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Variation of faecal calprotectin level within the first three months after bowel resection is predictive of endoscopic postoperative recurrence in Crohn's disease

Running title: Calprotectin and CD postoperative recurrence

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ABSTRACT:

Background: Early prediction of postoperative recurrence (POR) remains a major concern in Crohn's disease (CD).

Aims: To assess serial faecal calprotectin (Fcal) monitoring within the first three months to predict CD endoscopic POR.

Methods: In a multicenter randomized controlled trial, CD patients received azathioprine 2.5 mg/kg/day with oral curcumin (3g/day) or placebo. Fcal was measured at baseline, one month (M1) and M3. Endoscopic POR at M6 was defined as Rutgeerts' index ≥ i2b (central reading).

Results: Among the 48 patients included, there was no significant difference of median Fcal levels at baseline (p=0.15), M1 (p=0.44) and M3 (p=0.28) between patients with or without endoscopic POR at M6. Fcal kinetics during the first 3 months after surgery was significantly different between the patients with or without POR at M6 (p=0.021). The median variation between Fcal level at baseline and M3 (ΔFcal M3-M0) was significantly higher in patients with endoscopic POR compared to those without POR (p=0.01). ΔFcal M3-M0 >+10 % demonstrated the best performances to predict endoscopic POR at M6 (AUC=0.73, sensitivity=64.7%[41.1-82.7], specificity=87.5%[68.0-96.3], negative predictive value=77.8%[57.5-91.4] and positive predictive value=78.6%[49.2-95.3]).

Conclusion: Fcal variation within the first three months after ileocolonic resection is a promising predictor of early endoscopic POR in CD patients.

Key words: Postoperative recurrence; Crohn's disease; Faecal calprotectin; surgery; monitoring

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease that can lead to altered quality of life and high disability for the patients[1,2]. Despite an increased ~~widespread~~ use of biologics, approximately one half of the patients still require~~ing~~ ~~a~~ CD-related surgery during the course of the disease[1]. As bowel resection is not curative, postoperative recurrence (POR) remains a major concern in CD. In referral centers, up to 75 % of the patients experienced a significant endoscopic POR within the first year after surgery [3]. In 1990, Rutgeerts and colleagues proposed an index based on early endoscopic findings, so-called the Rugeerts' index, which was highly predictive of clinical and surgical POR[4]. More recently, the landmark POCER trial [5] confirmed previous data [6–8] showing that performing a colonoscopy at 6 months with therapeutic intensification according to the Rutgeerts' score was associated with a decreased risk of endoscopic POR at 18 months. Then, it is recommended in daily practice[9]

Several risk factors, assessed immediately after the surgery, have been identified to predict endoscopic POR in order to stratify the patients and to select those who will benefit from a more aggressive management[3]. Unfortunately, the performances of these predictive factors remain disappointing. For example, in the POCER trial almost 50% of the low-risk patients experienced endoscopic POR at 6 months. Rather than predicting POR at surgery, monitoring disease activity with biomarkers during the early postoperative period may guide the management of CD after ileocolonic resection [5]. In this context, the use of faecal calprotectin (Fcal) could be of great value as it has been shown as a surrogate marker of endoscopic activity as well as a reliable predictor of clinical relapse in IBD patients in clinical remission [10–14].

The aim of the present study was to assess the performance of serial Fcal monitoring within the first three months following intestinal resection to predict endoscopic POR in CD.

PATIENTS AND METHODS

Ethical considerations

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements including patients' consent. The study was approved by the local Ethics Committee ("CPP Sud-Est VI", #AU1109).

Design of the study

It was an ancillary study from a multicenter (8 centers), randomized controlled trial (#NCT02255370) comparing curcumin to placebo. All adult patients with CD who underwent ileocolonic resection with restoration of bowel continuity were recruited from November 2014 to September 2017. Patients received azathioprine 2.5 mg/kg once a day within the first 21 days after surgery and were randomized for either oral curcumin (3 g/day) or a placebo. Curcumin, a 95%-pure curcumin preparation, and identical placebo capsules were purchased (Europhartec, Lempdes, France). The primary endpoint was endoscopic POR at 6 months defined by an endoscopic Rutgeerts' score ≥ i2b.

Faecal calprotectin measurement

According to the study protocol, stools were collected for Fcal testing at inclusion (M0), one (M1) and 3 months (M3). For M0, the stools collection was performed the same day as the beginning of preventive treatment (azathioprine + curcumin or placebo). Stools samples were collected in the morning and immediately stored at 4 °C. Patients were instructed to transport the stool samples in a dedicated container at 4 °C. Faecal samples were immediately transferred, upon patient arrival, to Biochemistry Laboratory of each center to perform a local testing. Stool cultures were performed on all IBD samples to exclude gastrointestinal infection. NSAIDs use was forbidden during the study. Fcal was measured, as routinely performed in each IBD centre, using quantitative immunoassay (Bühlmann

Laboratories AG, Schönenbuch, Switzerland) and the results were expressed in µg/g. Fcal measurements were blinded from clinical disease activity and physicians managing the patients were blinded from Fcal results. Besides the level of Fcal, the relative variation of Fcal between two time points (expressed as percentage) was assessed as predictor.

Endoscopic evaluation

As recommended[5,9] an endoscopic assessment was performed six months after restoration of bowel continuity (M6). Patients were excluded when it was not possible to reach the anastomosis. All patients underwent a colonoscopy under general anesthesia after bowel cleansing. Colonoscopies were video-recorded for central reading to assess the presence of endoscopic POR according to the modified Rutgeerts' index by two experienced readers (G.B and A.B) blinded from clinical or biological data. In case of conflicting assessment, the two readers met to consensually determine the degree of endoscopic activity. Endoscopic POR was defined as Rutgeerts' index ≥ i2b. Clinical POR was defined as Rutgeerts' index.

Data managing and statistical analyses

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Clermont-Ferrand University Hospital [16]. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

The statistical analyses were carried out using the statistical software Stata (version 13, StataCorp, College Station, US). All statistical tests were conducted for a two-sided type I error at 0.05. Continuous variables were described as mean and standard-deviation or median

and interquartile range, according to statistical distribution (assumption of normality studied using Shapiro-Wilk test). Concerning non-repeated data, univariate analyses were performed using Student t-test or Mann-Whitney test when assumptions of t-test were not met (normality, homoscedasticity assessed by the Fisher-Snedecor test) for continuous variables, and Chi-squared or Fisher's exact tests for categorical data. ROC curve analysis was performed to determine the best cut-off value of relative variation of Fcal to predict endoscopic POR. In addition, the optimal threshold of Fcal variation was determined according to usual indexes reported in the available literature (Youden, Liu and efficiency) and to clinical relevance. Sensitivity, specificity and negative and positive predictive values were estimated with 95% confidence intervals. Repeated correlated data (evolution of calprotectin value) were analyzed using random-effects models, useful to study fixed effects (group, time-point evaluation and their interactions), taking into account between and within patient variability (subject as random-effect). A Sidak's type I error correction was applied to take into account the multiple comparisons. The normality of residuals was studied using the Shapiro-Wilk test and a logarithmic transformation of Fcal was proposed to achieve the normality. Multivariable analyses were carried out (for repeated or not data) in order to adjust results on usual risk factors of endoscopic POR: smoking status, CD behavior, prior bowel resection, gender, prior medications as well as the interval between time of surgery and Fcal measurement. A particular attention was paid on study of multicollinearity.

RESULTS

Baseline characteristics of the patients

Overall, 48 patients were included in our study. The main characteristics of these patients are detailed in **Table 1**. Among them, 18 patients (36%) presented with endoscopic POR (Rutgeerts score ≥ i2b) 6 month after surgery. The distribution of patients according to Rutgeerts' index was: i0 = 14 patients, i1 = 9 patients, i2a = 7 patients, i2b = 9 patients, i3 = 4 patients and i4 = 5 patients.

Early measurement of faecal calprotectin in predicting endoscopic POR

The interval between the time of surgery and the time of inclusion was not associated with the level of Fcal at baseline (p=0.48). Among the whole population, median levels of Fcal were 112 [81-298] µg/g at baseline, 100 [50-139] µg/g at M1 and 100 [58-192] µg/g at M3.

We did not observe any difference of Fcal levels at baseline (100 [50-190] *vs*. 166 [89-312] µg/g; p=0.15), M1 (93 [48-104] *vs*. 100 [50-180] µg/g; p=0.44) and M3 (100 [68-328] *vs*. 99 [50-100] µg/g; p=0.28) between patients with or without recurrence (**Figure 1**). Despite this, we searched for the best thresholds of Fcal at baseline, M1 and M3 to predict endoscopic POR at M6. The best cut-off values of FCal were ≥ 76 µg/g at M1 and > 102µg/g at M3 to predict endoscopic POR at M6. The results are presented in Table 2.

Variation of faecal calprotectin within the first three months in predicting endoscopic POR

We compared the kinetics of Fcal within the first three months after inclusion in patients with or without endoscopic POR at 6 months (**Supplementary Figure S1**). We found an interaction between the time of Fcal measurement and the level of Fcal to predict endoscopic POR at 6 months (p=0.021), meaning that the kinetics of Fcal values within the first three months following surgery was different between patients with or without endoscopic POR (**Figure 2**).

We calculated the relative variation (median) between the level of Fcal at baseline and M1 (ΔFcal M1-M0), at baseline and M3 (ΔFcal M3-M0) and at M1 and M3 (ΔFcal M3-M1) (**Table 3**). We did not find any significant difference regarding ΔFcal M1-M0 (p=0.48) or ΔFcal M3-M1 (p=0.17) comparing the patients with or without early endoscopic POR, respectively (**Table 3**). In contrast, the median ΔFcal M3-M0 was significantly higher in patients with endoscopic POR compared to those who did not (p=0.01) (**Figure 3**) (**Table 3**). The result was confirmed after adjusting the analysis on smoking status, CD behavior, prior history of bowel resection and concomitant therapy with curcumin or placebo (p = 0.021).

Using a ROC curve (area under the curve = 0.73) (**Supplementary Figure S2**), we determined that an increase of Fcal between baseline and M3 (ΔFcal M3-M0) > +10 % demonstrated the best performances to predict endoscopic POR at 6 months (sensitivity = 64.7 % [41.1-82.7], specificity = 87.5 % [68.0-96.3], negative predictive value = 77.8% [57.5-91.4] and positive predictive value = 78.6% [49.2-95.3]) (**Table 2**).

DISCUSSION

In this study, we showed that the variation of Fcal level within the first three months after intestinal resection could be helpful to predict the risk of early endoscopic POR in patients with CD.

The identification of non-invasive tools that can improve therapeutic management to prevent CD POR is still crucial. As the accuracy of the available factors remains poor to stratify the patients according to their risk of early endoscopic POR, serial Fcal testings within the first three months after surgery could enable to tailor postoperative management for each patient. The current medications, especially biologics, will be probably more effective at the earliest stage of the POR. It is why early detection of endoscopic POR using repeated Fcal measurement is a promising way to decrease the prevalence of endoscopic POR.

The Rutgeerts' index is hitherto the best predictor of symptomatic recurrence (clinical POR) in patients with CD[4]. The best cut-off value of this index is still matter of debate. While the historical works from Leuven, Belgium, suggested to use an index ≥ i2 [4], some authors proposed recently to differentiate i2-patients into two groupes, *i.e.* i2a (lesions confined to the anastomosis) and i2b (more than 5 apthous ulcers)[15–19]. This recommendation aimed to avoid the misclassification of the lesions confined to the anastomosis, which could be due to ischemic lesions. We chose to define endoscopic POR as Rutgeerts' index ≥ i2b. This choice was reinforced by some data from our group showing that the main factor impacting the level of Fcal is the area of affected lesions[11]. Then, it was expected to achieve higher performances with Fcal testing in choosing this threshold.

In our study, the levels of Fcal at baseline (= time of medication onset), M1 and M3 were not significantly different between patients with or without early endoscopic POR. These data seem conflicting with the study from Sorrentino *et al.* [15], which observed a

difference as soon as after two months. However, the sample size was small in this pilot study (25 patients) with only a few patients with available stools samples at each time point. In addition, as we investigated the interval between medication onset and early systematic endoscopy (at M6), our data were not comparable with those demonstrating that the level of Fcal at M6 was significantly higher in patients with POR with Fcal > 100 µg/g as the best threshold to detect endoscopic POR[20–23]. In the same way, Yamamoto and colleagues found that the serial monitoring of Fcal after the 6 months-colonoscopy was helpful to predict late endoscopic POR within 24 months after the endoscopy[24]. They identified a level of Fcal > 140 µg/g as the best threshold[24]. In contrast, as suggested by Sorrentino and colleagues[15], we confirmed that the variation of Fcal is significantly different between patients with or without early endoscopic POR. We showed, for the first time, that the variation between baseline and M3 was highly predictive of endoscopic POR. We identified a relative increase > 10 % as the best predictor with negative and positive predictive values around 80%. Accordingly, we recommend to anticipate the ileocolonoscopy for the patients with a significant Fcal increase. Despite the substantial performances of this faecal biomarker, the Rutgeerts' index is still the best predictor of the postoperative course in CD. Accordingly, we proposed a new algorithm using Fcal in ~~in~~ the management of POR in patients with CD after ileocolonic resection **Figure 4**).

We have to underline some limitations in our study. We did not perform any central testing of Fcal, which could partly explain that we did not identify any threshold of Fcal, especially at M3, to accurately predict endoscopic POR at M6. Besides, as it was an ancillary study from a clinical trial, we did not perform any sample size calculation. However, it is the first study dedicated on the potential role of Fcal in the very early postoperative period to predict POR, with a systematic stools collection at baseline, M1 and M3. The sample size was two-fold higher than the Sorrentino's study, which investigated this topic as a secondary

endpoint, and our sample size was sufficient to show significant difference with suitable power. The design of our initial clinical trial scheduled Fcal testing at baseline, M1 and M3. According to the data from Sorrentino's study showing that Fcal requires approximately two months to be normalized after bowel resection in patients with CD, it would have been interesting to explore the kinetics of Fcal values at baseline, M2, M4 and M6.

In conclusion, the variation of Fcal during the first months after intestinal resection is probably a reliable tool to predict early endoscopic POR. Our results advocate for the widespread use of serial Fcal monitoring in the early postoperative period. However, additional data from independent cohorts are warranted to confirm our results.

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TABLES

Table 1: Baseline characteristics of the 48 patients with Crohn's disease included in the analyses of this study.

Age at inclusion, (years), mean ± SD	35.3 ± 11.5
Disease duration, (years), median [IQR]	5.0 [1.0-10.0]
Female gender, n (%)	29 (60.4%)
Active smokers, n (%)	16 (33.0%)
Prior bowel resection, n (%)	23 (47.9%)
Montreal Classification	
CD location	
L1, n (%)	21 (43.7%)
L2, n (%)	2 (4.2%)
L3, n (%)	25 (52.1%)
CD behaviour	
B1, n (%)	9 (18.8%)
B2, n (%)	22 (45.8%)
B3, n (%)	17 (35.4%)
Perianal lesions, n (%)	3 (6.3%)
Prior steroids use	48 (100.0%)
Immunosuppressants-naïve patients	18 (37.5%)
Anti-TNF-naïve patients	10 (20.8%)
Current medications	
Thiopurines, n (%)	48 (100.0%)
Small bowel resection length, median [IQR], cm	20.5 [13.3-30.0]

n : number; CD: Crohn's disease; SD: standard deviation; IQR: interquartile range; Immunosuppressants: thiopurines or methotrexate

Table 2: Performances of faecal calprotectin to predict endoscopic postioperative recurrence at 6 months

Fcal cut-off value	**Time of evaluation**	**AUC**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
≥ 76 µg/g	M1	0.43 [0.26-0.64]	62.5% [38.5-81.5]	37.9 % [22.7-56.1]	35.7% [22.0- 54.3]	64.7% [40.0-82.5]
> 102µg/g	M3	0.59 [0.33-0.75]	44.4% [24.6-66.3]	76.0% [56.1-88.7]	57.1% [33.8-75.0]	65.5% [55.9-80.8]
> +10%	ΔFcal M3-M0	0.73 [0.57-0.89]	64.7 % [41.1-82.7]	87.5% [68.0-96.3]	78.6% [49.2-95.3]	77.8% [57.5-91.4]

Fcal: faecal calprotectin; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value; M1: at one month; M3: at 3 months; ΔFcal M3-M0: relative variation (median) between the level of Fcal at baseline and M3

Table 3: Comparison of the relative variation of faecal calprotectin within the first three months after surgery in patients with or without endoscopic postperative recurrence in Crohn's disease

	Overall population	Patients with endoscopic POR at 6 months	Patients without endoscopic POR at 6 months	p-value
ΔFcal M1-M0	- 20% [- 63%; +0%]	0% [- 63%; + 155%]	-33% [- 63%; 0%]	0.48
ΔFcal M3-M0	- 9% [- 60%; +60%]	+60% [- 47%; +217%]	-38% [- 64%; 0%]	0.01
ΔFcal M3-M1	0% [- 25%; +45%]	20% [- 8%; +110%]	0% [-33%; +7%]	0.17

Fcal: faecal calprotectin; M0: at baseline; M1: at one month; M3: at 3 months ΔFcal M1-M0: relative variation (median) between the level of Fcal at baseline and M1; ΔFcal M3-M0: relative variation (median) between the level of Fcal at baseline and M3; ΔFcal M3-M1: relative variation (median) between the level of Fcal at M1 and M3

FIGURES LEGENDS

Figure 1: Level of faecal calprotectin according to the occurrence of endoscopic POR at the time of medication onset, at one and three months after the surgery of the intestinal continuity restoration.

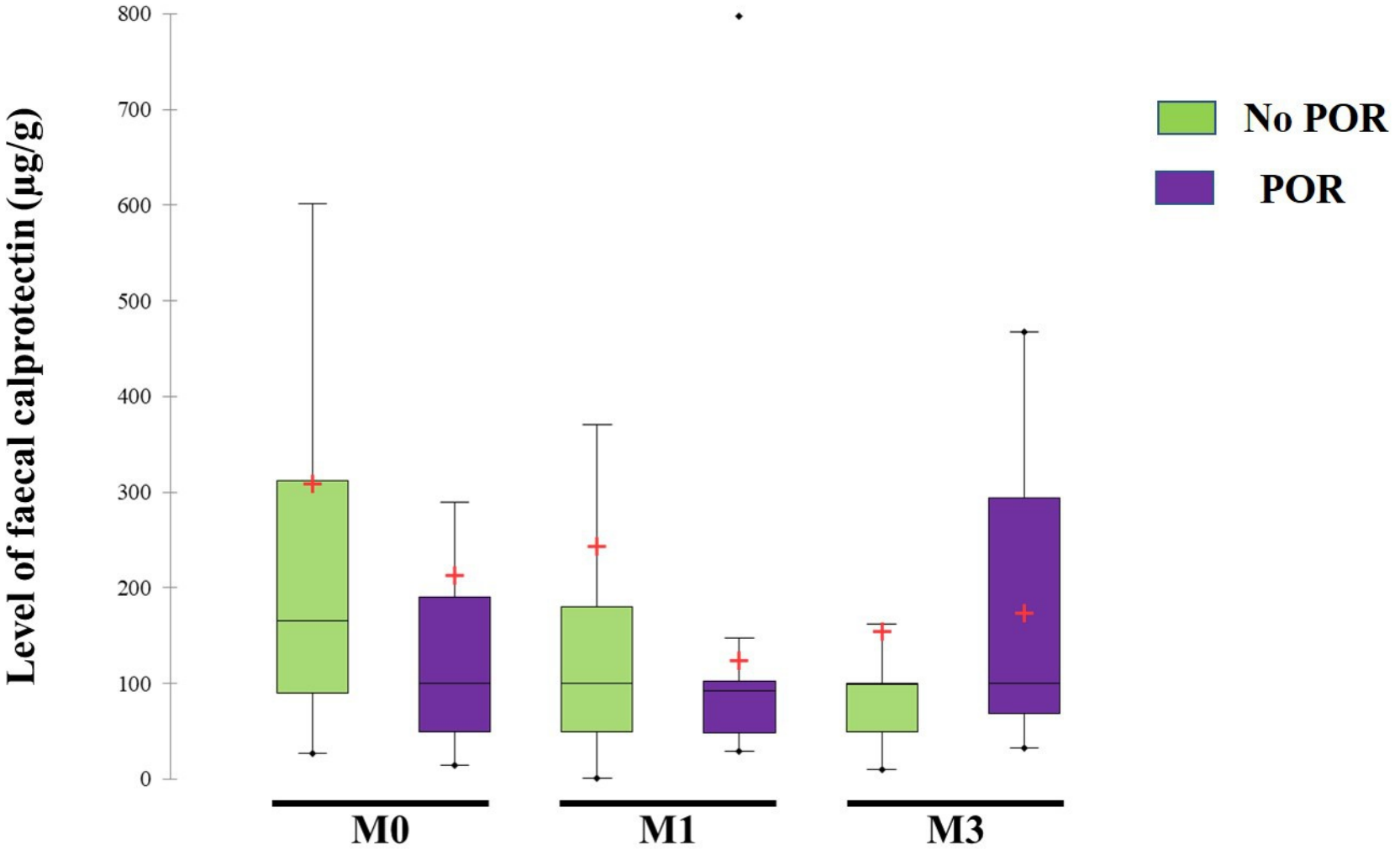
Figure 2: Kinetics of faecal calprotectin level in patients with or without postoperative recurrence (POR) within the first 3 months after surgery (represented as mean and standrad error).

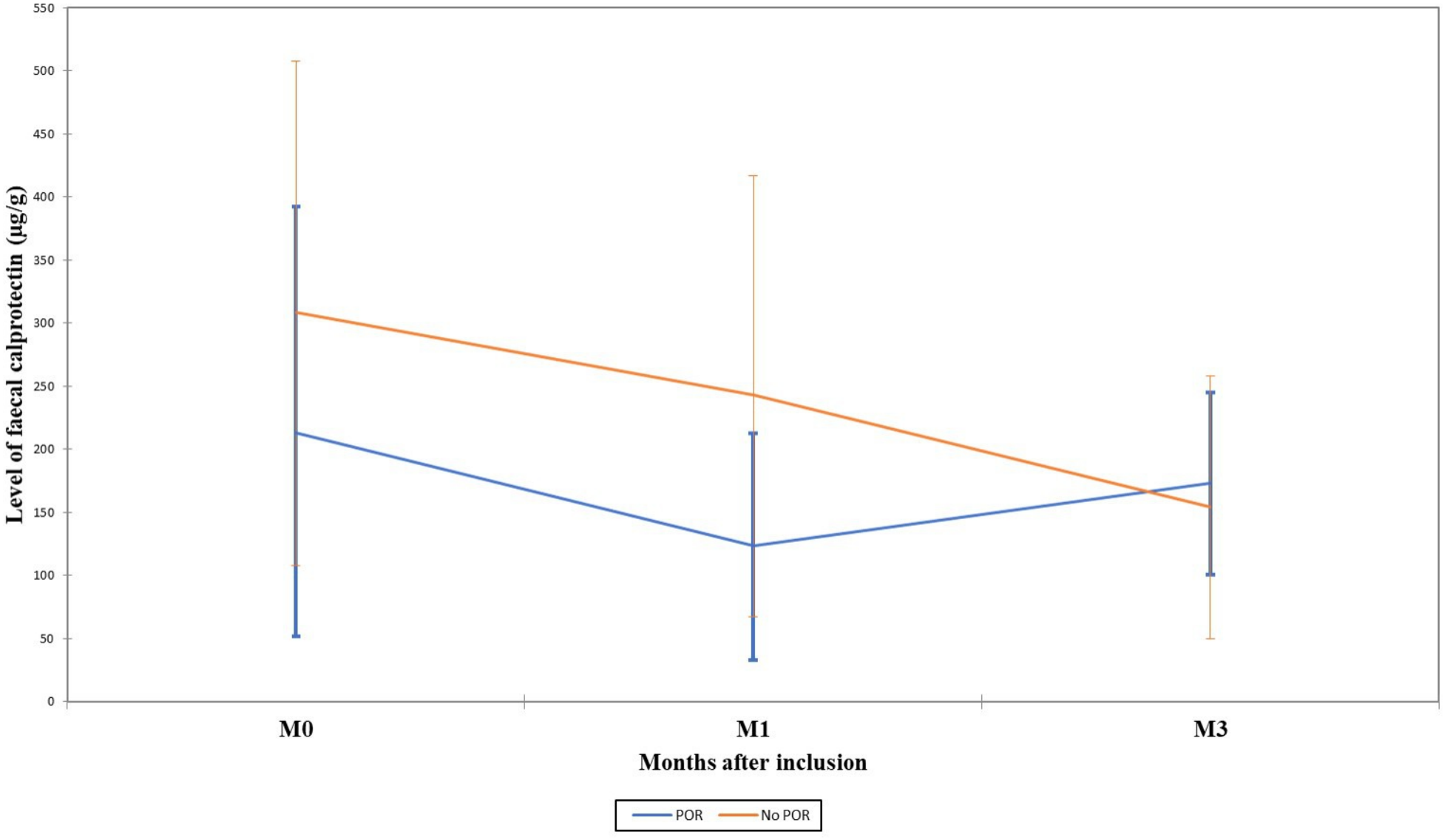
Figure 3: Relative variation of faecal calprotectin level (median) in patients with or without postoperative recurrence (POR).

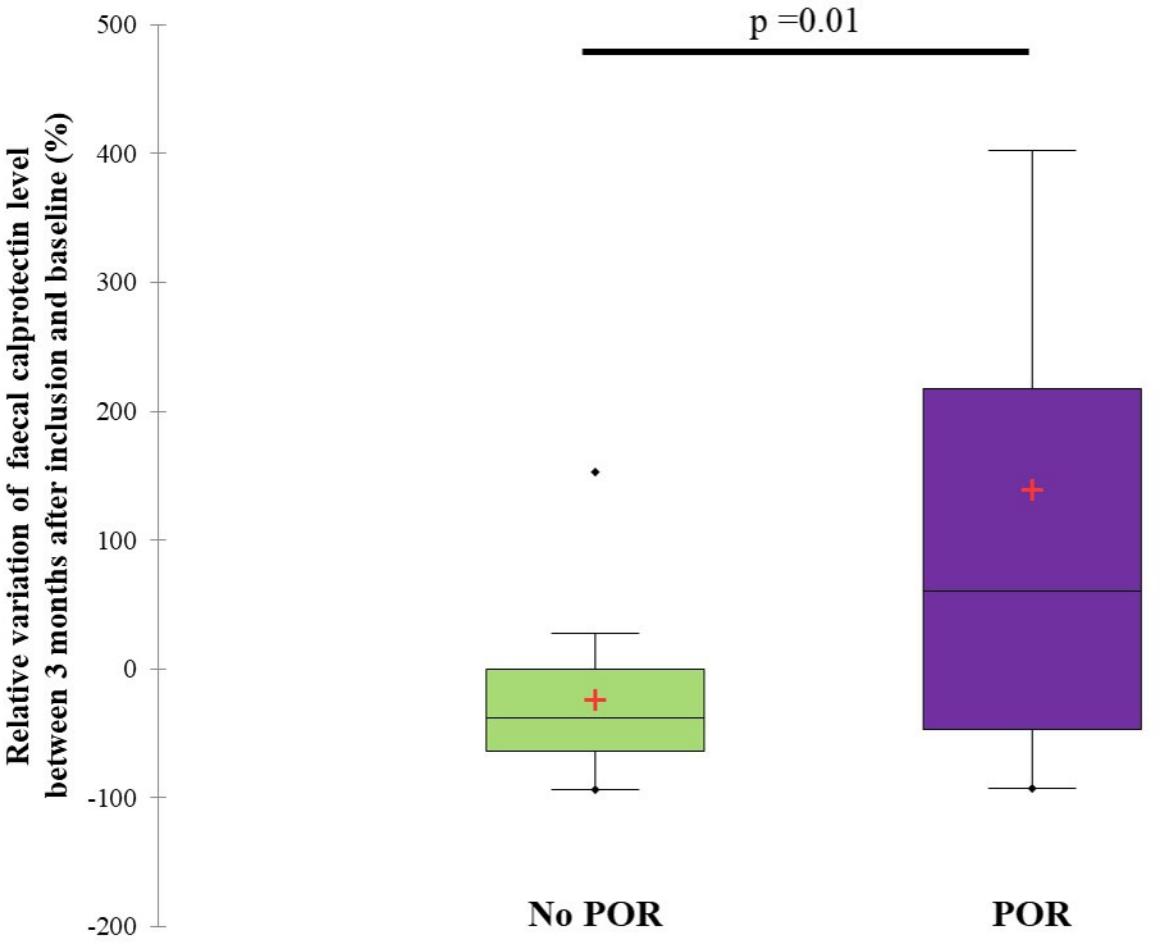
Figure 4: Algorithm summarizing the monitoring of patients with CD within the first months after ileocolonic resection using serial faecal calprotectin testings.

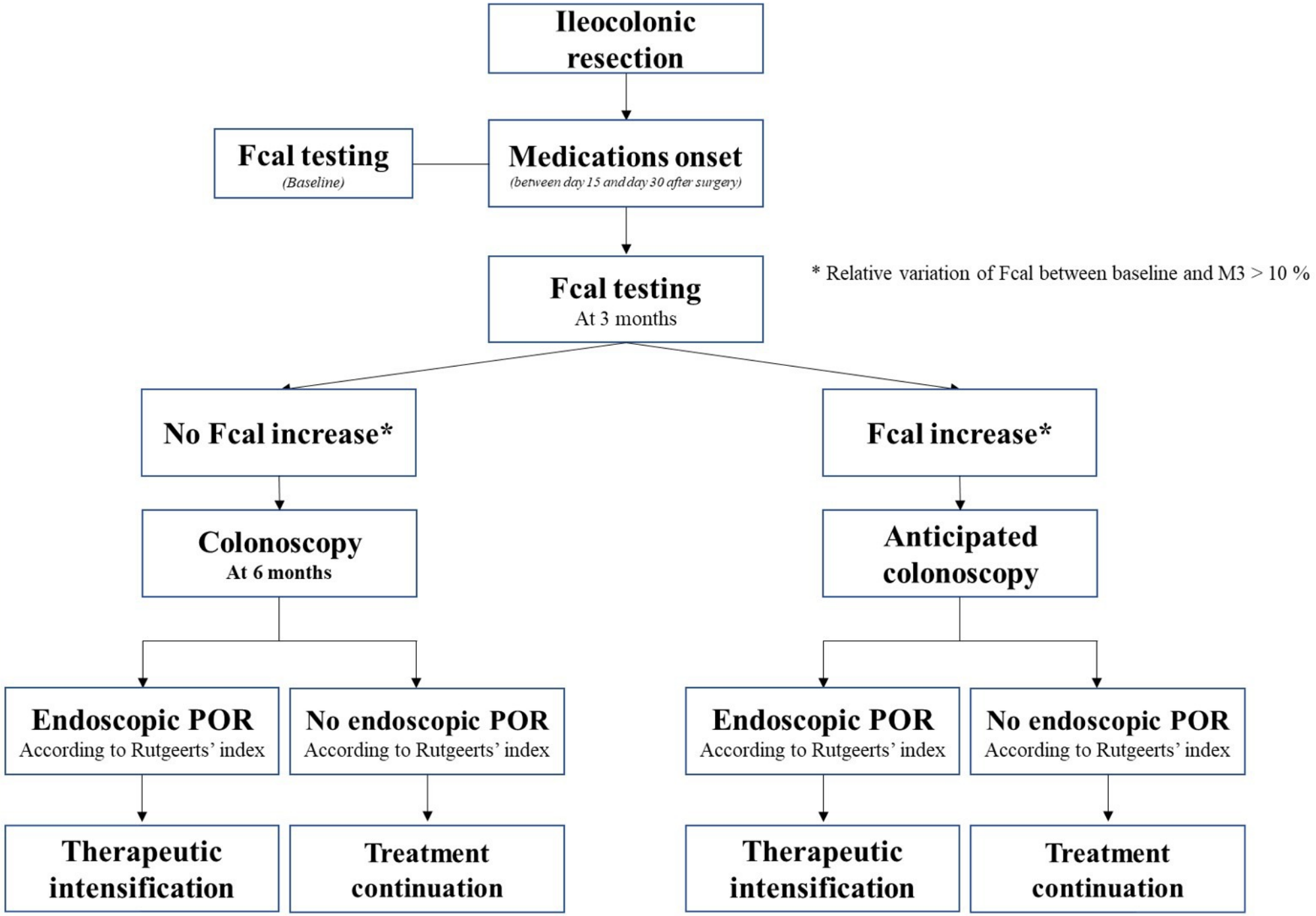
Supplementary Figure S1: Kinetics of faecal calprotectin level for each patient with or without postoperative recurrence (POR) within the first 3 months after surgery.

Supplementary Figure S2: ROC curve illustrating the performances of the relative variation of faecal calprotectin level (median) between baseline and M3 to predict endoscopic postoperative recurrence at M6.


Level of faecal calprotectin (µg/g)
800
700
600
500
400
300
200
100
0
M0
M1
M3
No POR
POR


550
500
450
400
350
300
250
200
150
100
50
0
Level of faecal calprotectin (µg/g)
M0
M1
M3
Months after inclusion
POR
No POR


p =0.01
Relative variation of faecal calprotectin level between 3 months after inclusion and baseline (%)
500
400
300
200
100
0
-100
-200
No POR
POR


Ileocolonic resection
Fcal testing
(Baseline)
Medications onset
(between day 15 and day 30 after surgery)
Fcal testing
At 3 months
* Relative variation of Fcal between baseline and M3 > 10 %
No Fcal increase*
Fcal increase*
Colonoscopy
At 6 months
Anticipated colonoscopy
Endoscopic POR
According to Rutgeerts' index
No endoscopic POR
According to Rutgeerts' index
Endoscopic POR
According to Rutgeerts' index
No endoscopic POR
According to Rutgeerts' index
Therapeutic intensification
Treatment continuation
Therapeutic intensification
Treatment continuation