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**How to predict clinical relapse in inflammatory bowel disease patients**

Liverani E *et al.* Predictors of clinical relapse in IBD

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**Abstract**

Inflammatory bowel diseases have a natural course characterized by alternating periods of remission and relapse. Disease flares occur in a random way and are currently unpredictable for the most part. Predictors of benign or unfavourable clinical course are required to facilitate treatment decisions and to avoid overtreatment. The present article provides a literature review of the current evidence on the main clinical, genetic, endoscopic, histologic, serologic and fecal markers to predict aggressiveness of inflammatory bowel disease and discuss their prognostic role, both in Crohn’s disease and ulcerative colitis. No single marker seems to be reliable alone as a flare predictor, even in light of promising evidence regarding the role of fecal markers, in particular fecal calprotectin, which has reported good results recently. In order to improve our daily clinical practice, validated prognostic scores should be elaborated, integrating clinical and biological markers of prognosis. Finally, we propose an algorithm considering clinical history and biological markers to intercept patients with high risk of clinical relapse.

**Key words:** Crohn’s disease; Ulcerative colitis; Clinical relapse; Clinical predictors; Fecal calprotectin

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**Core tip:** Natural course of inflammatory bowel diseases (IBD) is mostly unpredictable so far. Predictors of benign or unfavourable clinical course are required to facilitate treatment strategies. Our aim is to review current evidence on the main clinical and biological markers to predict the aggressiveness of IBD and to discuss their prognostic role. No single marker is reliable as a flare predictor but a combination of clinical and biological indicators better serves our requirements; we propose an algorithm applicable in our daily practice, arising from a combination of clinical history and biological markers.

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**INTRODUCTION**

Inflammatory bowel diseases (IBD) are characterized by a relapsing and remitting course. Aim of therapy is both to induce and maintain an enduring remission and to avoid disease progression. Disease flares occur in a random way and are mostly unpredictable, and persistent inflammatory activity negatively affects the patient’s physical and psychological well-being, social performance and working capacity.

Despite an effective medical therapy that could guarantee clinic remission, a degree of subclinical inflammation may persist within the mucosa of the gut, contributing to a risk of “symptomatic” relapse, which occurs when the inflammatory process reaches a critical intensity[1]*.* Identifying objective markers able to reveal such subclinical inflammation could represent an important advance in clinical practice, allowing the gastroenterologist to select patients and plan a tailored treatment.Clinical, genetic, endoscopic, histologic, serologic and fecal markers have been studied over many years, but we have not yet found an ideal tool to be used for prognostic purposes. Several authors have focused their efforts on this matter, but studies show conflicting and variable results.

**CLINICAL PREDICTORS**

Clinical predictors of IBD recurrence have probably been the most widely studied and have been revieved recently[2-4] (Table 1).

Brignola *et al*[5] first found in a cohort of Crohn’s disease (CD) patients, that when comparing the clinical features of patients relapsing within 18 mo with those of non-relapsing patients in persistent remission, a shorter period of remission before relapse seemed to have prognostic relevance*.*

This observation was confirmed by GETAID group[6] a few years later in a retrospective study; the authors, considering 178 quiescent CD patients not induced by surgery (CDAI < 150) within a median follow up of 23 mo, found that a young age (< 25 years) whether at first symptoms, at diagnosis or at consultation, was related to a high risk of clinical relapse. Furthermore, a short interval since the previous relapse (< 6 mo) and colonic involvement were associated with a poor prognosis. In this study neither the presence of anoperineal lesions nor a history previous intestinal resection was found to be of prognostic value.

Population-based studies with a fixed 5-year or 10-year study period after diagnosis of IBD have confirmed that young age at onset, but also disease location, are associated most strikingly with disease course, both in CD and in ulcerative colitis (UC). As regards CD, some authors assumed that the need for steroid treatment at the first presentation, together with perianal disease and young age at onset could be factors associated with a poor outcome[7]*.* In particular, patients younger than 40 years at diagnosis have been proven to experience a debilitating chronic disease [OR = 2.1 (95%CI: 1.3-3.6)][7]*.* Terminal ileal location seems to be a strong predictor of stricturing and internal penetrating behaviour (including perianal fistulas and abscesses) and an increased rate of surgery[8,9]*.* Proximal small bowel and upper gastrointestinal tract location are associated with increased risk of recurrence and surgery[10,11]. As regards extraintestinal manifestations, the presence of erythema nodosum and pyoderma gangrenosum at diagnosis or later have been demonstrated to be unable to predict a more severe CD course[12].

Looking at the same issue but from a reverse perspective, we could define a “non severe” evolution of the disease as a clinically inactive disease for longer than 12 years with less than one intestinal resection without a permanent stoma. The factors independently associated with a “non-severe” 15 year clinical course were non smoking status, rectal sparing, high educational levels, older age and longer disease duration[13].

In UC, young age at diagnosis and female gender are associated with more frequent relapses[11,14]. In a study by Bitton *et al*[15], UC patients with a younger age at onset, particularly the age group between 20-30 years, had a shorter time to relapse (*P =* 0.003). A greater number of prior flares was associated with a shorter time to relapse in women but not in men. Extensive colitis at presentation consistently appears as an independent predictor of colectomy within 10 years after diagnosis. Furthermore, extensive colitis is associated with increased risk of colon cancer as well as a slight increase in mortality[14,16,17]*.* A high level of systemic clinical symptoms at presentation (fever, weight loss) was linked to a trend toward infrequent relapses and chronic disease, but a higher risk of colectomy[16]*.*

**Environmental factors**

It has been argued that environmental factors might play a role in precipitating clinical relapse, with particular reference to some medications and lifestyle factors[18] (Table 1). Smoking is considered one of the stronger predictors of disease course: it globally increases disease severity in CD[19,20]*,* while an inverse association has been surprisingly documented for UC[21]*.* As with smoking, appendectomy is another environmental factor that seems to have opposite effects based on the disease. It is still debated whether appendectomy can increase the risk of CD onset[22,23]*.* Appendectomy has been supposed to increase the risk of surgical resection in CD[24]*,* while some authors failed to find an association with an increased disease severity[25]*.* In UC, appendectomy not only decreases the risk of developing disease, but it also seems a protective factor against developing severe disease and reduces the need for colectomy[22,26]*.*

The tolerability and safety of nonsteroidal anti-inflammatory drugs (NSAIDs) in an IBD setting have been reviewed recently. Conventional NSAIDs may cause clinical relapse in about 20% of patients with quiescent disease[27]. Some studies suggest that cyclooxygenase (COX)-2-selective NSAIDs, in particular celecoxib and etoricoxib, do not lead to exacerbations of disease, but these data need to be validated with further randomized controlled trials[28]*.* Generally, guidelines suggest a prudent use of NSAIDs in IBD patients.

As regards estrogens, a quite old prospective investigation showed that the current or former use of oral contraceptive (OC) pills leads to an increase risk for CD relapse (HR = 3.0, 95%CI: 1.5-5.9, *P <* 0.001)[20]*.* In contrast, no evidence of a connection between prior or current usage of OC was found for UC patients in the only literature-reported study that has assessed this association[15].For hormone replacement therapy, an inverse association with IBD activity as a whole has been reported (HR = 0.18, 95%CI: 0.04-0-72, *P =* 0.001)[29]*.* However, these results have not been validated by other studies and could suffer from bias due to patients’ age, different dosages and estrogen formulations.

Antibiotics could rationally play a role in defining the risk of relapse according to the way they influence the composition of intestinal microbiota. General antibiotic use has been documented to prevent CD relapse when compared with placebo (RR of relapse = 0.62; 95%CI: 0.46-0.84); all antibiotic combinations studied had some antimycobacterial properties. On the contrary, antibiotic administration in order to prevent UC relapse did not influence long-term relapse rates[30].

In both UC and CD, patients under conditions of low stress and with good coping strategies (the capacity to modulate the effects of life stressors on illness experience) were least likely to suffer relapse[31,32]. Particularly, relapse was positively associated with both stress (HR = 4.5, 95%CI: 1.9-10.7, *P <* 0.001) and coping strategies (HR = 1.9, 95%CI: 1.2-2.8, *P =* 0.004)[32]*.* On the contrary, no association was found between disease relapse and depression in UC patients[31].

**MICROBIOTA**

Intestinal microbiota seems to play a role in the pathogenesis of IBD. The currently accepted hypothesis is that a disruption of tolerance towards the commensal microbiota is produced in an individual with genetic vulnerability[33]*.* Dysbiosis, defined as a reduction in bacterial biodiversity resulting in fewer bacteria with anti-inflammatory properties compared with healthy controls, has been observed in IBD[34]*.* Potentially, gut microbiota can drive pathogenicity throughout an expansion of “pro-inflammatory” species or a reduction in the protective compounds of the microbiota[35]*.* Several studies have reported that members of the Bacteroidetes and Firmicutes phyla were reduced in IBD[36]; in contrast, a greater relative abundance in Enterobacteria, mostly *Escherichia coli* was observed[37]*.* Among Firmicutes, Faecalibacterium prausnitzii, a butyrate-producing bacteria, seems to have anti-inflammatory properties and several reports have demonstrated a decrease in population of this bacteria in patients with CD[36,38].

Only a small number of studies have evaluated the role of gut microbiota in predicting clinical relapse in IBD. It has been demonstrated that a low proportion of *F. prausnitzii* in resected ileal mucosa from CD patients was associated with higher risk of post-operative recurrence[38]. Furthermore, Rajca *et al*[39] have recently analysed fecal microbiota of 33 CD patients and found that a decrease in Firmicutes (in particular in *F. prausnitzii*) correlated with the time to relapse after infliximab withdrawal, so a deficit in some bacterial group, such as *F. prausnitzii*, may represent a predictive factor for relapse. Also, in UC patients, quantitative variations in different species of Lactobacillus have been identified between patients with relapse and patients in remission[40]. In particular, Varela *et al*[41] analysed a wide cohort of UC patients in remission and demonstrated a consistent decrease of *F. prausnitzii*; a subsequent subanalysis of the cohort showed a more significant decrease in that bacterial species when patients had suffered a relapse in the previous 12 mo. The authors found that low levels of *F. prausnitzii* could be associated with a four-fold increase in the risk of relapse.

These findings underscore the interest of testing whether increasing the *F. prausnitzii* population in the gut microbiota would be a useful strategy for maintaining remission in IBD patients. In that case, restoring normobiosis in IBD patients could be a new goal for optimal management.

**GENETIC PREDICTORS**

No differences in disease behaviour have been observed when comparing familial IBD (that is, having a first-degree relative with the disease) and sporadic IBD. As such, disease severity is unaffected by family history[42]*.* Despite this, familial cases are usually diagnosed at younger age and have an increased risk of extraintestinal manifestations and proving refractory to medical therapy[43,44]*.* A family history of CD increases the risk of subsequent CD after ileo-pouch anal anastomosis (IPAA)[45]*.*

With the arrival of the genome-wide association study era, the ambition of identifying genetic prognostic factors in IBD has become somewhat attractive. The main quality of these markers is their long-term stability and the fact that they are already present not only at disease onset, but even earlier. The presence of the NOD-2/CARD15 polymorphism has been linked to more aggressive clinical course of CD; *i.e.,* higher risk of intestinal strictures, earlier need for surgery, reduced postoperative disease-free interval[46]*.* Individuals carrying an increasing number of risk alleles in NOD2, IBD5 locus, DLG5, ATG16L1 and IL23R genes are more likely to experience a severe disease course. In particular, mutations in the ATG16L1 (autophagy-related 16-like 1) gene, encoding for a protein that partecipates in autophagy, have been associated both with stricturing disease and perianal involvement in CD[47]. Polymorphisms in multidrug resistance 1 gene (MDR1) were supposed to determine a more severe IBD and influence refractoriness/sensitiveness to medical therapy[48].

**LABORATORY MARKERS**

***Serological antibody markers***

Several immune-mediated antibodies have been described in IBD. Anti-*Saccharomyces cerevisiae* antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) can help to differentiate CD from UC, particularly when used in combination, as ASCA are mainly associated to CD, while pANCA are linked to UC[49,50]*.* Reactivity to ASCA was predictive of an aggressive disease phenotype; in particular it has been associated with early CD onset, fibrostenosing/penetrating CD behaviour and a need for CD-related surgery[51,52]*.* In CD patients, pANCA has been linked to less severe disease, UC-like disease and minor risk of small bowel complications[53]. In UC, pANCA are associated with a more severe disease course and need for surgery. In patients who undergo total proctocolectomy, higher levels of p-ANCA in the pre-surgical situation predict an increased risk of chronic pouchitis after IPAA[54]*.* Bitton *et al*[15] reported that higher pANCA titres (*P =* 0.02) and total ANCA titers (*P =* 0.03) were significantly predictive of relapse only in univariate time-dependent analysis; no significance was observed in multivariate analysis. However, reliability of these antibodies in assessment of disease activity has not been found, and the entity of immune response to ASCA or pANCA has an inconsistent role in predicting disease relapse[50]*.* In last years, the role of serum granulocyte macrophage colony-stimulating factor auto-antibody (GM-CSF Ab) in identifying IBD patients at risk of disease relapse at an early stage has been investigated, showing promising results both in UC and in CD[55]*.*

More recently, in addition to ANCA and ASCA, antibodies against specific bacterial wall products have gained increasing interest for their ability to help gastroenterologists in diagnosis, disease stratification and behaviour in IBD (antibodies to the *Escherichia coli* outer-membrane porin C - OmpC, anti-*Pseudomonas* associated sequence I2 and anti-bacterial Cbir1 flagellin). In particular, reactivity to ASCA, OmpC, anti-I2 and Cbir1 has been associated with with early CD onset, fibrostenosing and penetrating CD and need for early small bowel surgery[52].

New anti-glycan antibodies, including anti-chitobioside IgA (ACCA), anti-mannobioside IgG (AMCA), anti-laminaribioside IgG (ALCA), anti laminarin (anti-L) and anti-chitine (anti-C) have been recently added to the armamentarium of serologic markers in IBD. Anti-glycan antibodies are associated with a progression to a more aggressive disease course and a higher risk for IBD-related surgery[56,57]. Similarly to ANCA and ASCA, these promising biomarkers may help clinicians to identify certain IBD patient subgroups according to disease phenotype and risk of complications, but so far they are not suitable for prediction of relapse in the routine clinical practice.

***Serological inflammatory markers***

The potential role of inflammatory markers in predicting IBD relapse has been widely investigated, with special reference to C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (Tables 2 and 3)**.** Other laboratory markers, including leucocyte and platelet count, haemoglobin, albumin, α1-acid glycoprotein, fibrinogen, lactoferrin, β2-microglobulin, α2-globulin, α1-antitrypsin have been studied less extensively, showing less consistent results as a whole.

Brignola *et al*[58] observed that acid α1-glycoprotein, CRP, ESR, α1-antitrypsin and white blood cell count, as well as being altered during clinically active phases, may also be abnormal in about 50% of CD patients in remission.On the basis of these findings, they assumed that altered laboratory parameters in patients in apparent clinical remission - in particular, higher levels of α1-glycoprotein, α2-globulin, ESR, CRP and α1-antitrypsin - may reflect the early stage of subclinical inflammation of disease. Thus, these patients in remission phase might run a greater risk of clinical relapse within one-/two-year period than those in clinical remission with normal laboratory findings[5]*.* A simplified prognostic index (“New Index”) was developed with the aim of predicting CD relapse within 18 months, finding a relapse rate of 75% in those patients with at least one of the laboratory tests deranged (*i.e.,* α1-glycoprotein > 130 mg/dL, α2-globulins > 9.0 gm/L or ESR > 40 mm/h) *vs* 13% in those with normal test results[59]*.* Another study[60] confirmed that serum CRP is a valid marker in aiding prediction of CD course and in contributing to risk stratification among subgroups of patients. The likelihood of relapse after 2 years of participation was higher in the subgroup of patients who presented increased CRP levels compared with those with normal CRP at baseline.Many years later, the GETAID group[61] proposed a simple binary biological score for predicting short-term relapse in CD patients. They selected only two predictive inflammatory markers of relapse: CRP > 20 mg/L and ESR > 15 mm/h. A positive score (at least one of the two markers raised) was associated with 8-fold increase risk in relapse compared with patients negative for both markers (95%CI: 2.8-22.9; score sensitivity and specificity: 89% and 43% respectively). Assuming a 10% relapse rate every 6 wk, they observed negative and positive predictive values of 97% and 15%, respectively, suggesting that normal CRP and ESR could almost certainly rule out relapse in the next six weeks.

Kallel *et al*[62] reported that CRP at baseline is a predictive factor for CD relapse (cut off levels 34 mg/L, risk of relapse 7.6). High-sensitivity (hs)-CRP was able to predict short- and medium-term relapse during the follow up, in patients hs-CRP positive at diagnosis. The predictive potential of hs-CRP was limited to those patients hs-CRP-positive at diagnosis[63]*.*

CRP levels were also found to be an independent risk factor both for colectomy in extensive UC at diagnosis (when above 23 mg/L) and for intestinal resection in CD involving the terminal ileum (when above 53 mg/L); however, in the same study, no association was found between the risk of relapse and CRP levels at diagnosis in patients with UC or CD as a whole, or in any subgroup according to disease localization[64]*.* Another negative study comes from the results by D’Inca *et al*[65], where the predictive role of CRP seemed inconsistent for both UC and for CD patients. These authors postulated that ESR (and not CRP) could have a significant role in predicting clinical relapse in CD patients only, with a 72% sensitivity and an 85% specificity (cut-off 25 mm/h)*.*

Nevertheless, neither ESR nor CRP values were found to be useful in predicting relapse in IBD as a whole in several studies primarily focusing on the prognostic value of fecal markers[66-70]. In the prospective, single-centre study by Garcia-Sanchez *et al*[69], median ESR (17.5 mm/h) and CRP (4.6 mg/L) in the CD relapsed group did not differ significantly (*P =* 0.23 for ESR, *P =* 0.79 for CRP) from that in the non-relapsed group (ESR 16.2 mm/h, CRP 5.6 mg/L), nor there was a significant difference in the median ESR or CRP values (*P =* 0.18 for ESR; *P =* 0.06 for CRP) in the relapsed and non-relapsed UC patients (ESR 14.1 mm/h *vs* 7.6 mm/h; CRP 3.8 mg/L *vs* 1.7 mg/L). In agreement with these results, Gisbert *et al*[68] found that mean ESR and CRP in the IBD relapse group did not differ significantly from that in the non-relapse group.

The explanations for this conflicting data regarding the role of CRP in predicting IBD relapse may be its short “half life” and a known genetic CRP polymorphism in the general population that can reach a 20% rate[71].

Other laboratory indices, including plasma cytokines – interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, IL-16, IL-2 soluble receptor, tumor necrosis factor-α (TNF-α), TNF-α soluble receptor, INF-γ - have been analysed, examining their potential predictive role. High soluble IL-2 receptor serum level was found to be strongly predictive of CD relapse[72]*.* The same group showed that IL-6 serum level had great potential to predict the time-to-relapse in quiescent CD patients, alone or in association with other biological parameters such as α1-glycoprotein or soluble IL-2 receptor serum level. In particular, patient with an IL-6 serum level above 20 pg/mL had a 17-fold chance of relapse within 1-year period (*P <* 0.001)[73]*.*

In UC patients, higher IL-8 levels in the rectal mucosa were significantly associated with relapse, while no correlation was found for IL-1β, IL-6 and TNF-α levels in rectal mucosa, conventional blood markers or for plasma cytokines (IL-1β, IL-6, IL-8 and TNF-α).Thus, local IL-8 has been proposed as an additional objective tool for assessment of relapse[74]*.*

In contrast with the previous works, other authors failed to demonstrate a connection between detection/concentration levels of cytokines and the risk of IBD relapse, concluding that these systemic cytokines have little predictive value both in UC and CD patients[15,75]*.* Bitton *et al*[15] found no evidence that serum IL-1β, IL-6 and IL-15 predict relapse in UC (*P =* NS). The detection and baseline concentrations of the various cytokines tested (TNF-α, TNF-α-R1 and R2, IL-16, IL-1β, IL 2, IL-R2, IL-6, IL-10, and IFN-γ) in a prospective study including 135 patients in clinical remission (66 CD and 69 UC patients; relapse rate: 30%) were not shown to be associated with the risk of relapse[75]*.* Since the results are conflicting, no valid reasons exist to refer to these plasma cytokines, instead of cheaper serum markers such as CRP and ESR.

**INTESTINAL PERMEABILITY**

Increased intestinal permeability (IP) has been documented in IBD patients. It remains unclear whether barrier dysfunction precedes disease or results from active inflammation, however it is assumed that the intestinal tight-junction barrier is dynamically regulated by cytokines and pathogens.

The lactulose/mannitol test is frequently used for investigating small intestinal permeability. The permeability index is calculated as the ratio of relative lactulose/relative mannitol urinary excretion. 51Cr-EDTA is another common compound used to test small bowel permeability.

Elevated IP has also been found in clinically inactive CD patients. Consequently, permeability testing has been proposed as a non-invasive indicator of subclinical disease, preceding overt clinical relapse. Permeability testing with lactulose/mannitol has been demonstrated to be reliable in predicting relapses of CD within 1 year, with a PPV > 60%[76]. In particular, the vast majority of studies that focused on IP as a predictor of disease relapse showed an increase in relative risk (RR) of relapse within 1 year for patients with increased sugar permeability (3.1 < RR < 18)[66,77-80]*.* Only the study with 51Cr-EDTA failed in revealing IP to be a useful predictor of relapse in patients with small intestinal CD[81]*.*

Permeability testing is not recommended in patients with isolated colonic involvement, consequently its application as a predictor tool is not feasible in the UC setting. It should be considered that permeability test is rather unspecific, as several non-IBD related conditions could increase IP (infection, NSAIDs or alcohol), resulting in a decrease of the positive predictive value.

**endoscopy**

In a retrospective study, during a median follow-up period of 52 mo, the rate of colonic resection among the 102 patients included with active colonic or ileo-colonic CD was significantly higher in patients who exhibited deep and extensive ulcerations at colonoscopy than in those without such severe endoscopic lesions (RR = 5.43, 95%CI: 2.64-11.18)[82,83]*.* In UC patients affected with severe acute attacks, the presence of deep ulcerations and extensive disease seems to be predictive of more aggressive disease, failure of medical treatment and a higher rate of colectomy[84]*.*

The achievement of mucosal healing (MH) after induction therapy has been supposed to have a good prognostic value both in UC and CD. MH is thought to be associated with a generally favourable outcome of disease, including sustained clinical remission, treatment efficacy, reduced rate of surgery and hospitalizations[85]*.* Documented MH obtained with immunosuppressant or anti-TNFα agents is predictive of sustained clinical remission in patients with early stage CD and it is linked to a decreased risk of surgery in the long term[86].

Also, for UC, MH is associated with a better outcome, with a decreased rate of relapse and a reduced risk of major surgery[85,87].

Although suggestive for remission, normal mucosal appearance at routine colonoscopy might not reveal persistence of microscopic mucosal abnormalities, smouldering histopathological inflammation responsible for later relapse[1]*.*

Magnifying colonoscopy (MCS) examinations seems superior to conventional endoscopy in evaluating the inflammatory activity of UC, because it better correlates with histopathological grade[88,89]. Moreover, altered mucosal pattern as defined by high-resolution video-magnifying examination may predict exacerbations in UC patients in clinical remission[89]*.* Fujiya *et al*[89]reported that UC patients showing minute defects of epithelium during clinical remission frequently had a relapse within a short period (6 MO), compared with those without these findings (*P =* 0.02). Data published by Watanebe *et al*[90] confirmed these findings.In another study by Ando *et al*[91], 112 UC patients in remission were followed up until relapse, or a maximum of 12 mo. MCS was shown to be a significant predictor of future flares and the rate of relapse within 12 mo was found to increase with increasing MCS grade (0% for grade 1, 19% for grade 2, 43% for grade 3). They suggested a greater accuracy of MCS grading in predicting disease relapse compared to histological grade. Indeed, while biopsy specimens refer to a specific and limited mucosal portion, magnifying colonoscopy allows the observation of a more extended and representative area. In contrast with these findings, other authors reject the role of advanced endoscopy in predicting relapse over a 1-year period in patients with quiescent UC. Seventeen (27%) out of 64 UC patients with sustained clinical remission experienced a flare during the follow up period. Neither the mucosal pit pattern nor vascular pattern assessed through chromoendoscopy (CE) and narrow band imaging (NBI) was significantly different between relapsers and non-relapsers (*P =* 0.69 for CE pit pattern; *P =* 0.57 for NBI pit pattern; *P =* 0.72 for NBI vascular intensity)[92].

Confocal laser endomicroscopy (CLE) with intravenous fluorescein has been proven to accurately detect and quantify *in vivo* intramucosal changes during the clinical and endoscopic remission phase. These changes are potentially predictive of disease relapse, making CLE an attractive tool in IBD management[93-95]. Kiesslich *et al*[93] devised a simple endomicroscopic grading system for *in vivo* localization of local barrier dysfunction, defined as a discontinuity in the epithelium due to epithelial cell shedding (Watson grade). They prospectively followed up 58 IBD patients in clinical remission (47 UC, 11 CD; CAI ≤ 1 , CDAI ≤ 150) within a 12-mo period. Local barrier dysfunction in the small intestine of IBD patients, that is fluorescein leakage and microerosions (functional or structural defects identified as Watson grade II or III), was significantly associated with a higher rate of relapse (*P <* 0.001) compared with Watson grade I (normal, physiological cell shedding into the lumen). The sensitivity, specificity and accuracy of this grading system to predict relapse were 62.5%, 91.2% and 79%, respectively.Similarly, other researchers found that UC patients in clinical remission with active inflammation at CLE (grade C or D) were more likely to suffer a flare than those with a lower grade (normal or chronic inflammation; grade A or B respectively). Grade C and D (*i.e.,* acute inflammation) have a sensitivity of 64%, specificity of 88.9% and accuracy 74.4%, in predicting relapse[95].

**HISTOLOGY**

In CD, studies investigating the association between histological features and the risk of relapse are limited to the post-operative setting[96,97]. Literature is focused mainly on UC. Riley *et al*[1] showed that acute inflammatory indicators are associated with a two- to three-fold increased risk of UC relapse during a 12 mo follow up. Specifically, six histological features were assessed in this study: acute inflammatory cell infiltrate (polymorphonuclear cells in the lamina propria), crypt abscesses, mucin depletion, surface ephitelial integrity, chronic inflammatory cell infiltrate (round cells in the lamina propria), and crypt architectural irregularities. They reported a relapse rate of 52% among patients showing an acute inflammatory cell infiltrate on rectal biopsy specimens, while in the absence of such an infiltrate only 25% of the patients experienced a flare (*P =* 0.02). Similarly, relapse rates were considerably higher in the presence than in the absence of crypt abscesses (78% *vs* 27%, *P <* 0.005), mucin depletion (56% *vs* 26%, *P <* 0.02), and breaches in the surface epithelium (75% *vs* 31%, *P =* 0.01). On the other hand, neither a chronic inflammatory cell infiltrate nor crypt architectural abnormalities were of prognostic importance on subsequent relapse rate. Bitton *et al*[15]*,* reported data taking into accountbasal plasmacytosis, that is a dense infiltration of plasma cells extending into the lower one third of the lamina propria, an area where these cells are usually absent or barely present. The evidence of basal plasmocytosis on rectal biopsy specimens lead to a greater short-term relapse risk in UC patients (*P =* 0.003, HR = 4.5) even if patients receiving rectal enemas or suppositories were allowed to participate in this study.

The presence of basal plasmocytosis (*P =* 0.0007, OR = 5.13) and Geboes Index (GI)[98] ≥ 3.1 (*P =* 0.007) predicted relapse in UC patients with endoscopically inactive disease[99]. Data recently published by Popp *et al*[100] confirmed these findings*.*

In contrast, baseline histology features evaluated with Riley classification[1] were not statistically different between relapsing and non-relapsing UC patients in a recent study by Jauregui-Amezaga *et al*[92]and basal plasmacytosis did not appear as a predictor of relapse (*P =* 0.07). It was found in 38 (59%) patients but only 7 of these relapsed (18%), while 10 of the 24 (38%) patients without basal plasmacytosis relapsed.

**Fecal markers**

In recent decades, a number of stool biomarkers have been evaluated for their potential in the IBD scenario (fecal calprotectin, lactoferrin, S100A12, Indium 111-labeled leukocytes, α1-antitrypsin, α2-macroglobulin, myeloperoxidase, PMN-elastase). Their utility has been studied in relation to diagnosing, establishing the activity of the disease, monitoring treatment response and predicting clinical relapse[101,102]*.* Fecal tests have further advantages of being cheap, easy to perform, safe, simple for the patient and therefore very useful in clinical practice. Moreover, they have excellent stability in feces being resistant to bacterial degradation and stable in stool at room temperature for up to 7 d[103]. Most of them have only a low diagnostic performance, so their clinical role is doubtful. As regards the utility in prediction of clinical relapse, the accuracy of fecal calprotectin (FC), lactoferrin and S100A12 has been evaluated.

***Fecal calprotectin***

Fecal calprotectin (FC) is a calcium-binding protein derived from neutrophils, monocytes and reactive macrophages[104]. The FC test has been shown to correlate with both endoscopic and microscopic evidence of gastrointestinal inflammation in IBD[102], reflecting the migration of neutrophils through the inflamed bowel wall to the colonic/rectal mucosa.

In several clinical studies with both adults and children, elevated FC concentrations were found despite clinical remission[66,105-107]. It appears that FC can detect subclinical mucosal inflammation and thus may identify patients at risk of relapse (Table 4).

As shown in the STORI study, elevated FC seemed to predict relapse after stopping infliximab therapy in patients with CD. A FC concentration of over 300 μg/g was an independent risk factor associated with disease relapse[108]*.* A recently published meta-analysis of six prospective studies showed a pooled sensitivity of 78% and a specificity of 73% for FC in predicting IBD relapse[109]. The test results were comparable between UC and CD[110].

Previously, Costa *et al*[67] reported a twofold and 14-fold increased risk of relapse in CD and UC patients respectively, who had a baseline level of FC higher than 150 μg/g at inclusion. Sensitivity was high for both CD (87%) and UC (89%), but specificity was much lower in the case of CD (43%) compared with UC (82%).

FC appears to be less useful in predicting relapse in patients with ileal CD compared with colonic/ileocolonic CD or UC[65,68,69]*.* For this reason, some authors stress the need of stratification of CD patients according to phenotypical pattern to improve the predictive capacity of FC in CD[68,69]*.* The good predictive value of FC was confirmed when CD patients with only small bowel involvement were excluded, with the aim to obtain a more homogeneous group.Patients with colonic or ileo-colonic CD in remission and FC levels above 340 μg/g presented an almost 19-fold greater risk of relapse than those with lower concentrations[62].

A large prospective study of 92 CD patients provides evidence that adults with quiescent CD with an FC level below 240 μg/g were unlikely to relapse within 12 months (NPV 96.8%), while those with a FC level of 240 μg/g or above were associated with greater likelihood of relapse within 12 mo, 12.28 times higher than lower values (*P =* 0.002)[70].

As regards the performance of FC in UC populations, several authors identified cut off values ranging from 120 μg/g to 250 μg/g as being able to predict clinical relapse with good accuracy[65-69,110].

In parallel with this data, we have recently reported that an FC cut off value of 193 µg/g is able to predict clinical relapse in 74 UC patients in clinical remission with a Mayo endoscopic sub-score ≤ 1 followed up for one year (89% accuracy, 65% sensitivity, 98% specificity)[111]*.*

Tibble *et al*[66] found that FC levels in patients with an early relapse (< 1 mo) were somewhat higher than those in patients who relapsed later, but no statistically significant difference was noticed*.* No differences were found in the predictive capacity of this marker according to disease extent (distal or extensive colitis)[69].

FC has been evaluated also as a predictor of relapse in IBD patients under maintenance Infliximab therapy[112] finding a cut off of 160 μg/g able to predict clinical relapse with a sensitivity of 91.7% and a specificity of 82.9%. Previously Molander *et al*[113] reported that a normal FC after induction therapy with Infliximab or Adalimumab is a good predictor of clinical response to the scheduled therapy. Recently, in a prospective multicenter study, De Vos *et al*[114] found in eighty-seven UC patients in clinical remission after Infliximab maintenance therapy, that patients who flared had FC median > 300 mg/kg already three months before the flare. Two consecutive FC measurements of > 300 mg/kg with 1-mo interval were identified as the best predictor of a flare, increasing the specificity greater than that of a single measurement (specificity of 100% *vs* 93%).

Due to the FC variability in a day to day[115,116] and also during the same day[117,118] two measurements are suggested; the variation seems to be higher in patients with elevated concentration of FC[119].

***Lactoferrin***

Lactoferrin is an iron-binding glycoprotein and a major component of the secondary granules of polymorphonuclear neutrophils. The excretion of lactoferrin in stool increases during intestinal inflammation, as leucocytes invade the mucosa[119,120]. Similarly to FC, it is stable in stool for up to 4 d, thanks to its antibacterial activity and resistance to proteolysis[121]. Results on the potential utility of fecal lactoferrin measurements at remission to predict clinical flares seem promising, both in CD and UC patients. It has been shown that fecal lactoferrin may rise significantly prior to a clinically evident relapse[122].

A positive lactoferrin test was more frequent in relapsing than in non-relapsing IBD patients (62% *vs* 35%, *P <* 0.05). From another perspective, 10% of the patients with negative fecal lactoferrin test relapsed during follow-up, while this occurred in 25% of those having a positive test result (*P <* 0.05)[68].

Limited to UC, assuming a cut-off value of 140 μg/g, lactoferrin showed lower sensitivity and specificity than FC in predicting UC relapse (67% and 68% *vs* 76% and 76%, respectively) [110]*.*

Patients with IBD experiencing clinical relapse within the next 2 mo showed significantly higher lactoferrin levels[123]. In the study by Gisbert and colleagues, lactoferrin had a 46% sensitivity and 61% specificity to predict relapses in UC and of 77% sensitivity and 68% specificity in CD[68].

***S100A12***

Neutrophil-derived S100A12, also known as calgranulin C, is a protein expressed by activated neutrophils. Several studies have demonstrated a correlation between mucosal inflammation and S100A12 levels in blood and feces[124-126]. The role of S100A12 as a marker of future relapse in pediatric and adult IBD patients has been investigated in only one prospective study so far. A baseline fecal S100A12 level of > 0.5 mg/kg was significantly associated with clinical IBD relapse within 18 months. Fecal S100A12 levels seemed to be already increased up to 6 months before clinical relapse. In contrast, no differences were observed in serum S100A12 levels between relapsers and non-relapsers[127].

**POST-OPERATIVE RECURRENCE IN CD**

Surgical resection of the diseased bowel in CD is not curative, and approximately half of the patients require surgery within 10 years after diagnosis, despite the wide availability of immunosuppressive and anti-TNFα treatments[128].

Active smoking status is a strong predictor of post-operative recurrence. In particular, patients who continue smoking after surgery have a 2-fold increased risk of clinical relapse, with a further increase in the risk according to the number of cigarettes smoked per day[19,129]. History of repeated intestinal resection (more than twice) appears to be another undisputed predictor of postoperative recurrence[130]. Penetrating disease behaviour, perianal disease, extensive bowel resection, short disease duration prior to surgery, non-colonic disease location and long duration are other established risk factors for postoperative recurrence, but their predictive value has been shown to be less consistent[130]*.* The roles of young age at diagnosis and family history remain controversial[2].

It has been demonstrated that low proportion of *F. prausnitzii* in resected ileal mucosa from CD patients was associated with higher risk of post-operative recurrence[38].

Endoscopic findings with biopsy are unanimously considered a reliable predictor of subsequent clinical course and an ileocolonoscopy during the first post-operative year is highly recommended[131].

As regards histological features, an “active disease” at the margin of resection, characterized by myenteric plexitis[96]*,* lymphatic vessel density in the proximal margin of resection and morphological analysis of Paneth cells, may predict post-operative recurrence[98]. On the contrary, granulomas and chronic inflammation at the margin of resection seems to be less relevant as a predicting value[97]*.*

Since conventional endoscopy does not allow access to the small gut, wireless capsule enteroscopy is proposed but not widely used in this setting. Ionising radiation exposure limits the use of computed tomography enteroclysis, while magnetic resonance, perhaps the gold standard for imaging, remains of limited access[132]*.*

Fecal markers have been recently proposed, although “false positives” due to, for example, bile salt malabsorption may occur. Indeed, patients with low levels of FC and lactoferrin after resection are unlikely to have mucosal inflammation and cut-off values of > 50 µg/g and > 7.25 µg/g for FC and lactoferrin respectively have been considered to diagnose clinical post-operative CD recurrence[133]*.* This evidence is supported by Orlando *et al*[134] who showed that FC at a concentration of > 200 mg/L at three months after surgery can be an indication for colonoscopy in order to detect early endoscopic recurrence (sensitivity of 63% and specificity of 75%). A recent meta-analysis showed that FC is a useful marker in evaluating clinical and endoscopic recurrence in CD patients who had undergone previous surgical resection[135]. The authors evaluated ten articles, finding a pooled sensitivity of 0.82 and specificity of 0.61 for assessing endoscopic recurrence and a pooled sensitivity of 0.59 and specificity of 0.88 for evaluating clinical relapse. Wright *et al*[136] in a large (135 patients), prospective, randomized, controlled trial evaluated the utility of serial measurements (month 6, 12 and 18 postoperatively) of FC, CRP and CDAI in predicting endoscopic recurrence after CD resection. Combined 6- and 18-mo FC levels correlated significantly with presence and severity of endoscopic recurrence, whereas CRP and the CDAI did not. A cut-off of FC > 100 μg/g identified patients with endoscopic recurrence with 89% sensitivity and 58% specificity (NPV 91%).

Non-invasive biomarkers have substantial appeal in this setting because they can be repeated much more frequently than colonoscopy. Future studies should gather additional information to help to understand the optimal frequency to measure FC.

**Conclusion**

IBDs have a natural course characterized by relapsing and remitting phases. Disease flares occur in a random way and are mostly unpredictable. Prediction of relapse is a longstanding ambition of gastroenterologists, since it could have pivotal implications for future therapeutic strategies.

A “predictive” ideal marker should reveal inflammation at a pre-symptomatic stage, and at the same time, it should be easy and rapid to perform, cheap, as minimally invasive as possible and reproducible between patients and laboratories.

Clinical variables, serological, fecal markers and genetic tests are available, but no single one of them is highly predictive when used alone. Of course, data obtained from endoscopy and histology are of great value, but their utilization as predictors of clinical relapse are strongly limited by their invasiveness. An overview of the “probing items” available for the clinicians is reported in Figure 1.

In the 80s, Brignola first understood the need of stratifying patients in remission on the basis of their risk of relapse, for improving the therapeutic management of patients, and a “New Index” containing a mixture of serological markers demonstrated its ability to predict clinical relapse in a reasonably long period of time. Also, he stressed the concept that inflammatory markers need to be coupled to clinical history as a complementary predictor of flare up risk.

The GETAID group embraced this idea and showed that clinical course of the disease can tell us a great deal of information, such as that a short interval since the previous relapse is associated with a poor prognosis and also that a biological predictive score (BPS) can predict short-term maintenance of remission in patients with clinically inactive CD after recent weaning off steroids. The downside of this approach is that serological markers are not always displayed by patients, and also that they could be influenced by several extra-intestinal diseases; on the other hand, clinical manifestations suffer from subjectivity.

This tricky situation has been recently ameliorated by a new fecal marker, namely fecal calprotectin; an increasing body of evidence states its ability in mirroring mucosal inflammatory activity. A validated cut off value of FC for predicting IBD relapse in not yet well defined, however authors agree that different cut-offs should be considered according to the type of IBD and, among CD, subcategories of patients have to be distinguished according to disease location and extension. In general, higher cut off points have been noticed in CD than in UC.

Both in CD and in UC, we prefer to observe at least two measurements of FC above the cut-off point, as day-to-day variability in FC levels has been described.

In our opinion, in our daily clinical practice, validated prognostic scores should be elaborate, including a combination of the most promising markers, either clinical and biological. For that reason wepropose an algorithm of current use in our daily practice, including both blood tests and faecal markers, enhanced by characteristics of the clinical history.

In CD setting, the presence of at least 2 among: young age at onset, extensive disease, perianal involvement, steroid requirement at the onset, short previous remission and history of previous more than one surgery event, together with the presence of CRP > 20 ml/L and/or FC above 250 µg/g in at least two determinations, make a CD patients deserving aggressive treatment (Figure 2). Similarly, clinical history and disease extent have to be kept in mind when evaluating a patient affected by UC. We consider young age at onset, extensive colitis and the number of previous relapses as fundamental elements of clinical history that should be evaluated. The presence of at least one of the previous items and the measurement of an FC above 190 µg/g in at least two determinations, legitimize more aggressive therapy and close monitoring (Figure 3).

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**Figure 1 “Probing items” available for the clinicians to predict clinical relapse in inflammatory bowel diseases.**

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**Figure 2 Algorithm to identify Crohn’s disease patients with high risk of clinical relapse.** CRP: C reactive protein; FC: Fecal calprotectin.

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**Figure 3 Algorithm to identify ulcerative colitis patients with high risk of clinical relapse.** FC: Fecal calprotectin.

**Table 1 Clinical and environmental predictors of relapse in inflammatory bowel diseases patients**

|  |  |  |
| --- | --- | --- |
| **Clinical factors** | **CD** | **UC** |
| Age | Young age at diagnosis[6-8,10]  → Disabling chronic disease | Young age at diagnosis[11,14,15]  → Rate of relapse |
| Sex |  | Female[11,14]  → Rate of relapse |
| Disease location | Perianal disease[7,9]  → Poor outcome  Terminal ileal location[8,9]  Predictor of stricturing/penetrating disease  ↑ risk of surgical resection  Proximal small bowel /  Upper gastro-intestinal tract[10,11]  ↑ risk of relapse  ↑ risk of surgical resection  Colonic disease[6]  ↑ risk of develop perianal disease | Extensive colitis[8,14,16]  → ↑ risk of colectomy, CRC, mortality |
| No. prior relapses | Short period of remission before relapse[5,6]  → poor prognosis | Greater number of prior relapse  → shorter time to relapse |
| EIM | NS[12] | NS[12] |
|  |  |  |
| **Environmental factors** | **CD** | **UC** |
| Smoke | ↑ disease severity[19,20] | ↓ disease severity[21] |
| Appendectomy | ↑ risk of surgical resection[24] | ↓ risk of colectomy[22,26] |
| Drugs |  |  |
| NSAIDs/  COX-2 selective | Contrasting evidences[28] | Contrasting evidences[28] |
| OCPs | ↑ risk of relapse[20] | NS[15] |
| HRT | ↓ disease severity[29] | ↓ disease severity[29] |
| Antibiotics | ↓ risk of relapse[30] | NS[30] |
| Stress | ↑ risk of relapse[32] | ↑ risk of relapse[31] |

CD: Crohn’s disease; UC: Ulcerative colitis; CRC: Colon-rectal cancer; EIM: Extraintestinal manifestation; NS: No significant; NSAIDs: Non-steroidal anti inflammatory drugs; COX-2: Cyclooxygenase-2; OPCs: Oral contraceptive pills; HRT: Hormone replacement therapy.

**Table 2 C-reactive protein as predictor of relapse in** **inflammatory bowel diseases patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **No. Pt** | **No. R** | **Relapse rate (%)** | **Mean CRP values R** | **Mean CRP values NR** | ***P* value** |
|  |  |  |  |  |  |  |
| Brignola *et al*[5], 1986 |  |  |  |  |  |  |
| CD | 41 | 17 | 41% | 2.2 mg/dL | 0.7 mg/dL | 0.01 |
|  |  |  |  |  |  |  |
| Tibble *et al*[66], 2000 |  |  |  |  |  |  |
| CD | 43 | 25 | 58% | 13.1 mg/L | 9.1 mg/L | 0.1 |
| UC | 37 | 19 | 51% | 3 mg/L | 9.7 mg/L | 0.4 |
|  |  |  |  |  |  |  |
| Bitton *et al*[15], 2001 |  |  |  |  |  |  |
| UC | 74 | 27 | 36.5% | 0.08 mg/dL | 0.25 mg/dL | NS |
|  |  |  |  |  |  |  |
| Costa *et al*[67], 2005 |  |  |  |  |  |  |
| CD | 38 | 15 | 39% | 8 mg/L | 6 mg/L | 0.373 |
| UC | 41 | 19 | 46% | 5 mg/L | 4.5 mg/L | 0.45 |
|  |  |  |  |  |  |  |
| D'Incà *et al*[65], 2008 |  |  |  |  |  |  |
| CD | 65 | 20 | 31% | 5.49 mg/L | 3.13 mg/L | 0.05 |
| UC | 97 | 37 | 38% | 3.15 mg/L | 3.08 mg/L | 0.69 |
|  |  |  |  |  |  |  |
| Garcia-Sanchez *et al*[69], 2010 |  |  |  |  |  |  |
| CD | 66 | 18 | 27% | 4.6 mg/L | 5.6 mg/L | 0.79 |
| UC | 69 | 21 | 31% | 3.8 mg/L | 1.7 mg/L | 0.06 |
|  |  |  |  |  |  |  |
| Kallel *et al*[62], 2010 |  |  |  |  |  |  |
| CD1 | 53 | 10 | 18.9 % | 34 mg/L | 4 mg/L | < 0.001 |
|  |  |  |  |  |  |  |
| Naismith *et al*[70], 2014 |  |  |  |  |  |  |
| CD | 45 | 5 | 11% | 2 | 2.1 | 0.539 |

1Small bowel CD patients excluded. R: Relapsers; NR: Non relapsers; CRP: C reactive protein; CD: Crohn’s disease; UC: Ulcerative Colitis; IBD: Inflammatory bowel diseases.

**Table 3 Erythrocyte sedimentation rate as predictors of relapse in inflammatory bowel diseases patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **No. Pt** | **No. R** | **Relapse rate (%)** | **Mean ESR values R (mm/h)** | **Mean ESR values NR (mm/h)** | ***P* value** |
|  |  |  |  |  |  |  |
| Brignola *et al*[5], 1986 |  |  |  |  |  |  |
| CD | 41 | 17 | 41% | 24 | 9 | 0.0006 |
|  |  |  |  |  |  |  |
| Tibble *et al*[66], 2000 |  |  |  |  |  |  |
| CD | 43 | 25 | 58% | 21 | 13 | 0.2 |
| UC | 37 | 19 | 51% | 13 | 20 | 0.2 |
|  |  |  |  |  |  |  |
| Bitton *et al*[15], 2001 |  |  |  |  |  |  |
| UC | 74 | 27 | 36.5% | 13.8 | 11 | NS |
|  |  |  |  |  |  |  |
| Costa *et al*[67], 2005 |  |  |  |  |  |  |
| CD | 38 | 15 | 39% | 20 | 15 | 0.077 |
| UC | 41 | 19 | 46% | 15 | 11 | 0.056 |
|  |  |  |  |  |  |  |
| D'Incà *et al*[65], 2008 |  |  |  |  |  |  |
| CD | 65 | 20 | 31% | 25 | 15 | 0.005 |
| UC | 97 | 37 | 38% | 14 | 11 | 0.69 |
|  |  |  |  |  |  |  |
| Garcia-Sanchez *et al*[69], 2010 |  |  |  |  |  |  |
| CD | 66 | 18 | 27% | 17.5 | 16.2 | 0.23 |
| UC | 69 | 21 | 31% | 14.1 | 7.6 | 0.18 |

R: Relapsers; NR: Non relapsers; ESR: Erythrocyte sedimentation rate; CD: Crohn’s disease; UC: Ulcerative Colitis; IBD: Inflammatory bowel diseases.

**Table 4 Fecal calprotectin as a predictor of relapse in inflammatory bowel disease patients**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **IBD type** | **Criteria for defining relapse** | **No. Pt** | **No. R** | **Relapse rate %** | **Mean FC values R** | **Mean FC values NR** | **p** | **FC**  **cut off** | **Se** | **Spe** | **PPV** | **NPV** | **HR7** |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Tibble *et al***[66]**, 2000** | CD | CDAI > 150 ΔCDAI > 100 | 43 | 25 | 58% | 122 mg/L (610 μg/g) | 41.5 mg/L (220 μg/g) | < 0.0001 |  |  |  |  |  |  |
| UC | HBI > 4 ΔHBI > 2 | 37 | 19 | 51% | 123 mg/L | 29 mg/L | < 0.0001 |  |  |  |  |  |  |
| IBD |  | 80 | 44 | 55% | 123 mg/L | 32 mg/L | < 0.0001 | 50 mg/L (250 μg/g) | 90 | 83 |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Costa *et al***[67]**, 2005** | CD | CDAI > 150 | 38 | 15 | 39.5% | 220.1 μg/g | 220.5 μg/g | 0.395 | 150 μg/g | 87 | 43 | 50 | 83 | 2.2 |
| UC | UCAI > 4 | 41 | 19 | 46.3% | 220.6 μg/g | 67 μg/g | < 0.0001 | 150 μg/g | 89 | 82 | 81 | 90 | 14.4 |
| IBD |  | 79 | 34 | 43% |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **D'Incà *et al***[65]**, 2008** | CD | CDA ≥ 150 ΔCDAI > 50 | 65 | 20 | 31% | 207 mg/kg | 88 mg/kg | 0.055 | 130 mg/kg | 65 | 62 | 44 | 80 | 1.7 |
| Colonic CD |  |  |  |  | 176.7 mg/kg | 75.1 mg/kg | 0.041 |  |  |  |  |  |  |
| UC | ET > 4 | 97 | 37 | 38% | 190 mg/kg | 49 mg/kg | 0.001 | 130 mg/kg | 70 | 70 | 60 | 79 | 2.4 |
| IBD |  | 162 | 57 | 35.2% |  |  |  | 130 mg/kg | 68 | 67 | 52 | 79 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Gisbert *et al***[69]**, 2009** | CD | CDAI > 150 | 89 | 13 | 14.6 | 266 μg/g | 145 μg/g | 0.002 | 169 μg/g | 69 | 76 |  |  |  |
| UC | TW > 11 | 74 | 13 |  | 213 μg/g | 126 μg/g | 0.03 | 164 μg/g | 69 | 74 |  |  |  |
| IBD |  | 163 | 26 | 16% | 239 μg/g | 136 μg/g | < 0.001 | 167 μg/g | 69 | 75 | 35 | 93 | 2.8 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Garcia-Sanchez *et al***[69]**, 2010** | CD | CDAI ≥ 150 | 66 | 18 | 27% | 524 μg/g | 123 μg/g | < 0.01 | 200 μg/g | 80 | 65 | 46 | 88 | 4.35 |
| UC | TW ≥ 11 | 69 | 21 | 31% | 298 μg/g | 105 μg/g | < 0.01 | 120 μg/g | 81 | 63 | 49 | 88 | 6.48 |
| IBD |  | 135 | 39 | 30% | 444 μg/g | 112 μg/g | < 0.01 | 150 μg/g | 75 | 68 | 49 | 68 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Kallel *et al***[57]**, 2010** | CD1 | CDAI > 150 ΔCDAI > 100 | 53 | 10 | 18.9 | 380.5 μg/g | 155 μg/g | < 0.001 | 340 μg/g | 80 | 90.7 |  |  | 18.8 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Naismith *et al***[70]**, 2014** | CD | Treatment modification, progression disease phenotype, hospitalization, surgery | 92 | 10 | 11% | 414 μg/g | 96 μg/g | 0.005 | 240 μg/g | 80 | 74.4 | 27.6 | 96.8 | 12.18 |
| Colonic CD | 35 | 4 |  | 424 μg/g | 187 | 0.16 |  |  |  |  |  |  |
| Ileal CD | 16 | 3 |  | 371 μg/g | 57 | 0.057 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Yamamoto *et al***105]**, 2014**[ | UC |  | 80 | 21 | 26% | 173.7 μg/g | 135.5 μg/g | 0.02 | 170 μg/g | 76 | 76 |  |  | 7.23 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Scaioli *et al***[107] | UC | SCCAI > 3  Mayo > 1 | 74 | 20 | 27% | 218 μg/g | 48 μg/g | < 0.01 | 193 μg/g | 65 | 98 | 92 | 88 |  |

1Small bowel CD patients excluded. 12-mo follow-up period in all the studies cited; FC assay was Calprest for all the studies cited, except in the study by Tibble *et al*[66] (Roseth). R: relapsers; NR: non relapsers; FC: fecal calprotectin; Se: sensibility; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; HR: hazard ratio; CD: Crohn’s disease; UC: Ulcerative Colitis; IBD: Inflammatory bowel diseases; HBI: Harvey Bradshaw Index; CDAI: Crohn’s disease activity index; CAI: Colitis activity index; TW: modified Truelove-Witt; SCCAI: Simple Clinical Colitis Activity.