



**HAL**  
open science

## Serum calprotectin is useful to confirm inflammatory bowel disease activity but not to predict relapse

Pauline Veyrard, Xavier Roblin, Céline Pansart, Ren Mao, Stéphane Nancey, Martin Killian, Louis Waeckel, Anne-Emmanuelle Berger, Nicolas Williet, Laetitia Bastide, et al.

### ► To cite this version:

Pauline Veyrard, Xavier Roblin, Céline Pansart, Ren Mao, Stéphane Nancey, et al.. Serum calprotectin is useful to confirm inflammatory bowel disease activity but not to predict relapse. *Clinical Immunology Communications*, 2022, 2, pp.33-38. hal-04888938

**HAL Id: hal-04888938**

**<https://hal.science/hal-04888938v1>**

Submitted on 15 Jan 2025

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License



## Full Length Article

## Serum calprotectin is useful to confirm inflammatory bowel disease activity but not to predict relapse



Pauline Veyrard<sup>a,1</sup>, Xavier Roblin<sup>a,e,1</sup>, Céline Pansart<sup>b</sup>, Ren Mao<sup>c,d</sup>, Stéphane Nancey<sup>e</sup>, Martin Killian<sup>f,g</sup>, Louis Waeckel<sup>b,f</sup>, Anne-Emmanuelle Berger<sup>b,f</sup>, Nicolas Williet<sup>a</sup>, Laetitia Bastide<sup>a</sup>, Mathilde Barrau<sup>a</sup>, Quentin Tournier<sup>a</sup>, Stéphane Paul<sup>b,f,\*</sup>

<sup>a</sup> Department of Gastroenterology, CHU Saint-Etienne, Saint-Etienne, France

<sup>b</sup> Department of Immunology, CHU Saint-Etienne, venue Albert Raimond, Saint-Etienne 42270, France

<sup>c</sup> Department of Gastroenterology, First Affiliated Hospital of Sun Yat-sen University, China

<sup>d</sup> Department of Inflammation and Immunity, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

<sup>e</sup> Department of Gastroenterology, Hospices Civils de Lyon, Lyon, France

<sup>f</sup> CIRI – Centre International de Recherche en Infectiologie, Team GIMAP, Univ Lyon, Université Claude Bernard Lyon 1, Inserm, U1111, CNRS, UMR530, CIC 1408 Vaccinology, Saint-Etienne, France

<sup>g</sup> Department of Internal Medicine, CHU Saint-Etienne, Saint-Etienne, France

## ARTICLE INFO

## Keywords:

Serum calprotectin  
Inflammatory bowel diseases  
Crohn's disease  
Ulcerative colitis  
Relapse  
Mucosal healing  
Fecal calprotectin  
C reactive protein

## ABSTRACT

**Aim:** Serum calprotectin (SC), a novel biomarker of inflammatory bowel diseases (IBD), has been recently investigated with conflicting results. The purpose of this study was to assess the ability of SC to predict relapse in IBD patients treated by biologic therapies, and to evaluate the correlation between SC, clinical and endoscopic relapse and other biomarkers as fecal calprotectin (FC) and C-reactive protein (CRP).

**Methods:** All consecutive IBD patients in deep remission (clinical, endoscopic or imaging remission) were followed 12 months in this prospective study. Blood and stool samples were collected for SC, serum CRP and FC. SC was measured the day of inclusion (baseline, D0), 3 months (M3) and at 6 months (M6) or during the study period for clinical relapse. Relapse was defined as clinical, biomarkers, or endoscopic/imaging activities. Evolution of SC was quantified before relapse to analyze a predicting value of loss of response (LOR). SC for patients with active IBD and those with symptoms without inflammation were also compared.

**Results:** Among the 119 patients included, 54 (46.4%) patients experienced a disease relapse during follow-up. Median SC levels did not increase in patients with clinical relapse (3.15 µg/ml at baseline, 3.38 µg/ml at M3, 3.33 µg/ml at M6 and 3.99 µg/ml in case of relapse ( $p = 0.63$ )). SC were compared during relapse in patients with endoscopic remission but clinical symptoms defined as secondary Irritable Bowel Syndrome (IBS). SC levels were higher in active IBD and similar between the groups of patients with IBS or deep remission (3.05 µg/ml IBS vs 2.99 µg/ml remission vs 5.1 µg/ml for clinical relapse,  $p = 0.04$ ). In patients with clinical symptoms, SC presents a good predictive value for relapse (AUROC 0.764, IC95: 0.68–0.88), with a sensitivity of 72%, a specificity of 77%, using a cut-off value of 4.45 µg/ml. A weak, but significant correlation was found between SC and FC levels ( $r = 0.35$ ,  $P = 0.001$ ). A combined score with CRP, FC and SC is not efficient to improve IBD diagnostic.

**Conclusion:** SC was significantly higher in patients with clinical relapse compared to those with endoscopic remission with or without clinical symptoms. SC allow to discriminate patients with active IBD or with IBS but failed to predict relapse.

**Abbreviations:** SC, serum calprotectin; FC, fecal calprotectin IBD, Inflammatory bowel disease; CRP, C reactive protein; CD, Crohn's disease; PPI, Pomp proton inhibitor; NSAID, Non steroidal anti inflammatory; LOR, loss of response; LF, fecal lactoferrin; PNN, Neutrophil polynuclear; PPV, predictive positive value; PNV, Predictive negative value.

\* Corresponding author at: Department of Immunology, CHU Saint-Etienne, venue Albert Raimond, Saint-Etienne 42270, France.

E-mail address: [stephane.paul@chu-st-etienne.fr](mailto:stephane.paul@chu-st-etienne.fr) (S. Paul).

<sup>1</sup> These authors contributed equally to this work.

<https://doi.org/10.1016/j.clicom.2022.02.001>

Received 20 December 2021; Received in revised form 4 February 2022; Accepted 4 February 2022

2772-6134/© 2022 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

## Introduction

Mucosal healing has been emphasized as a therapeutic target in IBD. In Crohn's disease (CD), mucosal healing has been reported as the optimal parameter associated with sustained clinical remission, reduced disease related hospitalization rates and risk of surgery [1]. Although endoscopy is the gold standard to evaluate mucosal healing [2], its invasiveness with potential risk and low patient's acceptability substantially limit its clinical utility. Hence, the development of more convenient and non-invasive tools capable to assess mucosal healing remains of high interest.

Biomarkers are widely used in IBD to measure intestinal inflammation. Fecal calprotectin is widely measured in IBD patients and plays a critical role in the management of treatment [3]. Recently, Pouillon et al. reported the usefulness of fecal calprotectin (FC) during the follow-up of IBD [4]. This was supported by the CALM study conducted by Colombel et al., in which treatment escalation with anti-TNF therapy based on inflammatory biomarkers (including FC) combined with clinical symptoms, resulted in better mucosal healing than symptom-driven decisions alone in CD patients [5]. In the last STRIDE recommendations, normalization of FC was sustained as an objective for remission in IBD [6]. Moreover, it was also shown that FC increases more than 3 months before clinical relapse [7]. Even if FC is more acceptable than endoscopy, its acceptability remains still relatively low [8] and its measurement heterogeneity a non-negligible issue [9]. An intra-individual heterogeneity in FC during the day has been also reported in active UC [10].

Identification of new systemic inflammatory biomarkers such as SC, could be an interesting issue. The value of SC has been previously described in rheumatological diseases [11]. Recently, SC has been also described as a predictive marker of COVID-19 severity [12] and for lymphoma and cardiovascular disease [13,14]. Combination of SC with CRP may also reflect inflammatory disease activity in patients with rheumatoid arthritis [15]. Only few studies have investigated the value of SC in IBD patients with conflicting results. Kalla et al. reported that SC was significantly increased in IBD compared to controls [16]. Meuwis et al. showed a significantly higher SC level in CD compared to controls [17]. Suarez Ferrer et al. reported that the level of SC was well correlated with endoscopic disease severity in UC, but not in CD [18]. Therefore, the performance of SC in reflecting disease activity of IBD needs further investigation. To date, any study have evaluated the evolution of SC before clinical relapse to predict loss of response.

In this prospective study, we aimed to evaluate evolution of SC in IBD patients in deep remission at the inclusion, and under biologic treatment. Utility of SC to predict secondary LOR and IBS was also assessed. Finally, correlation between SC, FC and CRP were measured.

## Methods

### Patients and design of the study

This is a prospective study of consecutive patients recruited in the IBD Unit of the University Hospital Center of Saint Etienne between June 2017 and June 2018. Patients were part of the CNIL cohort (n° 1,849,323), and all were informed and accepted by written consent to participate in the study. To be included, patients had to be in deep remission (defined by clinical with endoscopic or Magnetic Resonance Imaging (MRI) healing) for at least three months, with a diagnosis of IBD for more than twelve months and followed in the IBD center of Saint Etienne, France. Patients are under biologic treatment, with stable dose for at least 6 months. Exclusion criteria were patients younger than 16 years old, patients with any type of inflammatory arthritis, patients with active or recent neoplasia, pregnancy, patients with recent surgery not directly related to the IBD, patients with a recent abdominal surgery, (<6 months), patients with chronic infection like tuberculosis, with in-

fectious diarrhea or due to antibiotherapy, exclusive ano-perineal damages, recent use of non-steroidal anti-inflammatory drugs (NSAID), patients under treatment that can disturb fecal calprotectin level (Proton pump inhibitor, NSAID), and patients with poor adherence to treatment. (less than two meetings during one year). For all the included patients, clinical activity score was evaluated every 3 months for Adalimumab (ADA) or Ustekinumab (UST) and every 2 months for Infliximab (IFX) or Vedolizumab (VDZ). At least every 3 months, patients had blood and stool samples performed at each time. Patients were followed during 12 months or until relapse (Supplementary Fig. 1). When patients presented sign of clinical relapse with normal biomarkers, an imaging or an endoscopy had to be performed in less than 1 month.

### Definition and outcome

Clinical remission was defined by a CD activity index (CDAI) [19] <150 for CD and a total Mayo score <3 for ulcerative colitis. Mucosal healing was defined if Simple endoscopic score for CD (SESCD) was under 3 or absence of sign of activity (absence of ulcers, edema, strictures, fistula) or simplified MARIA <1 using Magnetic Resonance Enterography (MRE) for CD or when endoscopic mayo score was under 2 for UC [2]. Deep remission was defined by clinical and endoscopic or imaging mucosal healing. Relapse during follow-up was defined for CD by a CDAI >220, with simplified MARIA score ≥1 [20] or SESC D ≥4 and for UC with a Mayo total score >5 with an endoscopic Mayo score >1. Levels of SC, FC and CRP were measured during this follow-up, and either endoscopic or imaging evaluation. Results of these biomarkers were compared according with loss of response or not during the end the follow-up at the end of the study. IBS has been defined as patients with clinical symptoms, defined by CDAI >220 or Mayo score ≥1, or with mucosal healing (CRP <5, FC <250). To differentiate this group from clinical relapse, biologic, endoscopic or imaging parameters were used. IBS was defined as patients with normal parameters.

### Measurement of biomarkers

Serum used for SC assay were stored at -20 °C. Blood samples have been collected in vacutainer serum tubes and at least one hour after collecting, then centrifuged for 10 min at 10,000 rpm. SC levels were measured according to the manufacturer's instructions using the MRP8/14 ELISA kit using a monoclonal capture antibody highly specific to the MRP8/14 (calprotectin) complexes which do not bind monomer MRP8 or MRP14 (Buhlmann, Switzerland). Ultrasensitive CRP was measured using Roche reagents. Measurements of SC were blinded between clinical activity and immunology unit. During a flare, the SC value used was the last sample made before relapse.

### Statistical analysis

Continuous variables were reported as the mean with their corresponding standard deviations (SD) or median with interquartile ranges (IQR) and compared using student test or Wilcoxon-Mann-Whitney test. Categorical variables were reported as percentage and compared using the  $\chi^2$  test or Fisher's test as appropriate. Performances diagnostic of serum calprotectin, fecal calprotectin and CRP were evaluated by Receiver Operating Characteristic (ROC) curves. The optimal cut-off predicting relapse was determined for each of these biomarkers using the Youden test. The relationship between variables were evaluated using Pearson correlation coefficient. The statistical significance was considered when  $P < 0.05$ . Median SC values for clinical relapse and deep remission in IBS were compared with a Kruskal-Wallis test. All statistical analysis were performed using R, version 3.2.2 (R project, Auckland, New Zealand).

**Table 1**  
Patient's characteristics at baseline.

Characteristics	Total population (n = 119)
Median age (years) [IQR]	38 [28.5 - 50]
Female (N,%)	59 (49.6%)
Male (N,%)	60 (50.4%)
Median weight (kg) [IQR]	71 [63 - 80.2]
Crohn (N,%)	75 (63%)
Ulcerative colitis (N,%)	44 (37%)
Duration of follow up (month) [Median, IQR]	7.3 [2.8 - 16]
Combotherapy (N,%)	13 (10.9%)
Monotherapy (N,%)	100 (84%)
ADALIMUMAB (N,%)	4 (3.4%)
INFLIXIMAB (N,%)	90 (75.6%)
USTEKINUMAB (N,%)	3 (2.5%)
VEDOLIZUMAB (N,%)	17 (14.3%)
AZATHIOPRINE (N,%)	13 (10.9%)
METHOTREXATE (N,%)	1 (0.8%)
Mean albumine (g/l)	41.9 (± 5.5)
Protein C reactive (mg/dl) (median, IQR)	2.2 [0.8 - 5]
Disease duration (years) (Mean, SD)	3.3+/-1.5
PhénotypeA1 (N,%)	10(14%)
A2 (N,%)	57 (76%)
A3 (N,%)	6 (10%)
L1 (ileal) (N,%)	24(36%)
L2 (colonic) (N,%)	12(16%)
L3 (ileo-colonic) (N,%)	38(50.7%)
L4 (upper gastro-intestinal) (N,%)	13(17.3%)
B1 (luminal) (N,%)	34(45.3%)
B2 (stenosis) (N,%)	27(36%)
B3 (fistulizing) (N,%)	17(22.7%)
P (perineal) (N,%)	17(22.7%)
E1 (N,%)	4(13%)
E2 (N,%)	17(39%)
E3 (N,%)	21(48%)

## Results

### Population characteristics

Patients' characteristics are summarized in Table 1. One-hundred and thirty-five patients were screened and 16 were excluded. Finally, 119 patients (59 females) were included with a median age of 38 years. Among them, 75 (63.3%) had a CD and 44 (36.7%) an UC. 489 blood and fecal samples were obtained and analyzed. 4 samples in one year were obtained for 93.3% patients. (111 patients). Five patients had 3 samples and 6 patients had 5 samples.

### Measure of SC, FC and CRP evolution during clinical relapse

During follow-up, 54 patients (54/119, 46.4%) experienced relapse with a median time of 7 months (IQR, 6–10 months). SC median values in UC and CD patients were not statistically significant. During follow-up, no change of SC levels was observed prior and/or at the time of disease relapse in the 54 patients with active disease (Fig. 1). The median SC levels did not differ whatever the time-points considered during the follow-up at baseline, 3 months, 6 months and at the time of relapse 3.15 µg/ml [IQR 2044 - 5327], 3.38 µg/ml, 3.33 µg/ml and 3.99 µg/ml [IQR 2075 - 5264] respectively ( $p = 0.63$ ). Conversely, the median FC levels were gradually increasing in patients who relapsed within the period of follow-up from 26 µg/g at baseline to 105 µg/g, at 3 months, 177 µg/g at 6 months and 292 µg/g at the time of relapse ( $p = 0.049$  between baseline and time of relapse). Finally, serum CRP levels fluctuated during the follow-up, but a significant difference of median CRP levels was measured between CRP at baseline and at the time of relapse (1.5 mg/L vs 3.3 mg/L, respectively;  $p = 0.008$ ). However, median CRP levels remains normal under 5 mg/l.

### Interest of SC to predict clinical relapse during follow-up

Higher levels of SC were observed in patients with clinical relapse (4.1 µg/ml vs 3.02 µg/ml,  $p = 0.09$ ) (Fig. 2A). This difference was maintained during the follow up and at the end of the study.

**Table 2**  
Diagnostic accuracy, sensitivity and specificity of biomarkers to predict relapse.

	Serum calprotectin	Fecal calprotectin	CRP
AUC	0.764 (0.68–0.88)	0.86 (0.76–0.96)	0.74 (0.64–0.84)
sensitivity	0.72	0.76	0.6
specificity	0.77	0.86	0.79

### Use of SC to differentiate secondary IBS and IBD relapse

40 patients have presented symptoms during follow-up of activity without any sign of inflammation (25 CD and 15 UC). SC median values was similar between IBS and patients in clinical remission but significantly higher in patients in clinical relapse (3.05 µg/ml for IBS vs 2.99 µg/ml for remission vs 5.11 µg/ml for relapse,  $p = 0.03$ ) (Fig. 2B). The AUROC for SC to predict clinical relapse was 0.764 (IC95, 0.68–0.88), giving a sensitivity of 72% with a specificity of 77%, using a cut-off value of 4.45 µg/ml determined by a Youden test (Fig. 3).

### Respective diagnosis accuracy of SC, FC and CRP to predict relapse in patients with clinical activity

The AUROC for FC was 0.86 (IC 95, 0.76–0.97) to predict clinical relapse. FC cut-off value of 100 µg/g was optimal to discriminate between relapse and not, with a sensitivity of 76% and a specificity of 86% (Table 2). The performance of CRP to predict relapse in our cohort was intermediate, with an AUROC of 0.73 (IC95, 0.60–0.85). The best cut-off value for CRP has been determined as 1.45 mg/L giving a sensitivity of 60% and a specificity of 79%. Using a mixed score combining SC, FC and CRP to predict relapse, the accuracy was not improved with a sensitivity of 22.9%, a specificity of 97.5%, a VPP of 72.7%, and a VPN of 81.4% (Fig. 4).

Relationships between SC, FC and serum CRP levels and clinical disease activity (Table 3). Using a total of 489 serum samples, the correlation between SC concentrations and disease activity was analyzed using samples matched with clinical disease activity measured at different time points. The correlation between SC and disease activity was 0.44 ( $p = 0.006$ ). A weak but significant correlation between FC and SC was observed with a Pearson coefficient of 0.35 ( $p < 0.001$ ). The correlation between SC and CRP was even lower with a Pearson measured at 0.24. The correlation with increase of white blood cell count was also weak ( $r = 0.37$ ).

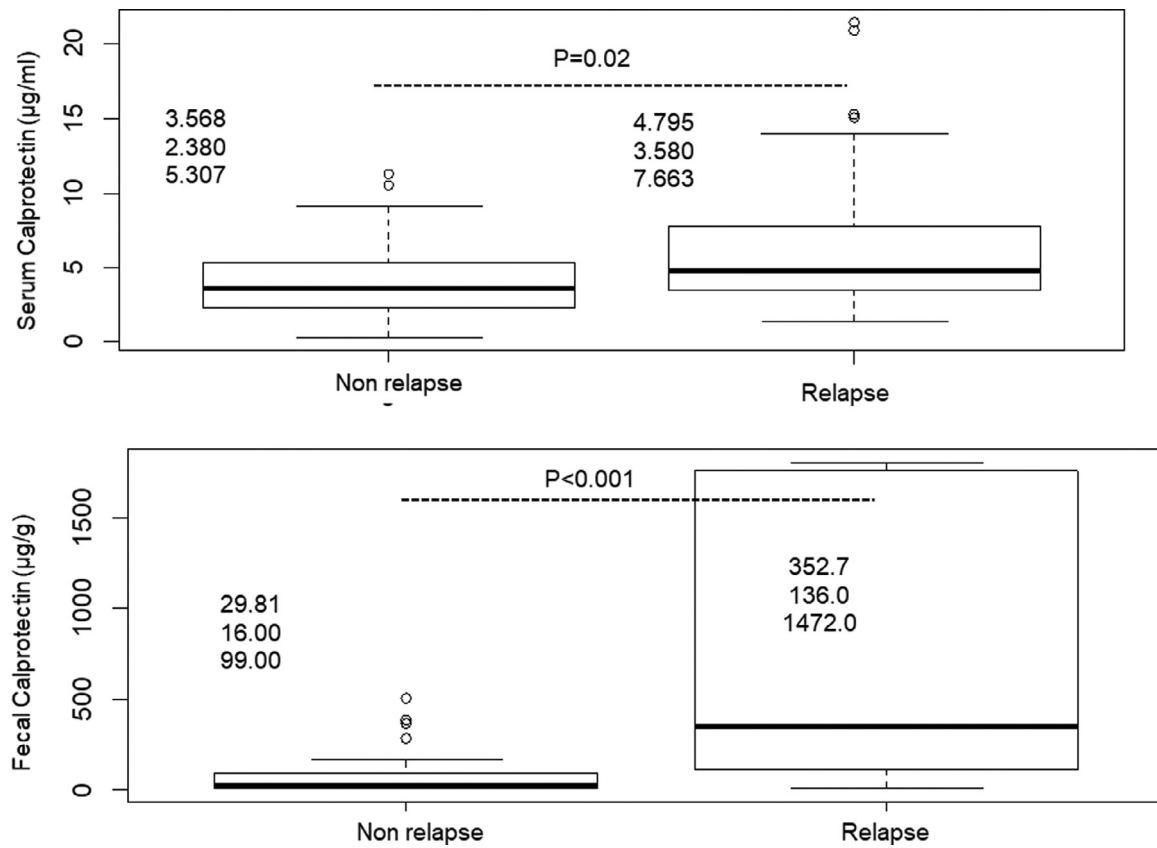
## Discussion

We report here the first study that evaluates the prognostic utility of periodic monitoring of SC in patients with quiescent IBD at baseline and to evaluate its diagnostic accuracy to predict clinical relapse. SC was unable to effectively predict clinical relapse in our cohort. No change of SC levels was observed in patients who experienced a relapse in comparison to patients in clinical remission.

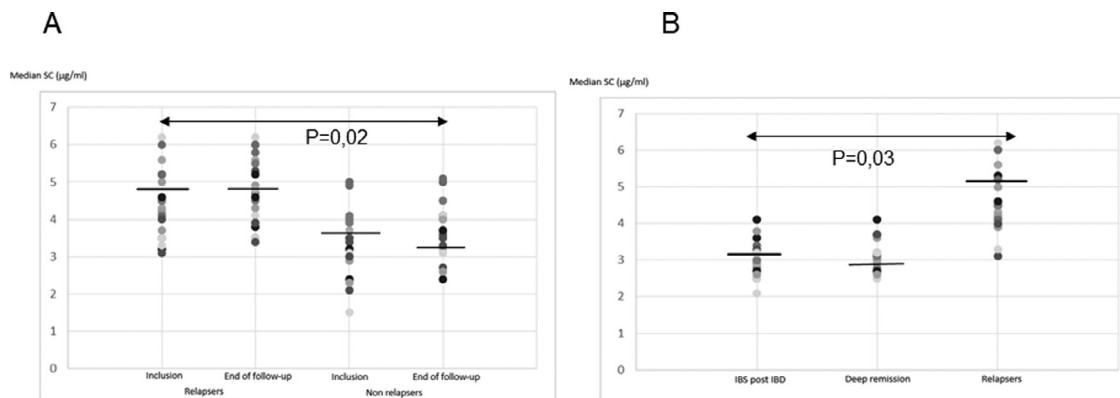
Conversely, a significant increase of FC was observed before the occurrence of a clinical relapse. De Vos et al. previously showed an increase of FC 3 months before relapse [21]. Likewise, Garcia Sanchez et al., also reported a good predictivity of FC before relapse in IBD patients with a significant increase of FC in the 30% of patients who further relapse [22]. Monitoring of SC seems to not be very useful to predict relapse.

In IBD patients with endoscopic or imaging remission with persistent IBS symptoms, SC was not different than SC of patients with remission and was significantly lower than SC of patients with clinical relapse ( $p = 0.04$ ). Moreover, sensitivity and specificity using a specific cut-off was quite good to distinct these two patient populations (72% and 77% respectively).

SC should be better than CRP to detect relapse but less interesting than FC. Indeed, FC has low acceptability and most of patients prefer



**Fig. 1.** Evolution of median serum calprotectin (A), fecal calprotectin (B), CRP (C), during follow-up (at inclusion, 240 days, 120 days and 30 days before relapse) for patients during clinical relapse. SC didn't increase before relapse whereas CRP and FC increased before relapse.



**Fig. 2.** (A) Comparison of median serum or fecal calprotectin between patients with remission and clinical relapse. SC was significantly higher at inclusion between patients who will relapse and those who will stay in remission but didn't increase in each group at the end of follow-up (B) Median serum calprotectin in patients in deep remission, with IBS symptoms and with clinical relapse during follow-up. Median SC was significantly higher in active patients compared to patients in clinical remission and those with IBS symptoms.

**Table 3**

Correlation between SC and disease activity, FC and CRP by Pearson analysis.

	SC and disease activity	SC and FC	SC and CRP
Coefficient of correlation	0.43 ( $p = 0.006$ )	0.35 ( $p < 0.001$ )	0.24 ( $p = 0.02$ )

to have blood sample than fecal collection. To date, any reliable and validated serum biomarker is available to accurately predict relapse in IBD [7]. Moreover, it has been shown an important heterogeneity in FC values depending on the quality of the sampling and assay used [8], even if, this point has to be confirmed by prospective study.

Finally, the correlation between SC and disease activity defined as clinical and endoscopic or MRE score were also measured. SC and FC levels were higher in clinically active disease when compared with inactive IBD. However, a low correlation was found between SC and FC and between CRP and SC. Such correlation between SC and disease ac-



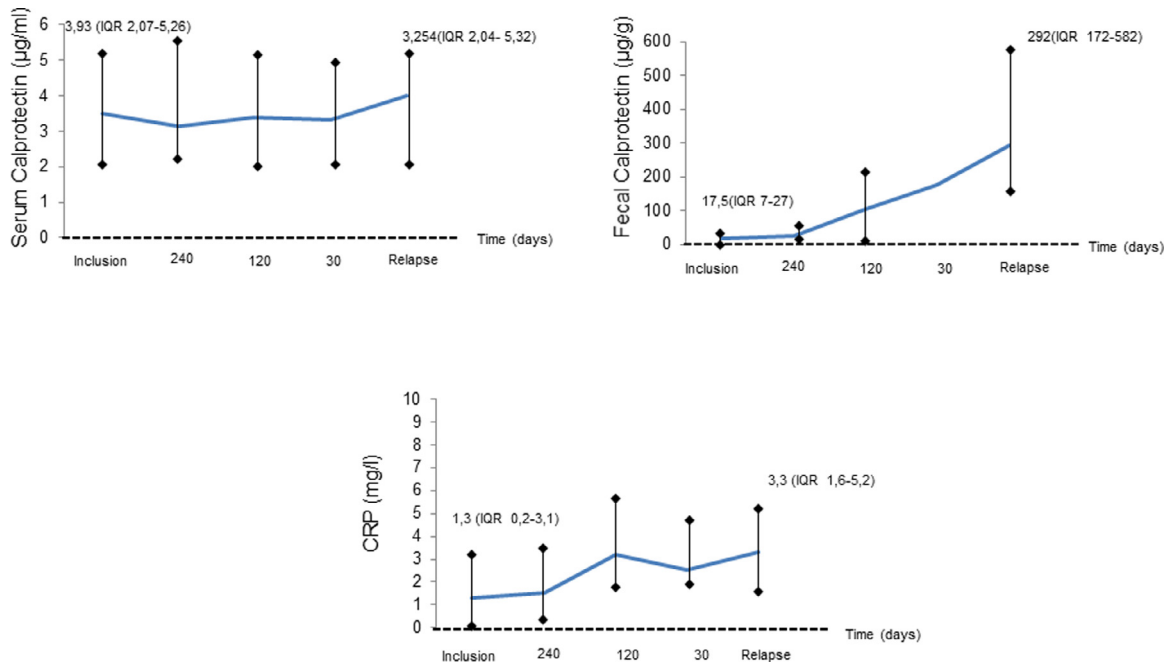


Fig. 3. Respective diagnosis accuracy of SC, FC and CRP to predict relapse in patients with clinical activity. AUROC curves obtained for SC (A), FC (B) and CRP (C).

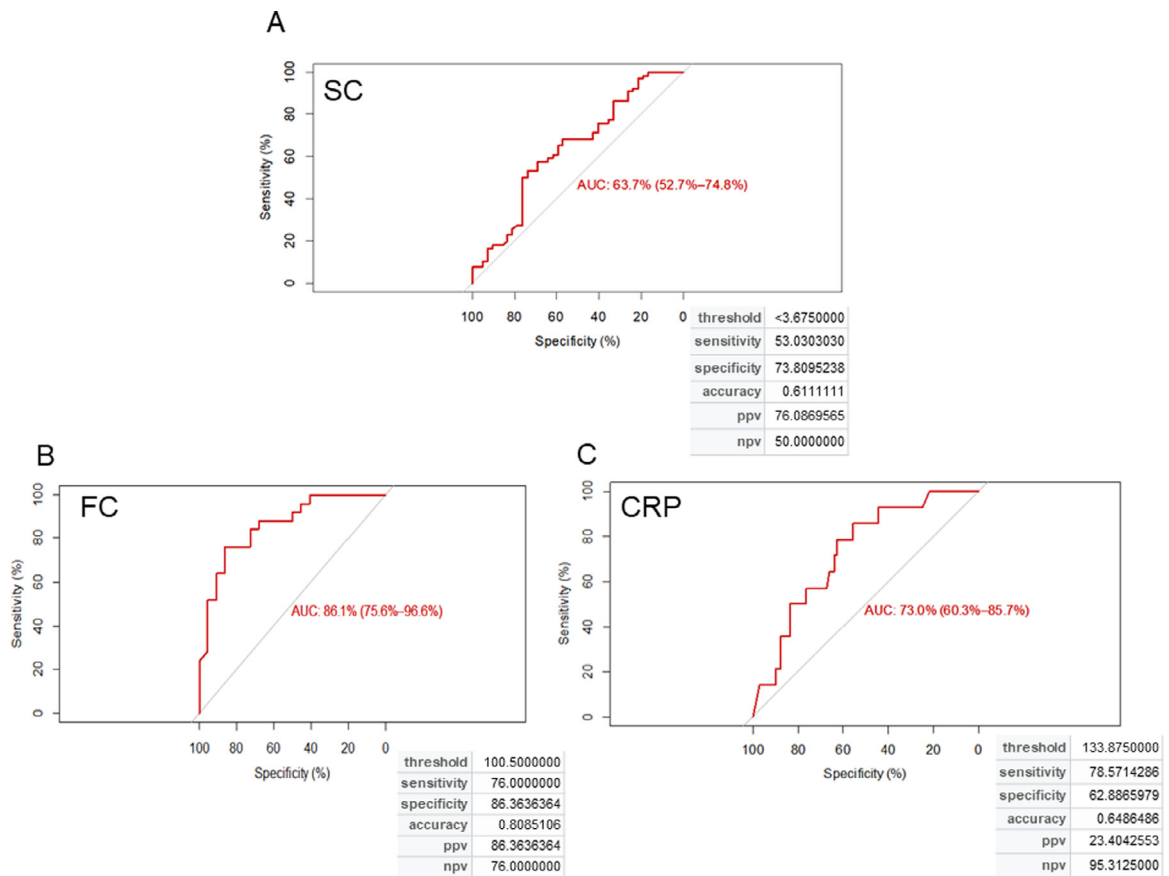


Fig. 4. Correlation between serum calprotectin and fecal calprotectin.

tivity has already been reported with discordant results. Kalla et al., who evaluated SC levels in a total of 156 patients [16] reported that SC concentrations strongly correlated with FC concentrations and were the strongest predictor of IBD diagnosis in comparison with other biomarkers such as C-reactive protein (CRP) and albumin. In our study, correlation between SC and FC was relatively weak. In a prospective study,

Mc Cann et al., have evaluated the role of SC in patients with various gastrointestinal disorders, including IBD or patients with chronic diarrhea [23]. They failed to detect any significant correlation between SC and FC or between SC and CRP. However, the enrolled population was more heterogeneous and substantially different from our study regarding inclusion criteria.

FC has already been shown to correlate with disease activity and it can be used to accurately predict disease activity in IBD patients [24]. Recently, Bertani et al. found that FC measured at 8 weeks was associated with mucosal healing at one year [25]. In our study, a significant correlation was observed between FC and SC. However, the diagnosis accuracy was measured also in patients who achieved a deep remission (endoscopic or imaging remission), which differ from the study of Kalla et al. [16].

Fukunaga et al., were also partially consistent with our findings [26]. Indeed, they reported a close correlation between FC, endoscopic and clinical disease activities and biomarkers (albumin and CRP), but failed to detect any correlation with SC. However, patients with both UC and CD had higher neutrophil and monocyte/macrophage calprotectin-positive cell expression levels, compared with those in non-IBD controls. In our study, a weak correlation between SC and CRP was also measured (Pearson coefficient of 0.24).

S100A8 and S100A9 alarmins, representing ~45% of the cytoplasmic proteins in neutrophils, are released under inflammatory conditions and form a stable heterodimer known as “calprotectin”. This heterodimer promotes cell migration and boosts NADPH (nicotinamide adenine dinucleotide phosphate) oxidase activity. Calprotectin is a TLR4 and RAGE (receptor for advanced glycation end products) ligand that, upstream of tumor necrosis factor alpha (TNF- $\alpha$ ) [27] and CXCL8 [28] synthesis and secretion, promotes NF- $\kappa$ B activation [29] and secretion of multiple inflammatory proteins, such as IL-6 [30]. Its production may be amplified by tissue damage, generating a harmful hyperinflammation loop [27] that precludes these peptides from exerting more protective functions [31–33]. Factors associated with an increase of SC in our study were analyzed. No correlation was observed between CRP and SC. A weak correlation with an increase of white blood cell count was measured ( $r = 0.37$ ). At this stage, we can't associate inflammatory markers with an increase of SC in our cohort.

The major strength of our study is its prospective design and the high number of analyzed samples. It is also the first study which investigated the performance and accuracy of SC to predict relapse of IBD patients in clinical remission or with IBS symptoms. Our study has also some limitations, including findings from a single center, and the definition of mucosal healing could be also based on endoscopy or imaging. However, the Stride consensus recommends MRE as an accurate tool to evaluate deep remission in CD.

In conclusion, an increase of SC is associate to clinical and endoscopic activity. Moreover, SC could be useful to oppose active IBD and IBS in patient with clinical activity of IBD. However, SC seems to not increase during the follow-up of IBD patients in clinical remission before clinical relapse. However, this marker remains an alternative of choice in view of its simplicity of use and the homogeneity of these determinations, unlike FC for example.

#### Declaration of Competing Interest

XR was a speaker for MSD, Abbvie, and Takeda and participated as an advisory board member for MSD, Takeda, Janssen, and Pfizer. PV was a speaker for Abbvie, Pfizer, Amgen. SP was a speaker for Therdiag, MSD and Abbvie. NW, CP, MK, LW, AB have no conflict of interests.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clicom.2022.02.001.

#### CRedit authorship contribution statement

**Pauline Veyrard:** Writing – original draft, Writing – review & editing. **Xavier Roblin:** Conceptualization, Supervision, Data curation, Writing – review & editing, Writing – original draft. **Céline Pansart:** Data curation, Methodology, Writing – original draft, Writing – review & editing. **Ren Mao:** Writing – review & editing. **Stéphane Nancey:** Writing – review & editing. **Martin Killian:** Writing – review & editing. **Louis Waeckel:** Writing – review & editing. **Anne-Emmanuelle Berger:** Writing – review & editing. **Nicolas Williet:** Formal analysis, Data curation, Writing – review & editing. **Laetitia Bastide:** Writing – review & editing. **Mathilde Barrau:** Writing – review & editing. **Quentin Tournier:** Writing – review & editing. **Stéphane Paul:** Conceptualization, Supervision, Data curation, Writing – review & editing.

#### References

- [1] S.C. Shah, J.F. Colombel, B.E. Sands, et al., *Clin. Gastroenterol. Hepatol.* 14 (9) (2016) 1245–1255 e8Epub 2016/02/02.
- [2] L. Peyrin-Biroulet, W. Sandborn, B.E. Sands, et al., *Am. J. Gastroenterol.* 110 (9) (2015) 1324–1338.
- [3] F. Vernia, M. Di Ruscio, G. Stefanelli, et al., *J. Gastroenterol. Hepatol.* 35 (3) (2020) 390–400 Mar.
- [4] L. Pouillon, L. Peyrin-Biroulet, *J. Crohns Colitis* 12 (4) (2018) 509.
- [5] J.F. Colombel, R. Panaccione, J. Petersson, et al., *Lancet* 391 (10129) (2018) 1482.
- [6] D. Turner, A. Ricciuto, A. Lewis, et al., *Gastroenterology* 160 (5) (2021) 1570–1583 Apr.
- [7] A.J. Foster, M. Smyth, A. Lakhani, et al., *World J. Gastroenterol.* 25 (10) (2019) 1266–1277.
- [8] A. Buisson, F. Gonzalez, F. Poullenot, et al., *Inflamm. Bowel Dis.* 23 (8) (2017) 1425–1433.
- [9] C. Pansart, X. Roblin, S. Paul, *Clin. Gastroenterol. Hepatol.* 18 (2) (2020) 524–525.
- [10] M. Calafat, E. Cabré, M. Mañosa, *Inflamm. Bowel Dis.* 21 (5) (2015 May) 1072–1076.
- [11] H. Hu, F. Du, S. Zhang, et al., *Mod. Rheumatol.* 29 (5) (2019) 836–842.
- [12] W. Bauer, E. Diehl-Wiesenecker, J. Ulke, et al., *J. Infect.* 82 (4) (2021) 84–123 Apr.
- [13] M.M. Oosterwijk, S.J.L. Bakker, T. Nilsen, et al., *Int. J. Mol. Sci.* 21 (21) (2020) 8075 Nov.
- [14] S. Şumnu, O. Mehtap, S. Mersin, et al., *Int. J. Lab. Hematol.* 27 (2021) Apr.
- [15] J. Hurnakova, H. Hulejova, J. Zavada, et al., *Clin. Rheumatol.* 37 (8) (2018) 2055–2062.
- [16] R. Kalla, N.A. Kennedy, N.T. Ventham, et al., *Am. J. Gastroenterol.* 111 (12) (2016) 1796–1805.
- [17] M.A. Meuwis, G. Vernier-Massouille, J.C. Grimaud, et al., *J. Crohns Colitis* 7 (12) (2013) e678–e683 Epub 2013/07/13.
- [18] C. Suarez Ferrer, M. Abadia Barno, E. Martin Arranz, et al., *Rev. Esp. Enferm. Dig.* 111 (10) (2019) 744–749.
- [19] K. Thia, W.A. Faubion, E.V. Loftus, et al., *Inflamm. Bowel Dis* 17 (1) (2011) 105–111 Jan.
- [20] Williet N., Jardin S., Roblin X.
- [21] M. De Vos, E.J. Louis, J. Jahnsen, et al., *Inflamm. Bowel Dis.* 19 (10) (2013) 2111–2117.
- [22] V. Garcia-Sanchez, E. Iglesias-Flores, R. Gonzalez, et al., *J. Crohns Colitis* 4 (2) (2010) 144–152. *Gastroenterology*20201581282-3.
- [23] R.K. McCann, K. Smith, D.R. Gaya, *Clin. Biochem.* 50 (9) (2017) 533–536.
- [24] T. Sipponen, K.L. Kolho, *Scand. J. Gastroenterol.* 50 (1) (2015) 74–80.
- [25] L. Bertani, C. Blandizzi, M.G. Mumolo, *Clin. Transl. Gastroenterol.* 11 (5) (2020) e00174 May.
- [26] S. Fukunaga, K. Kuwaki, K. Mitsuyama, et al., *Int. J. Mol. Med.* 41 (1) (2018) 107–118.
- [27] T. Vogl, A. Stratis, V. Wixler, et al., *J. Clin. Invest.* 128 (5) (2018) 1852–1866 May 1.
- [28] J.C. Simard, C. Noël, P.A. Tessier, D. Girard, et al., *FEBS Lett.* 588 (13) (2014) 2141–2146 Jun 13.
- [29] M. Riva, E. Källberg, P. Björk, et al., *Immunology* 137 (2) (2012) 172–182 Oct.
- [30] Wang S., Song R., Wang Z., et al. 2018 Jun 11;9:1298.
- [31] T. Ulas, S. Pirr, B. Fehlhaber, M.S. Bickes, et al., *Nat. Immunol.* 18 (6) (2017) 622–632 Jun.
- [32] J. Austermann, J. Friesenhagen, S.K. Fassl, et al., *Cell Rep.* 9 (6) (2014) 2112–2123 Dec 24.
- [33] T. Vogl, A. Stratis, V. Wixler, T. Völler, et al., *J. Clin. Invest.* 128 (5) (2018) 1852–1866 May 1.