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ORIGINAL ARTICLE



Low fecal calprotectin predicts clinical remission in Crohn's disease patients: the simple answer to a challenging question

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ABSTRACT

Background and aim: Fecal calprotectin (FC) is a noninvasive marker of intestinal inflammation. Predicting relapses in Crohn's disease (CD) patients can allow earlier changes in therapy. The aim of this study was to evaluate the role of FC in predicting relapse in CD patients in clinical remission within six months follow-up.

Methods: Patients with CD who were in clinical remission at least ≥ 3 months were included in this study. The first FC sample during the remission period was evaluated and was used as the baseline value. Relapse was defined as an unexpected escalation in therapy, hospitalization or need for surgery for active CD. The accuracy and optimal cutoff FC values for predicting clinical relapse at six months were assessed by the area under the ROC curve (AUC).

Results: One hundred and forty-four patients were evaluated, with mean age of 38.4 years. Of these, 13 (9%) had a relapse during the follow-up period. The mean FC value was significantly lower for non-relapsers (203.2 $\mu\text{g/g}$) than for relapsers (871.3 $\mu\text{g/g}$), $p < .001$. The AUC for predicting relapse by using FC values was 0.924. The optimal cutoff FC value to predict relapse was 327 $\mu\text{g/g}$; with values of sensitivity, specificity, negative predictive value and positive predictive value were 92.3%, 82.4%, 99.1% and 34.3%, respectively.

Conclusions: FC is more useful in predicting remission maintenance than relapse in patients with CD in clinical remission. Values of FC $\leq 327 \mu\text{g/g}$ can exclude relapse at least at six months follow-up period.

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Introduction

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterized by a chronic evolution with periods of remission and relapse, and a progressive bowel damage [1].

In patients who have achieved clinical remission, monitoring for early identification of a disease flare is paramount. The first step in monitoring these patients is to assess the symptoms; however, the discrepancy between inflammatory activity and symptoms is well known [2].

The shifting of therapeutic target from clinical remission to full control of inflammation, with the institution of optimized therapy in the early stages, can alter the natural history of CD and prevent structural changes in bowel [3].

Mucosal healing (MH), evaluated endoscopically, has become a therapeutic goal in CD since it may change the natural course of CD and is associated with better outcomes with lower relapse rates, hospitalization rates and need for surgery [4–7].

In order to avoid repetitive invasive tests and to overcome the subjectivity of clinical activity indices, the laboratory biomarkers have been used to investigate and monitor

the activity of IBD as well as to identify patients at high-risk of disease progression and its complications.

C-reactive protein (CRP) in blood and fecal calprotectin (FC) are the most widely biomarkers used in clinical practice.

CRP is a nonspecific, acute-phase reactant that correlates modestly with endoscopic activity in CD, and a normal result does not exclude inflammation [8].

FC is a specific, noninvasive biomarker for intestinal inflammation. It represents 60% of neutrophils cytosolic proteins and the presence of mucosal lesions that are associated with neutrophil migration, thereby resulting in an elevation of the FC levels [9].

FC has been identified as a surrogate biomarker of inflammation at endoscopy in CD [10, 11], and is an adjunctive measure of inflammation to endoscopy and cross-sectional imaging for monitoring in CD [12].

FC may predict relapse in patients with CD in remission [13], and consequently allow early treatment optimization and avoiding disease complications.

The aim of this study was to evaluate the role of FC in predicting short term relapse in patients with CD in clinical remission period.

Material and methods

We retrospectively evaluated patients with CD in clinical remission, followed at our outpatient clinic, between March 2015 and August 2017.

We included CD patients with the following criteria: with Crohn's Disease Activity Index (CDAI) [14] < 150 for a minimum of 3 months, on a stable dose of immunosuppressive and biologic agents for at least 3 months and not on corticosteroid therapy.

The following exclusion criteria were considered: bowel surgery in last six months, ileo- or colostomy, active perianal disease, and corticosteroids intake in last six months, consumption of non-steroidal anti-inflammatory drugs, pregnancy and lactation.

CDAI was calculated at each evaluation visit in our outpatient clinic. Patients' data, including demographic variables, IBD phenotype (Montreal classification) [15], duration of the disease, medications used in remission period and IBD-related surgeries were evaluated.

The FC morning sample in the remission period was collected and analyzed by BÜHLMANN Quantum Blue® (LF-CALE25) with an upper limit of the normal range of 30 µg/g.

The value of FC considered for data analysis was the first one collected during the period of clinical remission according to the criteria defined above.

The values of C-reactive protein (CRP) in serum, erythrocyte sedimentation rate (ESR), platelets and albumin, during the same period were also evaluated.

The outcome was evaluated at the end of six months after collecting the analytical parameters. Primary endpoint considered was relapse, defined as an unexpected escalation in therapy, hospitalization or surgery for active CD.

The patients with clinical relapse underwent ileocolonoscopy, and inflammatory activity was assessed by Simple Endoscopic Score for Crohn Disease (SES-CD) or Rutgeerts score.

Statistical analysis

Data analyses were performed using SPSS version 20.0 (IBM, Armonk, New York, NY). The discriminative ability of FC to predict relapse was assessed by the area under the ROC curve (AUC). Student's *T*-test was performed to compare continuous variables between relapsers and non-relapsers. Categorical data analyses were conducted using the Chi-Square or Fisher exact test. Test characteristics were determined using a 2 × 2 table and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

The cumulative proportion of relapse was calculated based on the Kaplan–Meier analysis, and log rank test was used to compare survival curves of FC.

Statistical significance was considered, using *p* values, at $\alpha = 0.05$.

Results

One hundred and forty-four patients were evaluated, with mean age of 38.4 years, 78 (54.2%) were females.

Table 1 summarizes the demographic and clinical characteristics of relapsers and non-relapsers patients.

Regarding the disease location, 71 (49.3%) had an ileal involvement (L1), 11 (7.6%) only colon involvement (L2) and 62 (43.1%) had an ileocolitis (L3).

The median time of CD disease duration was 85 ± 67.7 months.

Eighty-one patients (56.3%) were receiving immunomodulators, 25 (17.4%) were under anti-TNF drugs, and 38 (26.4%) were in combination therapy.

All patients had FC values ≥ 30 µg/g. According to the Montreal classification, no significant differences were found between the mean of FC and disease location, 311.5 µg/g, 178.7 µg/g and 223.6 µg/g for L1, L2 and L3, respectively ($p = .216$) and 169.6 µg/g for L4 ($p = .289$). Similarly, no differences were found between the mean of FC and the phenotype of the disease, 218.5 µg/g, 325.9 µg/g and 288.6 µg/g for B1, B2 and B3, respectively ($p = .211$).

Thirteen patients (9%) had a relapse during follow-up, and the median time for relapse from the collection of FC sample was 5.7 ± 0.8 (range 2 to 6) months. After an evaluation of their inflammatory activity by endoscopy - 11 patients by SES-CD (mean of 11.4 ± 5.5 [7–25]), 2 patients by Rutgeerts score (range 3–4) - nine patients were started on corticosteroids and four on anti-TNF drugs.

There was no significant difference in the mean CRP values between patients who had a relapse and those who did not have a relapse by the end of the six months, 7.02 mg/L vs. 4.9 mg/L, $p = .236$.

The mean FC value was significantly higher in relapsers than in non-relapsers, 871.3 µg/g vs. 203.2 µg/g, $p < .001$.

The AUC of FC for clinical relapse at six months was 0.924 (Figure 1). The optimal FC cutoff value was 327 µg/g, corresponding to a sensitivity of 92.3%, specificity of 82.4%, PPV of 34.3% and NPV of 99.1%.

Of the 109 patients with FC values ≤ 327 µg/g, only one had a relapse at the end of the six months. On the other hand, 12 of 35 (34.3%) patients with FC values > 327 µg/g had a relapse and 23 of 35 (65.7%) patients with FC values > 327 µg/g did not have a relapse.

Among patients who had a relapse during the follow-up period, nine (69.2%) patients had only ileal involvement (L1) and in those patients the mean FC value was statistically higher as compared to the group that maintained remission, 808.4 µg/g vs. 239.4 µg/g, $p = .011$. Of the 11 patients included with colonic involvement (L2), mean FC value of 178.7 µg/g, none had a relapse during follow-up. Four out of the 62 patients (6.5%) with ileocolic involvement (L3) had a relapse during the follow-up period and a higher mean FC values were observed in these patients as compared to the non-relapsed patients, 1012.8 µg/g vs. 169.2 µg/g, $p < .001$.

Among the patients with ileal involvement (L1), the AUC of FC that predicted a relapse was 0.873 at the optimal FC value of 327 µg/g, corresponding to sensitivity, specificity, PPV and NPV values of 88.9%, 80.6%, 40% and 98%, respectively. Of the 51 patients with FC values ≤ 327 µg/g, only one (2%) had a relapse at the end of the six months. Eight of 20 (40%) patients with FC values > 327 µg/g had a relapse, and 12 of 20 (60%) patients with FC values > 327 µg/g did not have a relapse.

Table 1. Demographic and clinical characteristics.

	Relapsers	Non-relapsers	<i>p</i> value	Overall (%)
Number of patients	13 (9)	131 (91)		144 (100)
Gender				
Female	7 (9)	71 (91)	.981	78 (54.2)
Male	6 (9.1)	60 (90.9)		66 (45.8)
Mean age at FC sample	36.1 ± 11.6	38.7 ± 12.3	.468	38.4 ± 12.2
Disease duration (months)	101.5 ± 68.7	83.4 ± 67.7	.377	85 ± 67.7 [12–300]
Remission duration	16.9 ± 9.6	15.1 ± 6.8	.371	15.2 ± 7.1 [4–36]
Disease extension				
L1	9 (69.2)	62 (47.3)		71 (49.3)
L2	0	11 (8.4)	.254	11 (7.6)
L3	4 (30.8)	58 (44.3)		62 (43.1)
+ L4	0	13 (9.9)		13 (9)
Disease behavior				
B1	5 (38.5)	71 (54.2)		76 (52.8)
B2	7 (53.8)	39 (29.8)	.735	46 (31.9)
B3	1 (7.7)	21 (16)		22 (15.3)
+ Perianal disease	2 (15.4)	29 (22.1)		31 (21.5)
Smoking status, <i>n</i> (%)				
Never smoked	9 (8.3)	100 (91.7)		109 (75.7)
Current smoker	3 (9.7)	28 (90.3)	.512	31 (21.5)
Ex-smoker	1 (25)	3 (75)		4 (2.8)
Previous surgery				
Yes	3 (9.1)	30 (90.9)	1	33 (22.9)
No	10 (9)	101 (91)		111 (77.1)
Therapy				
Azathioprine	7 (53.8)	104 (79.4)	.075	111 (77.1)
6-Mercaptopurine	1 (7.7)	2 (1.5)	.249	3 (2.1)
Methotrexate	1 (7.7)	4 (3.1)	.381	5 (3.5)
Anti-TNF	8 (61.5)	55 (41.9)	.242	63 (43.8)
Combination therapy	4 (30.8)	34 (47.9)	.745	38 (26.4)
CRP, mean ± SD, mg/L	7.02 ± 7.9	4.9 ± 5.7	.236	5.2 ± 5.9
FC, mean ± SD, µg/g	871.3 ± 434.9	203.2 ± 253.5	<.001	263.5 ± 333.5
Leukocytes, mean ± SD, mg/L	6.9 ± 1.3	7.3 ± 1.6	.406	7.2 ± 1.5
ESR, mean ± SD, mm/h	21 ± 9.9	21.8 ± 10.3	.786	21.7 ± 10.2
Albumin, mean ± SD, mg/L	3.6 ± 0.7	3.7 ± 0.7	.798	3.7 ± 0.7

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FC: fecal calprotectin; SD: standard deviation.

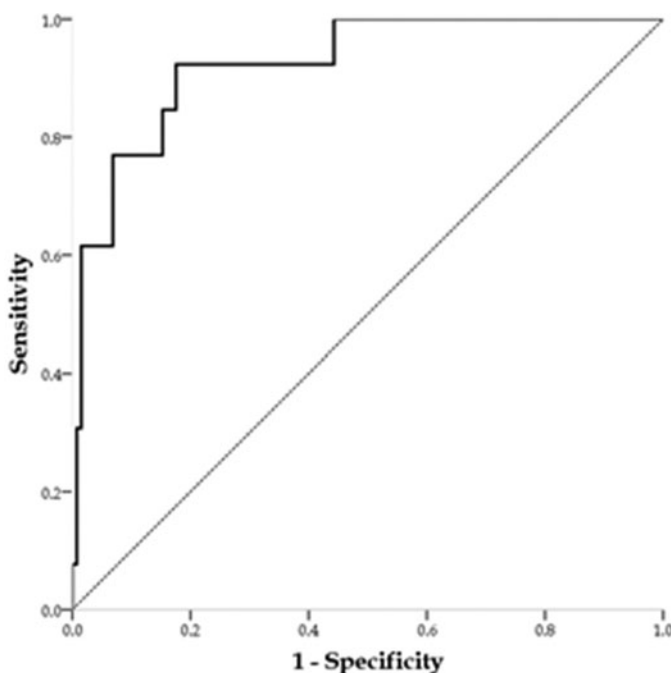


Figure 1. Receiver operator curve for fecal calprotectin in predicting relapse in patients with Crohn's disease. Area under the curve (AUC) for FC is 0.924 (95% confidence interval, 0.854–0.993; $p < .001$).

Of patients with L3 involvement, the AUC used to predict relapse was 1, and the optimal FC cutoff value that optimized both sensitivity and specificity of 100% was at 910

µg/g. At this cutoff value, of the 58 patients with FC values ≤ 910 µg/g, none had a relapse at the end of the six months. On the other hand, all patients, 4 (100%), with FC > 910 µg/g, had a relapse.

The Kaplan–Meier curve of time-to-relapse, according to FC, is presented in Figure 2. The estimated relative risk of relapse in patients with FC values > 327 µg/g is 45.17 time higher than in patients with FC values ≤ 327 µg, $p < .001$ using log-rank test.

Discussion

Mucosal healing is the endpoint which is associated with a better prognosis in CD [4–7].

Colonoscopy is considered the gold standard to detect and quantify bowel mucosa inflammation, but it is an invasive procedure and does not allow an evaluation of all the segments of the bowel. Hence, monitoring with noninvasive tests throughout the IBD treatment is attractive and allows early identification of relapse and optimization of therapy.

An ideal, noninvasive test for CD still does not exist, but it should be simple, easy to perform, acceptable for patients, well correlated with intestinal inflammation, responsive to appropriate treatment, be able to detect relapse with 100% sensitivity and specificity and should be reproducible.

In CD, literature evidence has consistently demonstrated the utility of FC as a screening tool to identify bowel inflammation [16], to predict clinical and endoscopic response to

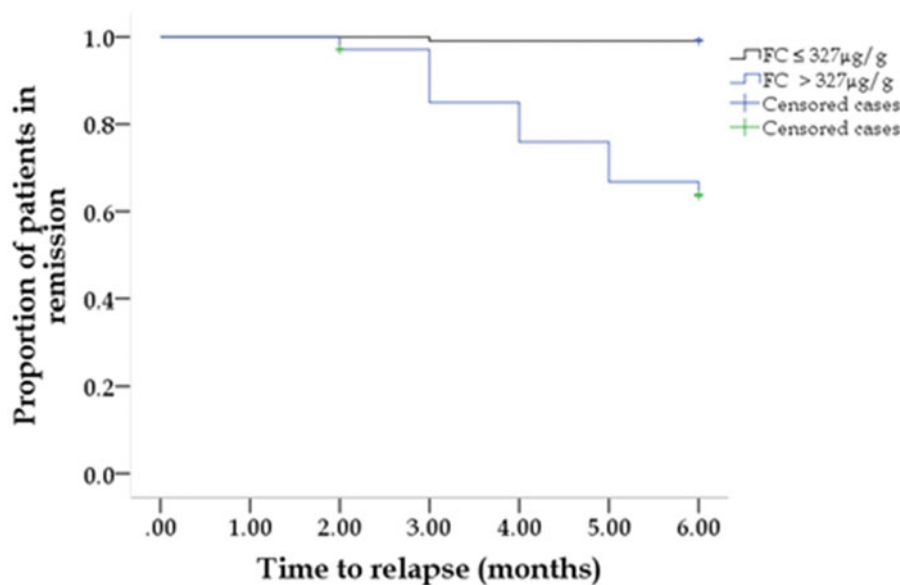


Figure 2. Kaplan–Meier curves of time-to-relapse according to $FC \leq 327 \mu\text{g/g}$ and $FC > 327 \mu\text{g/g}$. Log rank test for equality of survival distribution, $p < .001$.

treatment [17,18], clinical relapse in asymptomatic patients and predict early endoscopic recurrence [19].

In this study, 13 (9%) patients had a clinical relapse at six months. This value is relatively low [20,21], but similar to the series as Naismith et al. which showed this proportion to be 11% [22], and Mooiweer et al. found this proportion to be 2.8% [23]; this difference could be explained by the inclusion of patients under immunosuppressive therapy and the shorter follow-up periods used in our series as compared to others with at least 12 months of follow-up period [20,24,25].

In our study FC values $< 327 \mu\text{g/g}$ was predictive of low risk of clinical relapse within six months in CD patients with remission. FC has shown to have an excellent sensitivity for relapse (92.3%); however, it has a low PPV, 34.3%, suggesting that FC is more useful in predicting remission than relapse, similar to other series [22,23,26].

FC has been demonstrated as a relapse predictor biomarker in CD patients in clinical remission [13,17,20,22–29]. Molander et al. demonstrated that a normal FC ($< 100 \mu\text{g/g}$) after induction therapy with TNF alpha antagonists predicts sustained clinical remission in CD patients [17]. On the other hand, FC levels of $< 130 \mu\text{g/g}$ are associated with maintained disease remission, with an NPV of 100%, whereas $FC > 300 \mu\text{g/g}$ predicts relapse with a PPV of 78.3% [29].

FC has been shown to have a greater predictive capacity for relapse in patients with UC than in CD [26,30]. Regarding the disease location, the data on CD are conflicting, and the prediction of accuracy has been greater for colonic [20,28] or ileocolonic involvement [13] and for inflammatory behavior [20,26]. Regarding the small bowel involvement, the value of FC remains unclear [13].

The cutoff point to identify patients at increased risk of relapse varies in different studies, with a range of 50–340 $\mu\text{g/g}$ [13,17,20,22–29], which also seems to be disease and phenotype dependent.

In our study, we only included 11 patients at remission with colon involvement (L2), and none had a relapse at six months, which precludes an association between FC and this

involvement. Nevertheless, we have demonstrated that even in patients with single terminal ileum involvement (L1), FC is predictive of relapse, with AUC of 0.873, and this finding is consistent with the fact that FC is correlated to inflammatory activity detected in small bowel [31].

Although only four patients with ileocolitis involvement have relapsed, it has been verified in this group that the optimal cutoff is higher than for ileal disease and it also corresponds to a higher accuracy for relapse, with an AUC of 1, since no patient with an FC value $\leq 910 \mu\text{g/g}$ had a relapse, and all patients (100%) with $FC > 910 \mu\text{g/g}$ had a relapse at six months.

There are conflicting data regarding role of CRP in predict relapse, several studies have shown a positive association with this outcome [32–35]; however, in our study CRP was not demonstrated a predictor of relapse, which is in agreement with some others studies [20,24] and with the fact that it is a nonspecific inflammatory biomarker in IBD [8].

There are limitations in this study that need to be addressed. Clinical remission at baseline was defined by CDAI; this index has subjective criteria [14] and is poorly correlated with endoscopic inflammation [2,36]. Simultaneous endoscopic evaluation in remission period was not assessed, which could be a remarkable point, since data in literature suggest that a high proportion of CD patients in clinical remission still have subclinical mucosal inflammation [2,37]. However, previous studies have already established the correlation between FC values and endoscopic CD activity [10,11,38], which shows its utility in monitoring disease activity. Another limitation of this study is its retrospective nature and, coupled with the heterogeneity of clinical and analytical monitoring timings among patients in outpatient clinic, implies the need for a relatively short six-month follow-up period relative to FC.

Despite these limitations, this is one of the largest series in the literature including only CD patients in clinical remission.

The role of FC in monitoring CD activity is constantly evolving. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program recommends endoscopic healing combined with patient reported outcomes as therapeutic targets; nonetheless, CRP and FC are not treatment targets but adjunctive tools. Elevation of these biomarkers may reflect residual intestinal inflammation, and endoscopy and/or sectional imaging should be performed before optimizing medical treatment regardless of the patient's symptoms [12].

However, recently, the CALM trial demonstrated higher MH rates at 48 weeks in a tight control algorithm based on biomarkers such as CRP and FC in addition to clinical symptoms, 46%, compared to a clinical management group alone, 30%, in patients with moderate to severe CD [18].

Based on these findings, it is suggested that therapeutic optimization based on FC can be a reliable option in clinical practice and should be incorporated into the STRIDE guidelines [39].

Furthermore, in clinical practice, in patients with clinical remission, the systematic endoscopic evaluation to confirm resolution of inflammation ('treat to target' approach) is difficult to apply in all patients and is usually performed in patients with clinical relapse to determine inflammatory activity.

Therefore, a biomarker, such as FC, which reflects intestinal inflammation in patients in clinical remission, is really required.

In conclusion, FC may be an auxiliary, noninvasive tool to distinguish patients in clinical remission at low risk ($FC \leq 327 \mu\text{g/g}$) of high risk ($FC > 327 \mu\text{g/g}$) of relapse. This strategy improves the quality of IBD care by discerning the patients less likely to require intensive health care services, from those who need an early intervention, invasive procedures such as endoscopy, and also by determining the timing of surveillance on outpatient basis, allowing substantial resource savings.

Disclosure statement

The authors declare that there is no conflict of interests regarding the publication of this article.

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