Original Article

PORTO BIOMEDICAL JOURNAL
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Fecal calprotectin as an inflammatory biomarker in small bowel Crohn disease

Maria I. Sousa[a,b,*], Emanuel Dias[a], Patrícia Andrade[a], Guilherme Macedo[a]

Abstract

Background: Small bowel capsule endoscopy (SBCE) is an essential tool for evaluation of small bowel (SB) Crohn disease (CD). Fecal calprotectin (FC) represents an important biomarker of intestinal inflammation, widely used in ulcerative colitis and CD. Our aim was to evaluate the role of FC for diagnosing inflammatory activity in patients with isolated SB CD and how it correlates with SBCE findings.

Methods: This is a retrospective study conducted in a tertiary inflammatory bowel disease referral center that included patients with SB CD who underwent SBCE between January 2017 and February 2023. FC value was obtained from the closest stool examination to SBCE.

Results: One hundred ninety-six patients were included: 123 were women (63%) with a mean age of 44.2 years. In the SBCE, 127 (65%) patients had a Lewis Score ≥135 and, among the 94 patients with FC >200 μg/g, 23 had LS <135, 36 had LS between 135 and 790, and 35 had LS ≥790. FC levels were predictive of endoscopic lesions in SBCE, with significant correlation between FC level and total LS (Pearson correlation coefficient 0.43, $P<.001$). The sensitivity and specificity were calculated for each cut-off value being respectively 78% and 45% for FC = 100 μg/g, 69% and 59% for FC = 150 μg/g and 67% and 67% for FC = 200 μg/g.

Conclusion: FC showed moderate correlation with endoscopic findings in SBCE in SB CD. It is, therefore, a reasonable marker for predicting significant inflammatory lesions in SBCE; however, none of the cut-off had a high sensitivity or specificity.

Keywords: Small bowel Crohn disease, fecal calprotectin, small bowel capsule endoscopy

Introduction

Crohn disease (CD) is a chronic gastrointestinal inflammatory disease, with an estimated incidence rate ranging from 0.3 to 12.7 new cases per 100,000 people in Europe[1] and showing an increasing trend in both adults and children.[2,3] Most cases are diagnosed during third and fourth decades of life although it may also affect children or older individuals.[1] It may involve any segment along the gastrointestinal tract, most commonly terminal ileum and colon. Abdominal pain and diarrhea are the most common symptoms, followed by systemic complaints of fatigue, fever and weight loss.[4] It is characterized by segmental and transmural involvement.[1,5,6] It may also present with extraintestinal symptoms such as arthritis, uveitis, and skin rash, which sometimes precede diagnosis.[2,6] At diagnosis, 56%–81% of patients have an inflammatory phenotype, although 51% of them will develop into stricturing or penetrating phenotypes requiring surgery 20 years later.[7]

Clinical, biochemical, stool, imaging, and endoscopic findings, including ileocolonoscopy with biopsy and small bowel (SB) enteroscopy, are all important and complementary diagnostic tools.[3,4] Fecal calprotectin (FC) is a particularly important inflammatory stool biomarker that has demonstrated good correlation with clinical symptoms and endoscopic disease activity in colonic disease[8,9] and, therefore, can be clinically useful in selecting patients that require an invasive endoscopic evaluation. However, its role in SB inflammation has been less well studied.[10]

Therefore, we performed a study that aims to determine if FC levels correlate with the presence of lesions in small bowel capsule endoscopy (SBCE) and whether it may be a clinically useful tool to predict SB endoscopic activity.

Materials and methods

Study design and participants

All adult patients with follow-up in specialized inflammatory bowel disease (IBD) consultation at Centro Hospitalar Universitário de São João (Porto, Portugal) for known isolated SB CD who underwent SBCE for monitoring of CD and FC measurement between January 2017 and February 2023 were eligible for this retrospective study. These patients were consecutively selected. CD was classified according to Montreal classification (Table 1).[11] Patients were excluded if they had any evidence of colonic involvement by CD, if there was history of ingestion of

[a] Gastroenterology Department, Centro Hospitalar Universitário de São João, Porto, Portugal, [b] Faculty of Medicine, University of Porto, Porto, Portugal

* Corresponding author: Faculty of Medicine, University of Porto, Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal. E-mail address: iness0806@gmail.com (Maria I. Sousa).

Porto Biomed. J. (2024) 9:4(e263)

Received: 14 May 2024 / Received in final form: 8 July 2024 / Accepted: 14 July 2024

http://dx.doi.org/10.1097/j.pbj.0000000000000263

Table 1

Baseline characteristics.

Female sex, n (%)	123 (63)
Age, years	44.2
Hemoglobin, g/dL	13.7 (1.5)
Leucocytes, $\times 10^9$/L	21.4 (97.8)
Platelets, /L	267726.4 (84029.2)
Albumin, g/dL	41.9 (3.5)
CRP, mg/dL	5.0 (5,4)
FC, μg/g	157 (317)
Previous surgeries, n (%)	67 (34.2)
Previous hospitalizations, n (%)	75 (38.3)
Previous IV CCT, n (%)	15 (7.7)

Hemoglobin, leucocytes, platelets, albumin, and CRP are expressed by its mean and standard deviation, and FC is expressed by its median and IQR. Previous intravenous corticotherapy (IV CCT).

nonsteroidal anti-inflammatory drugs, glucocorticoids, or proton pump inhibitors in the 6 weeks preceding FC measurement, if there was active infection, or if there was history of colorectal cancer, human immunodeficiency virus infection, or graft-versus-host disease, according to clinical records. Clinical and demographic data were retrospectively reviewed from the hospital electronic medical records. Endoscopy reports from colonoscopy and SBCE were carefully reviewed for each patient. The time interval between SBCE and colonoscopy varied within range of 2–8 weeks.

All patients underwent SBCE after performing a patency capsule test to ensure there was no risk of capsule retention, particularly those with a history of stricturing disease, and after performing bowel preparation the day before with 1L of a polyethylene glycol-based solution. In our study, no adverse effects of SBCE were documented. Two main scores can be utilized (Lewis Score—LS and Capsule Endoscopy Crohn's Disease Activity Index—CECDAI) for analyzing activity in SBCE, both validated and with a high correlation.[12] In our study, inflammatory status was classified according to the Lewis score as no inflammation (LS <135), mild disease (135 < LS < 790), and moderate-to-severe disease (LS ≥790),[13] depending on the presence of edema and erythema, number of ulcers or aphthae, and presence of stenosis. FC level was collected from the closest stool examination to SBCE, with a maximum interval of 6 months between these two.

Statistical analysis

Statistical analysis was performed using the SPSS 27.0 software package. Categorical variables were expressed as frequencies and percentages and compared using the chi-square or Fisher exact test. Continuous variables were expressed as mean and standard deviation for variables with normal distribution or median and interquartile range for variables with skewed distribution and compared using the Student *t* test or nonparametric test. A 2-tailed $P < .05$ was considered statistically significant. The best cut-off value of FC to predict inflammatory lesions was chosen considering the point at which both sensitivity and specificity reached their maximum. The diagnostic accuracy of FC for the prediction of significant inflammatory lesions (LS ≥135) was assessed by the receiver operating characteristic (ROC) curve, which demonstrates the relationship between false positives and true positives of our test. The area under the receiver operating characteristic curve (AUROC) represents the probability of this test correctly assessing inflammation, in this case, between a randomly chosen false positive and a randomly chosen true positive value, in order to assess the diagnostic accuracy of FC in detecting SBCE inflammatory lesions. The relation between the variables was defined through Pearson correlation.

The present study complies with current regulations on bioethical research and was appropriately evaluated and approved by the Ethics Committee of Centro Hospitalar Universitário de São João in Porto, Portugal. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. This article does not contain personal information that could identify the study patients.

Results

A total of 196 patients were included (Table 1), including 123 (63%) female patients, with a mean age of 44.2 years. The flow of participants recruited for this study is shown in Fig. 1 and their

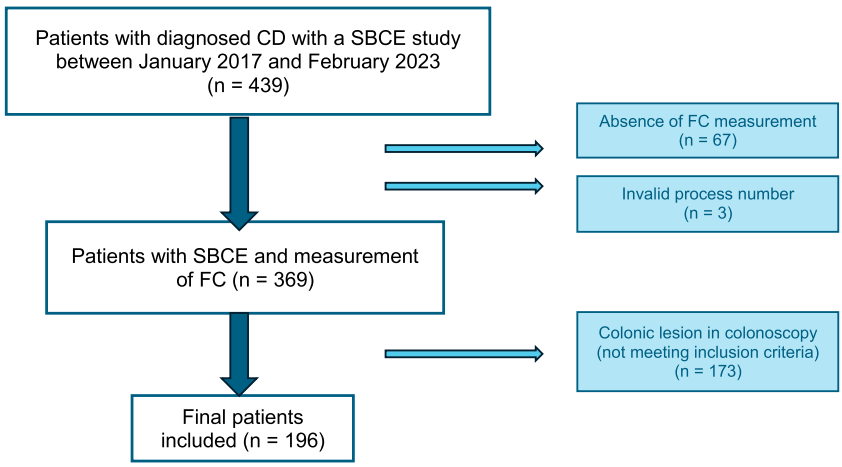

Figure 1. Flowchart for patient recruitment to this study.

Table 2

Montreal classification.

	Number of patients (%)
Age (A)	
A1: younger than 16 years	5 (3)
A2: 17 years–40 years	116 (59)
A3 older than 40 years	75 (38)
Location (L)	
L1: ileal	180 (92)
L2: colonic	0 (0)
L3: ileocolonic	0 (0)
L4: upper gastrointestinal tract	16 (8)
Behaviour (B)	
B1: non-stricturing, non-penetrating	168 (86)
B2: stricturing	7 (9)
B3: penetrating	11 (6)
p: perianal disease	14 (7)

Adapted from Satsangi et al.[11]

characteristics according to the Montreal Classification are described in Table 2.

SBCE was complete in 187 (95%) patients. Erosions were found in 157 (80%) patients and stenoses in 20 (10%). Additional investigation with colonoscopy was performed in 186 (95%) patients, 183 (93%) of whom additionally performed ileoscopy, which revealed ulcers in terminal ileum in 94 (48%) patients. Considering this subgroup of patients who performed ileoscopy during colonoscopy, out of 114 patients with FC >100 μg/g, 50 (44%) presented normal mucosa in the ileoscopy, whereas among 94 patients with FC >150 μg/g, 40 (43%) did not show lesions suggestive of CD. Out of 76 patients with FC >200 μg/g, 32 (42%) did not present CD lesions.

LS was provided for 151 (77%) patients. When stratifying FC values within 3 groups, an analysis of LS was performed (Table 3). Among patients with FC <100 μg/g (group I), 21 patients had LS <135, 25 patients had LS between 135 and 790, and 10 patients had LS ≥790. Among patients with FC <150 μg/g (group II), 26 patients had LS <135, 35 patients had LS between 135 and 790, and 14 patients had LS ≥790. Among patients with FC < 200 μg/g (group III), 31 patients had LS <135, 40 patients had LS between 135 and 790, and 16 patients had LS ≥790. Finally, among patients with FC > 200 μg/g, 23 patients had LS <135, 36 patients had LS between 135 and 790, and 35 patients had LS ≥790.

FC levels were predictive of endoscopic lesions identified in SBCE, with significant correlation between FC level and total LS (Pearson correlation coefficient 0.43, $P < .001$). When considering individual terciles, FC correlated with LS in the third tercile (Pearson correlation coefficient 0.33, $P = .003$), but not in the first ($P=.251$) or second tercile ($P = .300$).

For each FC value, sensitivities and specificities were analyzed for the detection of significant inflammatory lesions (LS ≥135), which are represented in Table 4. Hence, considering a cut-off of FC <100 μg/g, the sensitivity is 78%, and the specificity is 45%. If the cut-off value is FC <150 μg/g, the sensitivity decreases to 69%, and the specificity increases to 58%. Finally, if we consider FC <200 μg/g as the cut-off value, the sensitivity is 67%, and the specificity is 67%.

AUROC value is 0.689 (95% CI, 0.594–0.785), for $P < .005$, and its curve is represented in Fig. 2.

Discussion

Inflammatory biochemical markers, such as C-reactive protein (CRP), play a key role in diagnosis and monitoring of disease activity and treatment response in IBD patients.[14] Interestingly, FC has demonstrated better correlation with inflammatory status than CRP or leucocyte counts in these patients,[15-17] and recent prospective studies have suggested it may play an important role in SB CD,[18-20] even in the absence of colonic endoscopic abnormalities.[21] In fact, there is growing interest in FC as a novel gastrointestinal inflammatory biomarker for diagnosis and monitoring of patients with IBD[22,23] due to improved correlation with endoscopic activity when compared with other markers like CRP.[24-26]

Magnetic resonance enterography, computed tomography enterography, and intestinal ultrasound (IUS) are other useful complementary methods for evaluation of SB CD.[27] IUS is cheaper, widely available, and safer,[28] whereas all the three have comparable accuracy for assessing SB inflammatory activity.[29] However, they are costly and time-consuming, and there is a growing need to identify a noninvasive inflammatory marker that is cost-effective for accurately selecting patients that will mostly benefit from these examinations and improving the regular and somewhat invasive monitoring of these patients.

Studies focused on the accuracy of FC as inflammatory biomarker for SB CD are heterogeneous. In fact, some studies show that FC has limitations in evaluating SB inflammation,[30] whereas others found FC useful in predicting which patients would benefit from SBCE after normal endoscopy.[25,31,32] This difference between colonic and SB CD is based on multiple reasons because colon has a larger surface area, and therefore, more inflammation is present, being also more sensitive to it. There is less dilution and modification of FC as it is closer to the exit of gastrointestinal tract and, simultaneously, intestinal transit is faster. Finally, the fact that colonoscopy scores are better validated contributes to this.[33,34] Additionally, there are studies that suggest that FC has comparable accuracy in predicting endoscopic lesions in patients with isolated SB CD compared with those with colonic or ileocolonic CD[35,36] and that it is useful to distinguish between active and inactive SB CD[37] and as a reliable marker for endoscopic remission and mucosal healing.[38] Nevertheless, its true accuracy as well as the best cut-off value remain to be determined.

Regarding our study, and analyzing Table 3, we were able to understand that, considering patients with FC <100 μg/g, only 38% of them did not have significant lesions in the SBCE (LS <135). Considering FC <150 μg/g, only 34% of patients did not present these lesions. Finally, considering FC <200 μg/g,

Table 3

Relation between FC and LS values.

	FC <100 μg/g (group I)	FC <150 μg/g (group II)	FC <200 μg/g (group III)
LS <135	21 (38%)	26 (34%)	31 (36%)
LS 135–790	25 (44%)	35 (47%)	40 (46%)
LS ≥790	10 (18%)	14 (19%)	16 (18%)
Total	56 patients	75 patients	87 patients

Table 4

Sensitivities and specificities for FC at various cut-off levels.

	Sensitivity (%)	Specificity (%)
FC = 100 μg/g	78	45
FC = 150 μg/g	69	59
FC = 200 μg/g	67	68

36% of these patients did not present lesions. This information, along with the analysis of sensitivity and specificity values, suggests that even with a higher FC cut-off value, true negatives (LS <135) remain low. In fact, none of the cut-off had high sensitivity *and* specificity.

Literature review shows conflicting results.[39-42] A recent meta-analysis of 14 studies, encompassing 8 prospective studies, involving 1094 patients, indicated that a value of 100 μg/g correlated with SB CD lesions, showing a sensitivity of 0.725 (95% CI, 0.657–0.784) and a specificity of 0.728 (95% CI, 0.622–0.814).[8] Another study by Koulaouzidis et al,[42] showed that patients with a FC ≥200 μg/g should have higher indication to perform SBCE, since this cut-off was the one with a higher sensitivity (for a FC ≥200 μg/g, sensitivity 50% and a positive predictive value of 0.78). On the other hand, a study by Olsen et al[41] concluded that FC alone cannot be used as a selection method for SBCE in patients with CD, as the sensitivity and specificity for FC cut-off of 100 μg/g is 41.7% and 84.1%, respectively, with a ROC of 0.626 (95% CI, 0.523–0.730).

Overall, in our study, FC showed moderate correlation with LS but none of the cut-offs had high sensitivity or specificity. FC alone as a biomarker cannot be applied as a selective method for SBCE. Even considering a cut-off of 100 μg/g, the sensitivity remains low, thereby rendering it a moderate inflammatory marker. With respect to correlation with LS in specific terciles, a fair correlation was present only in the third tercile of LS, consistent with the findings of Monteiro et al,[39] possibly explained by the fact that the majority of inflammatory lesions are located in the third tercile.

Our study has some limitations, related to its retrospective single-center design and small sample size, which was mainly related to the fact that FC measurement was only introduced in 2017. Consequently, we had to admit a wide maximum interval time between SBCE and FC measurement of 6 months, which could interfere with correlation measurement, although there were no therapeutic changes or clinical relapse during that interval for any patient.

Prospective studies to better determine the correlation between FC and isolated SB CD activity are still needed. Perhaps additional investigations ascertaining the value of combinations of inflammatory biomarkers to assess disease activity may result in clinically useful information.

In conclusion, FC is a reasonable inflammatory biomarker for SB CD that can be a useful tool for patient monitoring and, together with clinical symptoms and other inflammatory markers, for selecting patients for SBCE, which remains an

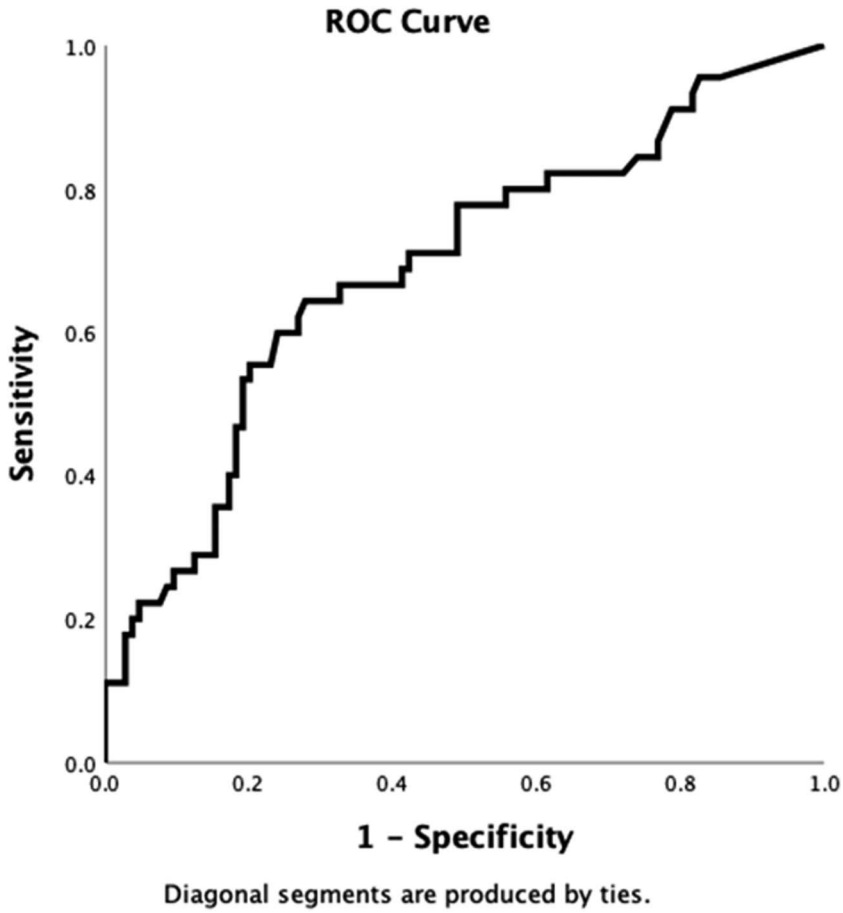

Figure 2. ROC curve for FC as a marker for predicting inflammatory lesions on SBCE.

essential tool for accurately diagnosing and monitoring patients with isolated SB CD.

Acknowledgements

Assistance with the study: The authors gratefully acknowledge the Department of Gastroenterology of Centro Hospitalar Universitário São João for allowing this study to be carried out, providing technical and consultancy support.
Financial support and sponsorship: none.
Conflicts of interest: none.
Presentation: none.

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