# Diagnostic Performance of Faecal Calprotectin among People with Chronic Inflammatory Diseases of the Bowel in Cameroon: A Pilot Study in Sub-Saharan Africa

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*Authors' contributions*

*This work was carried out in collaboration among all authors. Authors VJAM and PT conceived and designed the study. Authors ILSN, TDT, MDC and MPA collected the data and performed biological analyses. Authors VJAM, FA, ILSN, TDT, MPA, PT and BBA analyzed and interpreted the data. Authors ILSN, TDT, AF, MDC and BBA drafted the first manuscript. Authors ILSN, TDT, FA, MDC, BBA, MPA, PT and VJAM revised the first draft of the manuscript. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Inflammatory bowel diseases (IBDs) are relatively common in African countries. The use of faecal markers, Calprotectin in particular, is presently of considerable interest to IBD patients. The high faecal calprotectin level has a good diagnostic accuracy in discriminating

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intestinal organic and functional diseases and enables the selection of patients in need of other invasive diagnosis such as endoscopy.

**Aim:** To evaluate the diagnostic performance of faecal calprotectin as a useful diagnostic tool for IBD patients in Cameroon.

**Study design:** This was a case control cross-sectional multicentre study conducted in major gastroenterology units of the towns of Yaoundé and Douala involving 64 participants grouped as 32 IBD positive subjects and 32 IBD negative subjects.

**Methods:** Stool sample collected from participants at various recruitment sites were collected, conditioned and transported to the CIAB laboratory for analysis using a direct ELISA method. The R software was used for data analysis.

**Results:** The calprotectin levels of IBD patients were significantly higher than those of the control subjects ($P < .001$.) The area under the curve (AUC) was 0.96 [*95%CI*: 0.92 – 1.00; $P < .001$]. A threshold value of 2.51µg/g was chosen to exclude the diagnosis of IBD with an 87.5% sensitivity and 100% specificity. The CRP levels correlated with those of calprotectin (r=0.579, $P = .005$). Calprotectin concentrations became abnormally elevated in all UC patients with an Endoscopy Score greater than or equal to 6 ($P = .001$). Correlation between the endoscopy score for Crohn's disease and calprotectin concentration did not retain significance (ρ=0.800; $P > .05$).

**Conclusion:** Calprotectin dosage is a sensitive test for IBD, excludes unnecessary investigations and accurately predicts disease recurrence and response to treatment.

## 1. INTRODUCTION

Chronic Inflammatory Bowel Diseases (IBDs) are cryptogenic conditions primarily affecting the digestive tract [1]. They include Crohn's disease (CD), ulcerative colitis (UC) and undefined colitis [2]. IBDs are a major health problem in the western world where the cumulative lifetime risk of having an IBD is 0.5 - 1% [3,4]. The number of IBD cases in the Caucasian population is estimated at 0.7-17 per 100,000 inhabitants [5]. A study conducted in North America reported an incidence rate of IBD ranging from 2.2 - 14.3 cases per 100,000 person-years for UC and 3.1 - 14.6 cases per 100,000 person-years for CD. Very few studies have evaluated the incidence of these conditions in sub-Saharan Africa, as they were considered to be non-existent. In 2010 however, Diouf et al. obtained a prevalence of 1.2% of UC and no case of Crohn's disease in a gastroenterology department in Dakar, Senegal [6]. In Cameroon in particular, no study has been carried out yet.

The differential diagnosis of IBDs is important because of the similarity in their clinical manifestations with intestinal functional diseases [7]. The diagnosis of IBDs results from a bundle of clinical, biologic, endoscopic, radiologic and histologic arguments [8]. In addition, the gold standard for the diagnosis of organic diseases is based on the use of the clinical elements supplemented by an inflammatory assessment (C reactive protein) and digestive endoscopy to assess the intestinal inflammation. Biopsy is then performed for a definitive diagnosis [5]. However, frequent endoscopic procedures are unpleasant, time consuming, expensive for patients and require a skilled operator and adequate bowel preparation [9]. Several serum markers have so far been proposed as alternatives. These include anti-Saccharomyces cerevisiae (ASCA) antibodies, anti-neutrophil cytoplasm antibodies (ANCA), and CRP (C-reactive protein) [10]. Various authors have presented the limitations of these markers in making a reliable diagnosis, including the lack of specificity for the intestinal compartment [11,12]. The most recent is faecal calprotectin.

Faecal calprotectin (FC) is an abundant heterodimeric calcium-binding protein belonging to the S100 family (S100A8 and S100A9), which inhibits metalloproteinases and has antimicrobial and pro-apoptotic activities [13]. It is found within neutrophils, monocytes / macrophages and potentially epithelial cells, and it comprises up to 60% of the total cytosolic protein content of neutrophils [14]. Calprotectin has high stability at room temperature, a high resistance to denaturation and homogeneous distribution in stool [15]. It is evenly distributed and produced in an amount proportional to inflammation [16]. Waugh et al obtained a sensitivity of 83 to 100% and a specificity of 60 to 100% when using faecal calprotectin to differentiate between functional

and organic intestinal processes [17]. FC appears to be, in light of recent studies, a reliable endoscopic surrogate marker capable of reflecting intestinal inflammation [11,18,19].

While faecal calprotectin is used everywhere else, including in Magrebian Africa, as a diagnostic and follow-up tool for IBD, its importance and diagnostic threshold value have not yet been established in sub-Saharan Africa. The objective of this present study was to assess the diagnostic performance of faecal calprotectin in people with IBDs in Cameroon.

## 2. MATERIALS AND METHODS

### 2.1 Study Design and Duration

This was a case-control study comparing two population groups; cases (people with IBD) and controls (apparent healthy people). The study took place from September 8, 2020 to January 18, 2021 in Cameroon.

### 2.2 Study Site

This study was multicentre and was carried out in the cities of Yaoundé and Douala in Cameroon, which are the two most populous metropolitan cities in the country. The choice of recruitment sites was conditioned by the existence of a Gastroenterology department. Thus, the University Teaching Hospital, the General Hospital, the Cathedral Medical Centre and the Tsinga polyclinic were selected in the city of Yaoundé. In Douala, recruitment took place at the General Hospital, the Military Hospital, the *SOS HEPATITE* Clinic, the Medijoss Bonanjo Clinic, the Capucines Clinic and the Poitiers Clinic.

### 2.3 Participants

Sampe size justification was gotten from the recommendation of a study carried out by Browne et al (1995) which advises to use at least 30 subjects or greater to estimate a parameter, in a pilot study. Therefore, a total of 64 participants (32 cases distributed as 28 participants with UC, 4 with CD and 32 controls) were included from the various recruitment sites during the data collection period. The cases consisted of people with IBD confirmed by endoscopy and / or biopsy, while the controls were healthy people without the pathology of interest. Cases with the above-mentioned criteria

and a positive CRP result less than one month old were included. Controls were selected consecutively from a pool of volunteers who responded to placed ads and after careful screening for any exclusion criteria. Subjects who had no fever, abdominal pain or diarrhoea for the past six months, and had never been consulted in a gastroenterology units at any period in the past 3 months were recruited as the control group. Samples were not matched.

### 2.4 Data Collection and Biological Analyses

A structured questionnaire was used to collect socio-demographic, anthropometric and biological data from the participants.

#### 2.4.1 Specimen collection and Analysis

A specimen of approximately 3 grams of first morning stool was aseptically collected in a sterile stool container in a clean toilet at the data collection site. Faecal calprotectin was separated from stool specimens using PBS buffer (0.01M, pH = 7.4) (that is 1 gram of stool per 9 mL of buffer) by centrifugation at 3000rpm for 20 minutes. 2 mL of supernatant was then collected in 2 cryotubes and stored at -80℃. At the end of the data collection period, all the cryopreserved samples were defrosted and analysed at the CIAB-EXACT Laboratory in Yaoundé using a direct sandwich ELISA method with the Human CALP (Calprotectin) ELISA test kit (Elabscience Biotechnology Co., Ltd). A series of 7 standards with respective concentrations of 0 µg/g, 1.563 µg/g, 3.125 µg/g, 6.25 µg/g, 12.5 µg/g, 25 µg/g and 50 µg/g were prepared by serial dilution of a 100 µg/g reference standard and analysed with the patients' samples as indicated by the manufacturer. The faecal calprotectin concentrations in µg/g were then determined by extrapolation of the optical densities of individual samples on the calibration curve obtained (Fig. 1). The UC endoscopy score was defined according to the criteria of Bouhnik et al. [20].

### 2.5 Statistical Analyses

Data collected were recorded in the Microsoft Excel 2013 spreadsheet and analysed using the R software version 4.0.5 (r core team, New Zealand). The package used for the test was the stats package (4.0.5) which comes with the basic version of R. Quantitative data were expressed in terms of means and standard deviation after

performing the Kolmogorov-Smirnov normality test. Qualitative variables were expressed in terms of frequencies and percentages. The Student t test (or its variant Mann Whitney test) was used to compare means. The ROC curve was used for the determination of intrinsic and extrinsic values of calprotectin. Pearson's and Spearman's correlation tests were used to assess the correlation between quantitative variables for a significance level of 5%.

## 3. RESULTS

### 3.1 Socio-Demographic Characteristics of the Study Population

As shown in Table 1, participants' ages ranged from 22 to 62 years old with medians of 46.5 (IQR: 39.25 - 53.5) and 33 (IQR: 28.75 – 43.25) years in the case and control groups respectively. The most represented age group was that of people aged 50 years and above for IBD group and [30-40] years for non-IBD group. Among the 32 subjects with IBD, women and men represented 34.4% and 65.6% respectively with a sex ratio of 1.90. In the control groups, we had 43.8% women and 56.3% men with a sex ratio of 1.28. A family history of IBD was reported in 15.6% of cases with IBD. Most of the participants with family history of IBD had been diagnosed with Crohn's disease rather than ulcerative colitis. The two types of IBD obtained in this study were UC (87.5%) and CD (12.5%).

### 3.2 Diagnostic Performances of Faecal Calprotectin

From
Fig. **1**, the concentration of calprotectin was significantly higher in the case group compared to the control group ($P < .001$).

At the faecal calprotectin cut-off value of 2.515 µg/g as seen in
Fig. **2**, the sensitivity and specificity were 87.5% and 100%, respectively, with a Youden index of 0.875. At this threshold value a positive predictive value of 100% and a negative predictive value of 88% were obtained (Table 2). The faecal calprotectin diagnostic threshold of 2.515 µg/g was used for this study.

As seen in
Fig. **3**, there is a positive and significant correlation between the levels of Calprotectin and CRP (r = 0.579; $P = .0005$).

Fig. **4** shows that Calprotectin became abnormally elevated in all UC patients with an Endoscopy Score greater than or equal to 6 ($P = .001$).

There was a strong and positive correlation between the endoscopy score for Crohn's disease and Calprotectin concentration (ρ=0.800). Nevertheless, the test was not significant ($P > .05$) (Fig. 5 ).

**Table 1. Socio-demographic data of the study population**

| Variable | Case N (%) | Control N (%) | Overall N (%) | P value |
|---|---|---|---|---|
| Count (%) | 32 (50.0%) | 32 (50.0%) | 64 | |
| **Age - years** | | | | |
| Median (q1-q3) | 46.50 (39.25- 53.50) | 33.00 (28.75- 43.25) | 41.00 (30.75 - 52.00) | |
| < 30 | 3 (9.38%) | 9 (28.12%) | 12 (18.75%) | |
| [30, 40[ | 5 (15.62%) | 14 (43.75%) | 19 (29.69%) | .003 |
| [40, 50[ | 11 (34.38%) | 4 (12.50%) | 15 (23.44%) | |
| > 50 | 13 (40.62%) | 5 (15.62%) | 18 (28.12%) | |
| **Gender** | | | | |
| Female | 11 (34.38%) | 14 (43.75%) | 25 (39.06%) | |
| Male | 21 (65.62%) | 18 (56.25%) | 39 (60.94%) | .608 |
| **Family history** | | | | |
| IBD_ | 5 (15.62%) | 0 (0.00%) | 5 (7.81%) | .052 |
| Infectious colitis | 3 (9.38%) | 0 (0.00%) | 3 (4.69%) | .238 |
| **Types of IBD** | | | | |
| Crohn disease | 4 (12.50%) | N/A | N/A | |
| Ulcerative Colitis | 28 (87.50%) | N/A | N/A | 2.20905e-05 |

*q1: First quartile; q3: Third quartile; N: number; N/A: Not applicable*
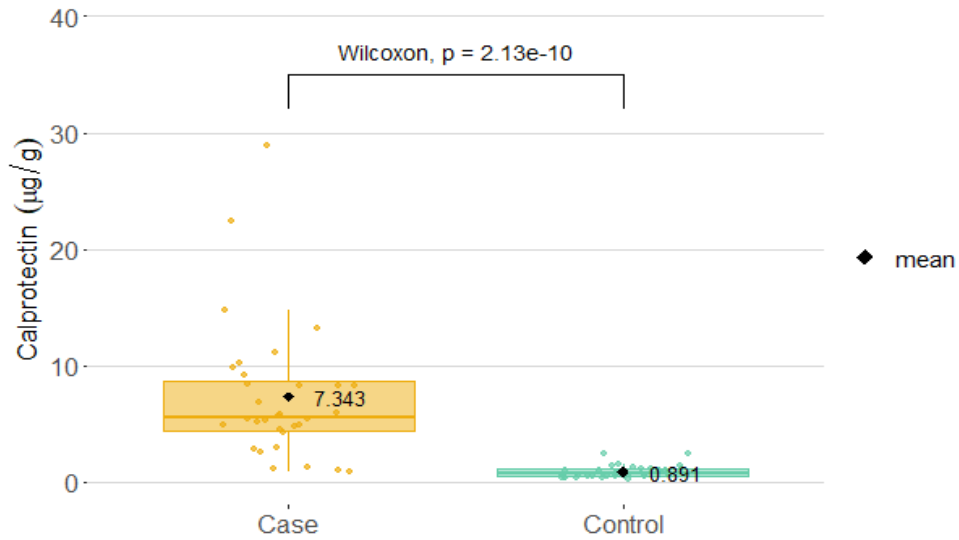
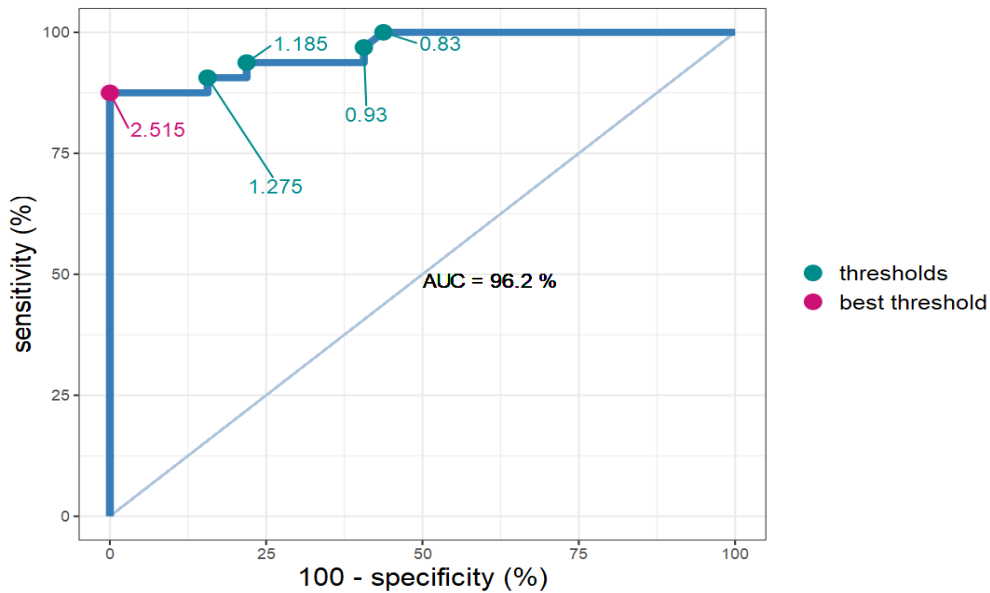**Fig. 1. Comparison of the concentration of calprotectin in the two groups**



**Fig. 2. Calprotectin ROC Curve**

**Table 2. Different threshold values of calprotectin according to the ROC curve**

| Calprotectin thresholds (µg/g) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Youden Index |
|---|---|---|---|---|---|
| 0.830 | 100 | 56.3 | 69 | 100 | 0.563 |
| 0.930 | 96.9 | 59.4 | 70 | 95 | 0.557 |
| 1.185 | 93.8 | 78.1 | 81 | 92 | 0.719 |
| 1.275 | 90.6 | 84.4 | 85 | 90 | 0.75 |
| 2.515 | 87.5 | 100 | 100 | 88 | 0.875 |

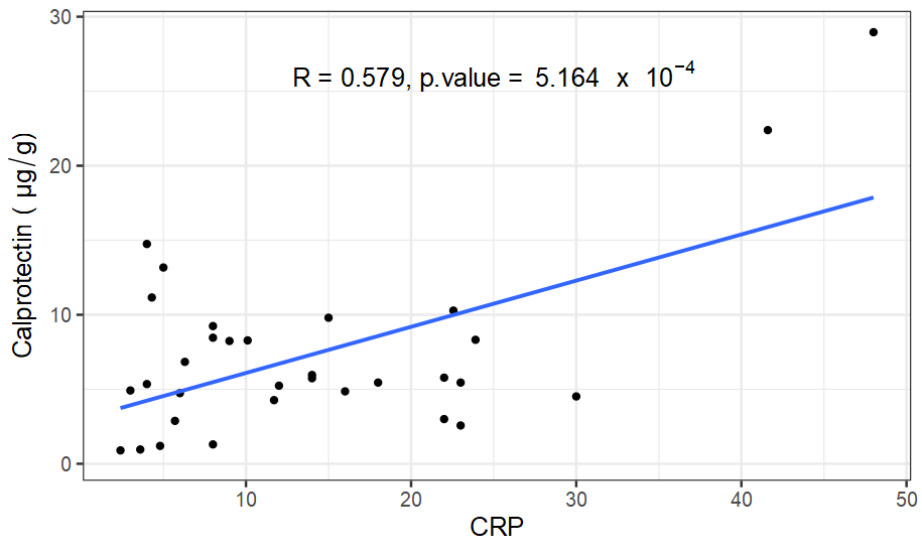*PPV: Positive predictive value; NPV: Negative predictive value*

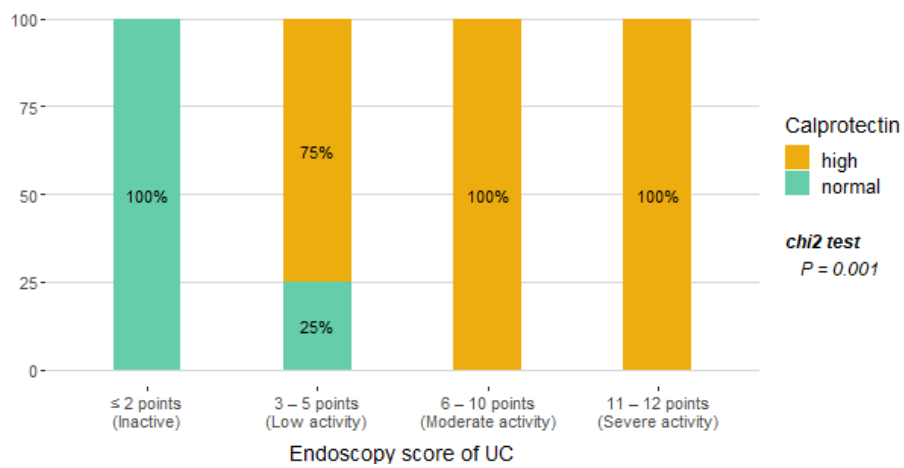**Fig. 3. Distribution of Calprotectin according to CRP**



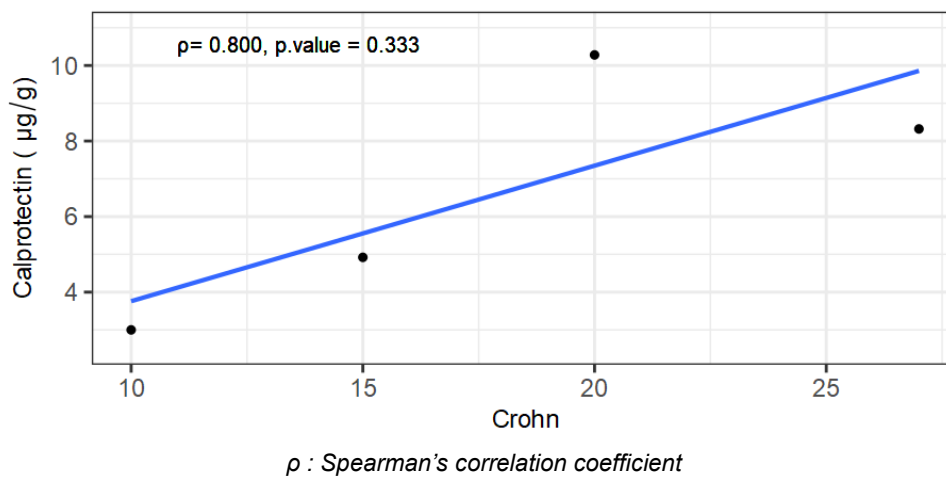**Fig. 4. Distribution of calprotectin according to the endoscopy score of Ulcerative colitis**



*ρ : Spearman's correlation coefficient*

**Fig. 5. Distribution of faecal calprotectin based CD endoscopy scores**

## 4. DISCUSSION

IBDs are distributed worldwide and in varying degrees depending on the geographic region. People aged over 50 years account for 40.6% of IBD cases. In 2018, Bosca-Watts reported that nearly 69% of patients involved in their study were over 60 years old [21]. On the other hand, according to a study conducted in Brazil by Delmondes *et al.* [22] a high incidence of IBD was seen in the 31-45 years age group. These results can be explained by the fact that the occurrence of IBD over time occurs in two peaks as described by Gower-rousseau in the Epimad register in 2013 [5]. In our study, the sex ratio for patients with IBD was 1.90 with a male predominance. A study carried out by Loste *et al.* in 2013, in a Spanish population, showed a male predominance in the different types of IBD [23]. These results are contradictory to that obtained in Senegal where the female gender was more represented with a sex -ratio of 0.68 [6]. As this pathology is not genetically linked to sex, the French High Authority for Health stated that it can affect people irrespective of gender [24].

Among our cases, 15.6% had a family history of IBD. Our study involved 32 IBD subjects made up of 28 cases of UC and 4 cases of CD. 50% and 10.7% of CD and UC cases respectively, had a family history of IBD, giving an overall percentage of 15.6%. These observations are similar to those of Loste *et al.* in 2013 [23]. Of the 12.8% of participants with a family history of IBD obtained in their study, 9.8% of cases were attributed to CD, 2.2% to UC and 0.8% to IC. It thus appears from observations up till present day that the risk of having an IBD is greater in people with a positive family history and is even more pronounced for CD (8 to 10%) than for UC (6%). However, the disease can occur earlier due to environmental factors. A predominance of UC cases, 87.5% versus 12.5% of Crohn's disease cases, was observed in this study. Similar observations were made in two African countries, notably in Burkina Faso and Senegal, where the investigators found 20 [25] and 32 [6] cases of UC with no case of CD, respectively. On the other hand, Gower-rousseau *et al.* [5] rather observed a continuous increase in CD cases (18.5%) compared to UC (10.5%) in France. This divergence can be justified by the differences in food habits and climatic conditions which predispose each population to mainly develop a particular type of IBD.

Faecal Calprotectin increased significantly (*P* < .001) in the group of participants with IBD with a mean of 7.34 compared to the control group with a mean of 0.89. Roseth *et al.* [26] first demonstrated in 1992 that FC value was significancy higher in patients with IBD compared to controls. Our findings are closer to those of Manz *et al.* [27] who noticed a significant difference but with an average of 7.5 for IBD patients and 0.93 for healthy people. Von Roon *et al.* also claimed in their study that the mean FC value was significantly higher in patients with IBD compared to controls with a mean difference of 219.23µg/g between two groups of patients made up of one with CD and the others with UC [28]. These observations from various backgrounds at different time intervals are prominent evidence of the contribution of faecal calprotectin in the diagnosis of chronic inflammatory syndrome in patients with IBD. The calprotectin ROC curve estimated sensitivity and specificity to be 87.5% and 100% respectively, this result is similar to that of Waugh *et al.* [17] in 2013 who obtained a sensitivity of 83 to 100% and specificity of 60 to 100% in discrimination between functional and organic intestinal conditions. The increase in Calprotectin correlated positively and significantly with that of CRP (r=0.579; *P* = .0005) in the caset group. C-reactive protein (CRP) is a marker of inflammation that increases in sera of patients with acute IBD. Increased CRP is more common in CD than in UC. However, some patients have normal CRP levels (20% of patients with relapsing IBD), even in the presence of active inflammatory disease. According to Gilles Boschetti, the sensitivity of CRP does not seem sufficient, especially in UC, to make it a diagnostic test for IBD, hence the establishment of the faecal calprotectin test which is more specific for intestinal inflammation and whose faecal Calprotectin levels rise almost systematically in cases of intestinal inflammatory activity [29].

From a UC endoscopy score of 6 upward, faecal calprotectin significantly raised in the case group (*P* = .001). Sipponen *et al.* [30] also found that FC correlated well, with an endoscopic activity score, and was a good predictor of an active disease with a sensitivity of 70% and specificity of 92%. FC therefore constitutes a useful marker in the detection of residual inflammatory activity in an asymptomatic patient.

The findings of this study should be interpreted in light of certain limitations. The sample size was

not calculated, but rather estimated on the basis of it being a pilot study. Furthermore, the data analyzed in this study was generated from subjects of a given geographic zone, and is thus susceptible to non-generalizability. Nevertheless, the results presented here are of clinical interest and provide preliminary data for further research.

## 5. CONCLUSION

Ultimately, faecal calprotectin increases significantly in patients with IBD than non-affected individuals in Cameroon. This increase is quite more evident in patients with ulcerative colitis with an endoscopy score equal to or greater than 6. An increasing faecal calprotectin concentration above the cut-off value revealed cases of active IBD for which CRP was normal. Thus, the presence of elevated concentrations of calprotectin in patients with chronic digestive disorders might be indicative of IBD and should prompt further investigations, including endoscopy with biopsies. In patients with IBD, the regular assessment of calprotectin would enhance diagnosis, proper and rapid management of patients.

## CONSENT

All the participants read and signed an informed consent before their inclusion in the study.

## ETHICAL APPROVAL

Ethical clearance n° 2020/020607 was obtained from the National Research Ethics Committee.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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