** | | | | | | | | | | | | | |
| Sipponen *et al*[17] | 19 |  | adults | SES-CD | ≤ 2 | | < 7.25 | - | 80\* | - | - | - | - |
| Pfefferkorn *et al*[38] | 54 |  | paediatrics | Unique score |  | | ≥ 7.25 | 100 | 43 | 70 | 100 | - | < 0.001 |
|  |  |  |  |  |  | | ≥ 60 | 84 | 74 | 81 | 77 |  |  |
| Sipponen *et al*[18] | 61 |  | adults | SES-CD (total) | ≤ 3 | | < 7.25 | - | - | - | - | 0.705 | < 0.001 |
|  |  |  |  | SES-CD (colon) | ≤ 3 | | < 7.25 | - | - | - | - | 0.627 | < 0.001 |
|  |  |  |  | SES-CD (ileal) | ≤ 3 | | < 7.25 | - | - | - | - | 0.18 | > 0.05 |
| Sipponen *et al*[19] | 15 |  | adults | CDEIS | ≤ 2 | | < 10 | 77 | 100 | 100 | 58 | 0.865 | < 0.001 |
| Sipponen *et al*[20] | 77 |  | adults | CDEIS | ≤ 2 | | < 10 | 66 | 92 | 94 | 59 | 0.773 | < 0.001 |
|  |  |  |  |  |  | | < 7.25 | 71 | 83 | 89 | 60 |  |  |
| Jones *et al*[24] | 164 |  | adults | SES-CD | ≤ 6 | | < 7.25 | - | - | - | - | 0.48 | < 0.05 |
| Langhorst *et al*[23] | 43 |  | adults | SES-CD |  | | > 7.25 | 81.8 | 60 | 87.1 | 50 | 0.42 | < 0.01 |
|  |  |  |  |  |  | | > 7.05 | 81.8 | 60 | 87.1 | 50 |  |  |
| Schoepfer *et al*[22] | 36 |  | adults | SES-CD | ≤ 19 | | 7 | - | - | - | - | - | < 0.0001 |
| Schoepfer *et al*[26] | 24 |  | adults | SES-CD | ≤ 19 | | <7 | - | - | - | - | - | 0.0008 |
| D' Inca *et al*[28] | 31 |  | adults | SES-CD |  | |  | - | - | - | - | 0.192 | 0.545 |
| **Mixed inflammatory bowel disease population studies** | | | | | | | | | | | | | |
| Vieira *et al*[30] | 38 | 40 | adults | CDEIS; Mayo | ≤ 2; ≤ 2 | | 4-8 | 93.2 | 76.5 | 83.7 | 89.7 | - | 0.000 |
| Schoepfer *et al*[22] | 36 | 28 | adults | SES-CD; Rachmilewitz | ≤ 19; ≤ 4 | | 7 | - | - | - | - | - | < 0.0001 |
| Silberer *et al*[32] | 21 | 18 | adults | Stange |  | | 6.64 | 33.3 | 95 | - | - | - | 0.0059 |
| **Ulcerative colitis studies** | | | | | | | | | | | | | |
| Langhorst *et al*[23] |  | 42 | adults | Mayo |  | | > 7.25 | 88.9 | 66.7 | 82.8 | 76.9 | 0.56 | < 0.001 |
|  |  |  |  |  |  | | > 7.05 | 92.6 | 66.7 | 83.3 | 83.3 |  |  |
| Schoepfer *et al*[22] |  | 28 | adults | Rachmilewitz | ≤ 4 | | 7 | - | - | - | - | - | 0.078 |
| Schoepfer *et al*[26] |  | 12 | adults | Rachmilewitz | ≤ grade 1 | | < 7 | - | - | - | - | - | 0.7815 |
| D' Inca *et al*[28] |  | 46 | adults | Mayo |  | |  | - | - | - | - | 0.354 | 0.023 |
|  |  |  |  |  |  | |  |  |  |  |  |  |  |

CD: Crohn’s disease; UC: Ulcerative colitis; PPV: Positive predictive value; NPV: Negative predictive value; SES-CD: Simple endoscopic score for Crohn’s disease[54]; CDEIS: Crohn’s disease endoscopic index of severity[55]; ELISA: Enzyme linked immunosorbant assay; QPOC: Quantitative point of care test; Mayo: Mayo endoscopic sub-scoring of ulcerative colitis[56]; Rachmilewitz: Rachmilewitz endoscopic score[57]; Saverymuttu: Non-standard endoscopic scoring system[58]; Stange: Non-standard endoscopic scoring system[59,60]; Farup: Non-standard endoscopic scoring system[61]; Baron: Baron score; Matts: Matts score[62]; Sandborn: Non-standard endoscopic scoring system[63]; Cal: Calpro ELISA: Calpro Calprotectin ELISA, Calpro AS, Norway; BM: BM ELISA, EK-CAL, Bühlmann Laboratories AG, Switzerland; Farmer: Non-standard endoscopic scoring system[64];Faecal Hb: Faecal haemoglobin; PMN-e: Polymorhonuclear elastase; Hb-Hp: Haemoglobin; Haptoglobin complex; D’Haens: Non-standard histologic scoring system[65]; Fazio: Non-standard histologic scoring system[66]; Floren: Non-standard histologic scoring system[67].

**Table 3 Studies investigating the correlation between other faecal marker concentrations and endoscopic activity in subjects with inflammatory bowel diseases**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Number of participants** | | **Population** | **Endoscopic index used** | **Endoscopic index**  **cut off** | **Faecal marker measured** | **Faecal**  **marker**  **cut off** | **Outcome measures** | | | | **Correlation** | |
| **CD** | **UC** | **Sensitivity %** | **Specificity %** | **PPV%** | **NPV%** | ***r* value** | ***P* value** |
| Nancey *et al*[45] | 78 |  | adults | SES-CD | ≤ 2 | Neopterin | 200 pmol/g | 74 | 73 | 73 | 74 | 0.47 | < 0.001 |
|  |  |  |  |  |  |  | 150 pmol/g | 80 | 65 | 68 | 78 |  |  |
|  |  | 55 | Adults | Rachmilewitz | ≤ 2 | Neopterin | 200 pmol/g | 74 | 100 | 100 | 73 | 0.72 | < 0.001 |
|  |  |  |  |  |  |  | 150 pmol/g | 84 | 100 | 100 | 78 |  |  |
| Nakarai *et al*[39] |  | 152 | Mixed | Mayo | 0 | Faecal Hb | < 100 ng/mL | 92 | 71 | 37 | 97 | 0.5409 | < 0.0001 |
|  |  |  |  |  |  | Faecal Hb | < 60 ng/mL | 94 | 74 | 40 | 98 |  |  |
|  |  |  |  | Mayo | ≤ 1 | Faecal Hb | < 100 ng/mL | 60 | 87 | 85 | 64 |  |  |
|  |  |  |  |  |  | Faecal Hb | < 60 ng/mL | 58 | 90 | 88 | 64 |  |  |
| Langhorst *et al*[23] | 43 |  | Adults | SES-CD |  | PMN-e | < 0.062 μg/mL | 81.8 | 70 | 90 | 54.8 | 0.32 | < 0.05 |
|  |  | 42 | Adults | Mayo |  | PMN-e | < 0.062 μg/mL | 70.4 | 66.7 | 79.2 | 55.6 | 0.36 | < 0.05 |
| Silberer *et al*[32] | 21 | 18 | Adults | Stange |  | PMN-e | 0.124 | 79.5 | 95 | - | - | - | < 0.0001 |
|  |  |  |  |  |  | Lysozyme | 1.3 | 47.5 | 95 | - | - | - | < 0.0001 |
|  |  |  |  |  |  | α1-AT | 158 | 20.0 | 95 | - | - | - | - |
|  |  |  |  |  |  | Faecal Hb | 1.8 | 61.5 | 95 | - | - | - | - |
|  |  |  |  |  |  | Hb-Hp | 0.8 | 64.1 | 95 | - | - | - | - |
| Moran *et al*[40] | 7 | 21 | Mixed | Farmer |  | α1-AT | ≤ 0.58 mg/g | - | - | - | - | 0.83 | 0.001 |
| Cellier *et al*[41] | 95 |  | Adults | CDEIS |  | α1-AT |  | - | - | - | - | 0.26 | 0.001 |

CD: Crohn’s disease; UC: Ulcerative colitis; PPV: Positive predictive value; NPV: Negative predictive value; SES-CD: Simple endoscopic score for Crohn’s disease[54]; CDEIS: Crohn’s disease endoscopic index of severity[55]; ELISA: Enzyme linked immunosorbant assay; QPOC: Quantitative point of care test; Mayo: Mayo endoscopic sub-scoring of ulcerative colitis[56]; Rachmilewitz: Rachmilewitz endoscopic score[57]; Saverymuttu: Non-standard endoscopic scoring system[58]; Stange: Non-standard endoscopic scoring system[59,60]; Farup: Non-standard endoscopic scoring system[61]; Baron: Baron score; Matts: Matts score[62]; Sandborn: Non-standard endoscopic scoring system[63]; Cal: Calpro ELISA: Calpro Calprotectin ELISA, Calpro AS, Norway; BM: BM ELISA, EK-CAL, Bühlmann Laboratories AG, Switzerland; Farmer: Non-standard endoscopic scoring system[64];Faecal Hb: Faecal haemoglobin; PMN-e: Polymorhonuclear elastase; Hb-Hp: Haemoglobin; Haptoglobin complex; D’Haens: Non-standard histologic scoring system[65]; Fazio: Non-standard histologic scoring system[66]; Floren: Non-standard histologic scoring system[67].

**Table 4 Studies investigating the correlation between FC concentrations and histologic activity in subjects with inflammatory bowel diseases**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Number of participants** | | | **Population** | **Histology index used** | **Histology index**  **cut off** | **Faecal calprotectin**  **cut off (μg/g)** | **Outcome measures** | | | | | **Correlation** | |
| **CD** | **UC** | | **Sensitivity %** | **Specificity %** | **PPV%** | **NPV%** | | ***r* value** | ***P* value** |
| **Crohn’s disease studies** | | | | | | | | | | | | | | |
| Sipponen *et al*[18] | 61 | |  | adult | D'Haens (ileocolonic) | | < 100 | - | - | - | | - | 0.563 | < 0.01 |
|  |  | |  |  | D'Haens (ileal) |  | < 100 | - | - | - | | - | 0.311 | > 0.05 |
| Sipponen *et al*[19] | 15 | |  | adult | D'Haens (pretreatment colonic) | | < 200 | - | - | - | | - | 0.522 | 0.046 |
|  |  | |  |  | D'Haens (posttreatment colonic) | | < 200 | - | - | - | | - | - | > 0.05 |
|  |  | |  |  | D'Haens (ileal) |  | < 200 | - | - | - | | - | - | > 0.05 |
| Canani *et al*[50] | 26 | |  | paediatric | Saverymuttu | ≤ 1 | 143 | - | - | - | | - | 0.681 | < 0.0001 |
| Kaiser *et al*[42] | 32 | |  | adult | Unique score | 0 | < 50 | - | - | - | | - | 0.412 | < 0.05 |
| D' Inca *et al*[28] | 31 | |  | adult | Fazio |  | * 80 | 81 | 80 | 95 | | - | 0.117 | 0.545 |
| Fagerberg *et al*[43] | 22 | |  | paediatric | Unique score |  | < 50 | 95 | 93 | 95 | | 93 | - | < 0.00001 |
| **Mixed inflammatory bowel disease population studies** | | | | | | | | | | | | | | |
| Vieira *et al*[30] | 38 | 40 | | adult | Unique score |  | >200 | 77 | 100 | 100 | | 68 | - | 0.000 |
| Canani *et al*[50] | 26 | 32 | | paediatric | Saverymuttu | ≤ 1 | 143 | 94 | 64 | 81 | | 87 | 0.655 | < 0.05 |
| D' Inca *et al*[28] | 31 | 46 | | adult | Fazio;Floren(SES-CD; Mayo) | > 80 | 79 | 74 | 92 | - | | - | - |  |
| Fagerberg *et al*[31] | 27 | 10 | | paediatric | Saverymuttu | ≤ 2 | <50 | 93 | 73 | 90 | | 80 | 0.75 | < 0.001 |
|  |  |  | |  |  |  | <85.7 | 93 | 82 | 93 | | 82 |  |  |
|  |  |  | |  | Saverymuttu |  |  | - | - | - | | - | 0.79 | < 0.001 |
| Kolho *et al*[44] | 9 | 16 | | paediatric | Farup |  | 50 | - | - | 69 | | 100 | - | - |
|  |  |  | |  |  |  | 100 | - | - | 72 | | 96 | - | - |
| Bunn *et al*[54] | 2 | 9 | | paediatric | Saverymuttu | ≤ 6 | 6.3 | 100 | 80 | - | | - | 0.74 | < 0.01 |
| **Ulcerative colitis studies** | | | | | | | | | | | | | | |
| Canani *et al*[50] |  | 32 | | paediatric | Saverymuttu | ≤ 1 | 143 | - | - | - | | - | 0.661 | < 0.0001 |
| D' Inca *et al*[28] |  | 46 | | adult | Floren |  | > 80 | 78 | 70 | 90 | | - | 0.323 | 0.042 |
| Kaiser *et al*[42] |  | 27 | | adult | Unique score |  | < 50 | - | - | - | | - | 0.311 | 0.14 |
| Roseth *et al*[37] |  | 62 | | adult | Farup | ≤ 1 | < 10 | - | 50 | - | | - | 0.70 | < 0.0001 |
|  |  |  | |  |  |  | < 20 | - | 81 | - | | - |  |  |

CD: Crohn’s disease; UC: Ulcerative colitis; PPV: Positive predictive value; NPV: Negative predictive value; SES-CD: Simple endoscopic score for Crohn’s disease[54]; CDEIS: Crohn’s disease endoscopic index of severity[55]; ELISA: Enzyme linked immunosorbant assay; QPOC: Quantitative point of care test; Mayo: Mayo endoscopic sub-scoring of ulcerative colitis[56]; Rachmilewitz: Rachmilewitz endoscopic score[57]; Saverymuttu: Non-standard endoscopic scoring system[58]; Stange: Non-standard endoscopic scoring system[59,60]; Farup: Non-standard endoscopic scoring system[61]; Baron: Baron score; Matts: Matts score[62]; Sandborn: Non-standard endoscopic scoring system[63]; Cal: Calpro ELISA: Calpro Calprotectin ELISA, Calpro AS, Norway; BM: BM ELISA, EK-CAL, Bühlmann Laboratories AG, Switzerland; Farmer: Non-standard endoscopic scoring system[64];Faecal Hb: Faecal haemoglobin; PMN-e: Polymorhonuclear elastase; Hb-Hp: Haemoglobin; Haptoglobin complex; D’Haens: Non-standard histologic scoring system[65]; Fazio: Non-standard histologic scoring system[66]; Floren: Non-standard histologic scoring system[67].

**Table 5 Studies investigating the correlation between FL concentrations and histologic activity in subjects with inflammatory bowel diseases**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Number of participants** | | **Population** | **Histology index used** | **Histology index**  **cut off** | | | **Faecal lactoferrin**  **cut off(μg/mL)** | **Outcome measures** | | | | **Correlation** | |
| **CD** | **UC** | **Sensitivity %** | **Specificity%** | **PPV%** | **NPV%** | ***r* value** | ***P* value** |
| **Crohn’s disease studies** | | | | | | | | | | | | | | |
| Sipponen *et al*[18] | 61 |  | adult | D'Haens (ileocolonic) | | | | < 7.25 | - | - | - | - | 0.543 | < 0.01 |
|  |  |  |  | D'Haens (ileal) |  | | | < 7.25 | - | - | - | - | 0.291 | > 0.05 |
| Sipponen *et al*[19] | 15 |  | Adult | D'Haens (pretreatment colonic) | | | | < 10 | - | - | - | - | 0.482 | 0.069 |
|  |  |  |  | D'Haens (posttreatment colonic) | | | | < 10 | - | - | - | - | - | > 0.05 |
|  |  |  |  | D'Haens (ileal) |  | | | < 10 | - | - | - | - | - | > 0.05 |
| D' Inca *et al*[28] | 31 |  | Adult | Fazio |  | | |  | 77 | 80 | 95 | - | 0.477 | 0.009 |
| **Mixed inflammatory bowel disease studies** | | | | | | | | | | | | | | |
| Vieira *et al*[30] | 38 | 40 | adults | Unique score | |  | 4-8 | | 90 | 92 | 96 | 83 | - | - |
| D' Inca *et al*[28] | 31 | 46 | adults | Fazio;Floren (SES-CD; Mayo) | |  | 7 | | 76 | 67 | 90 | - | - | - |
| **Ulcerative colitis studies** | | | | | | | | | | | | | | |
| D' Inca *et al*[28] |  | 46 | adults | Floren | |  | 7 | | 75 | 60 | 87 | 92 | 0.544 | 0.0001 |

CD: Crohn’s disease; UC: Ulcerative colitis; PPV: Positive predictive value; NPV: Negative predictive value; SES-CD: Simple endoscopic score for Crohn’s disease[55]; CDEIS: Crohn’s disease endoscopic index of severity[56]; ELISA: Enzyme linked immunosorbant assay; QPOC: Quantitative point of care test; Mayo: Mayo endoscopic sub-scoring of ulcerative colitis[57]; Rachmilewitz: Rachmilewitz endoscopic score[58]; Saverymuttu: Non-standard endoscopic scoring system[59]; Stange: Non-standard endoscopic scoring system[60,61]; Farup: Non-standard endoscopic scoring system[62]; Baron: Baron score; Matts: Matts score[63]; Sandborn: Non-standard endoscopic scoring system[64]; Cal: Calpro ELISA: Calpro Calprotectin ELISA, Calpro AS, Norway; BM: BM ELISA, EK-CAL, Bühlmann Laboratories AG, Switzerland; Farmer: Non-standard endoscopic scoring system[65];Faecal Hb: Faecal haemoglobin; PMN-e: Polymorhonuclear elastase; Hb-Hp: Haemoglobin; Haptoglobin complex; D’Haens: Non-standard histologic scoring system[66]; Fazio: Non-standard histologic scoring system[67]; Floren: Non-standard histologic scoring system[68].

**Table 6 Studies investigating the correlation between other faecal marker concentrations and histologic activity in subjects with inflammatory bowel diseases**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Number of participants** | | **Population** | **Histology index used** | **Histology index**  **cut off** | **Faecal marker measured** | **Faecal marker cut off** | **Outcome measures** | | | | **Correlation** | |
| **CD** | **UC** | **Sensitivity%** | **Specificity%** | **PPV%** | **NPV%** | ***r* value** | ***P* value** |
| **Crohn’s disease studies** | | | | | | | | | | | | | |
| Kaiser *et al*[42] | 32 | 27 | Adults | Unique score | 0 | S100A12 |  | - | - | - | - | 0.44 | < 0.01 |
|  | 32 |  |  | |  | S100A12 | 0.8 | 81 | 100 | - | - | 0.451 | 0.010 |
|  |  | 27 |  | |  | S100A12 | 0.8 | 91 | 100 | - | - | 0.44 | < 0.025 |

CD: Crohn’s disease; UC: Ulcerative colitis; PPV: Positive predictive value; NPV: Negative predictive value.