Biomedical & Pharmacology Journal, September 2025. Vol. **18**(3), p. 1947-1952

Fecal Calprotectin and CRP: Noninvasive Biomarkers in IBD

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https://dx.doi.org/10.13005/bpj/3227

(Received: 02 September 2025; accepted: 18 September 2025)

Inflammatory bowel disease (IBD) is a chronic, relapsing-remitting condition of the gastrointestinal tract with an unclear etiology. It is characterized by alternating periods of active inflammation and clinical remission. Among the biomarkers used to assess disease activity, serum C-reactive protein (CRP) and fecal calprotectin (FCP) have emerged as noninvasive, reliable indicators of intestinal inflammation, offering valuable insights into disease monitoring and management. A total of 150 patients with IBD, and 150 control subjects with no history of intestinal resections were included and were prospectively recruited from the IBD Clinic of the National Institute of Hepatology and Tropical Medicine (NHTMRI) and the Clinical Genetics Department of the National Research Centre. (FCP) and (CRP) markers were measured. Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of FCP and CRP for diagnosing inflammatory activity. The median values of these markers were significantly higher in IBD than in controls. FC was associated with higher sensitivity than CRP for the diagnosis of IBD. ROC curve analysis revealed FCP had higher sensitivity for diagnosing with a higher area under the curve than CRP. We concluded that both (CRP) and (FCP) demonstrated a strong association with colorectal inflammation. These biomarkers can serve as valuable tools for monitoring treatment response, screening asymptomatic individuals, and predicting disease relapse in patients with inflammatory bowel disease (IBD).

Keywords: Crohn's Disease; CRP; Fecal calprotectin; IBD; Ulcerative Colitis.

Inflammatory bowel diseases (IBDs) are chronic disorders of the gastrointestinal tract with an unclear etiology, characterized by alternating periods of remission and exacerbation.[1,2] One manifestation, colitis, often presents with chronic diarrhea as a primary symptom. Notably, colitis may display no visible abnormalities during colonoscopy; however, histological analysis of biopsy samples typically reveals enlarged intraepithelial lymphocytes within the colonic mucosa. Patients commonly experience lower gastrointestinal symptoms, including persistent

abdominal pain accompanied by diarrhea or constipation.[1] To assess disease activity, both invasive and noninvasive diagnostic methods are utilized. Among these, fecal calprotectin (FCP) testing has gained prominence due to its high sensitivity and noninvasive nature, making it a preferred tool for detecting gastrointestinal inflammation. [3]

C-reactive protein (CRP) levels and fecal calprotectin (FCP) testing are currently among the most widely recommended diagnostic tools for assessing gastrointestinal inflammation.[4,5] FCP is favored for its high sensitivity and non-invasive nature, making it especially suitable for routine clinical evaluation. We aimed to assess the utility of fecal calprotectin in monitoring inflammatory bowel disease (IBD) activity and to explore its correlation with serum CRP levels.

MATERIALS AND METHODS

This prospective study was carried out at the National Institute of Hepatology and Tropical Medicine's (NHTMRI) IBD Clinic and the National Research Center's Clinical Genetics Department 150 patients affected with IBD, 120 with Ulcerative Colitis (UC), and 30 with Crohn's Disease (CD), aged 25 to 65 years, and 150 healthy controls. Of all participants, 35 had positive consanguinity, whereas only 12 had similarly affected family members.

Informed consent was obtained from all participants before conducting this observational cross-sectional study. The National Hepatology and Tropical Medicine Research Institute's (NHTMRI) Research Ethics Committee provided ethical approval, under approval number 11-2022. The study was conducted in accordance with national regulations, institutional guidelines, and the principles outlined in the Declaration of Helsinki.

Expert gastroenterologists confirmed the diagnosis of ulcerative colitis and Crohn's disease at the specialized clinic of the National Hepatology and Tropical Medicine Research Institute (NHTMRI). Diagnostic confirmation was based on colonoscopic findings, histopathological evaluation of colonic biopsy specimens, relevant laboratory parameters, and clinical presentation. The control group consisted of healthy individuals matched by age and gender, randomly selected from among the patients' companions.

Each patient was carefully evaluated through detailed clinical examination and complete medical history documentation, encompassing age, consanguinity, familial occurrence of similar conditions, as well as anthropometric measurements such as weight and height.

Assessment of Fecal Calprotectin (FCP)

Dry stool sample was collected and mixed with a phosphate-buffered saline (PBS) in a 1:9 ratio (e.g., 9 mL of buffer for 1g of stool). The mixture is then typically shaken or vortexed to homogenize it, followed by centrifugation to separate the solid components from the liquid supernatant. This supernatant was collected and the ELISA kit (My Biosource Co., Ltd.), catalog number MBS7606803, was used to measure FCP according to the manufacturer's instructions.

Assessment of C-reactive protein (CRP)

The nephelometric technique (C-Reactive Protein Reagent, IMMAGE Immunochemistry Systems catalog number k981638) was used to assay CRP.

Statistical analysis

The statistical software SPSS version 20 was used for all analyses. The median and interquartile range (IQR) were used to describe the results for nonparametric data. The Mann–Whitney U test was used to compare two independent samples in groups. The best cut-off values for fecal calprotectin (FCP) and C-reactive protein (CRP) in the diagnostic evaluation were found using Receiver Operating Characteristic (ROC) curve analysis.

RESULTS AND DISCUSSION

IBD encompasses ulcerative colitis (UC) and Crohn's disease (CD), both of which are characterized by persistent gastrointestinal inflammation. [6,7] The pathogenesis includes Genetic susceptibility, environmental triggers, unbalanced microbiota, and immune dysregulation.[8] This results in mucosal damage, ulceration, and infiltration of immune cells, especially neutrophils, which play a key role in calprotectin release.[9] Calprotectin is a calcium-binding immune cell-derived protein found in neutrophils. It makes

up approximately 60% of their cytosolic protein. When neutrophils migrate to the intestinal mucosa during inflammation, they release calprotectin into the gut lumen. It is then excreted in stool, making it a specific marker of intestinal inflammation.[10] Calprotectin has inherent antimicrobial and anti-inflammatory properties and plays a pivotal role in immune regulation and intestinal homeostasis. [11]

Fecal calprotectin (FCP) has recently been recognized as a simple, noninvasive biomarker for assessing disease activity in patients with ulcerative colitis (UC). [12] Recent therapeutic strategies for IBD focus on suppressing pro-inflammatory cytokines and preventing leukocyte migration to inflamed intestinal tissue by targeting sphingosine-1-phosphate receptors and integrins. [13,14] Despite its clinical importance, studies evaluating the usefulness of fecal calprotectin (FCP) in IBD management are limited in this region. In our cohort, FCP demonstrated strong diagnostic performance, with a cut-off value of 200/ mg/kg, providing a sensitivity of 95%, a specificity of 85%, and an area under the curve (AUC) of 0.95. (Figure 1).

Calprotectin's clinical value includes monitoring disease activity and response to treatment, as well as helping to distinguish IBD from functional diseases like irritable bowel syndrome (IBS), predicting illness recurrence, and reducing the need for endoscopies.[15]

Table 1. CRP and FC median levels and interquartile range in IBD patients. The FCP and CRP levels in the IBD group were significantly higher than those in the control group

Median	IBD	Control	p
FCP (mg/kg)	255(202-407)	94(79-113)	0.01
CRP (mg/l)	41(28.6-55.6)	3.15(2.8-4.05)	0.01

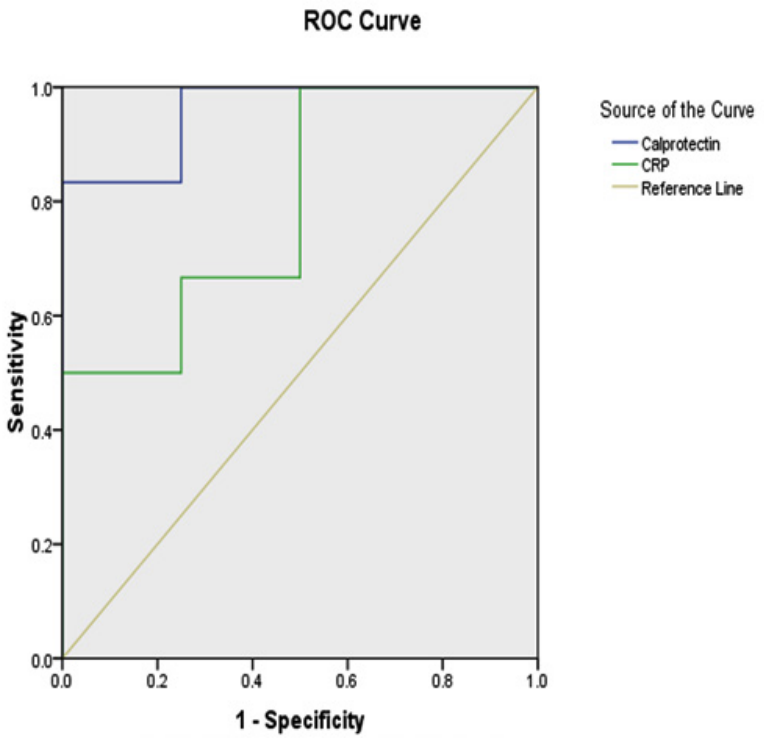

Fig. 1. When it came to diagnosing IBD, the FCP had a larger area under the curve (ROC) than the CRP

The liver produces CRP in response to systemic inflammation. CRP is triggered by signals comprising IL-6, TNF-á, and IL-1â released during immunological activation in IBD. [16] CRP correlates with disease activity, tracks the effectiveness of treatment, predicts flare-ups, and guides therapeutic decisions. [17,18] However, CRP levels may not always accurately reflect mucosal inflammation, particularly in UC.[19]

When measured in tandem, calprotectin and CRP provide a more comprehensive view of disease activity, aid in precise diagnosis, help customize treatment regimens, and avoid unnecessary procedures. [20] FCP and CPR levels have been used in several studies to diagnose inflammatory activity in IBD.[21-24] The cut-off values were chosen to determine the variety of sensitivity and specificity values. [25]

Compared to treatments based solely on symptoms, it was shown that treating CD patients based on clinical evaluation and biomarkers (FCP and CRP) produced better results.[26] However, the use of biomarkers alone versus in combination was not compared in that study. Furthermore, CD patients were not categorized based on the disease's clinical activity.[27,28] Moreover, the efficacy of these tests was established in three clinical settings. FCP was more sensitive than CRP in both diseases and showed greater sensitivity in ulcerative colitis than in Crohn's disease. [29,30] The area under the ROC curve analysis showed that FCP and CRP levels were highly accurate in identifying inflammatory activity in CD.[31] Studies from different parts of the world revealed wide variability in the FCP cut-off levels used to predict disease activity and distinguish from IBS patients.[32,33] The Mayo Score and MES in this investigation indicated a significant relationship between FCP concentration and disease activity. According to research on the best FCP cut-off levels for identifying disease activity and distinguishing this group from IBS patients, endoscopic inflammation in this group was associated with FCP, C-reactive protein, and erythrocyte sedimentation rate. Nevertheless, in patients with endoscopically active illness, FCP was higher more often than erythrocyte sedimentation rate and C-reactive protein. Our results confirm earlier findings that FCP predicts endoscopic inflammation better than other biomarkers. [34,35]

CONCLUSION

In conclusion, this study demonstrated that fecal calprotectin (FCP) and C-reactive protein (CRP) are effective non-invasive diagnostic tools for inflammatory bowel disease (IBD), exhibiting high diagnostic accuracy with a sensitivity of 95%, specificity of 85%, and an area under the ROC curve (AUC) of 0.95. However, considerable variability in FCP cut-off values was observed, particularly during the initial diagnosis of ulcerative colitis (UC) and in post-treatment follow-up. These findings underscore the need for standardized validation of available test kits and the establishment of population-specific cut-off thresholds to enhance diagnostic precision and clinical utility.

ACKNOWLEDGEMENT

We thank all the participants and the National Research Centre.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

The author(s) do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials

Author contributions

Hala Tabie El-Bassyouni, Moushira Zaki, and Hanaa Reyad Abdalla: Conceptualization, writing the original draft, and approved final draft; Dina Abdallah Nagi: Collect the data; Eman Refaat Youness, Hisham Abdel Aziz Orban, and

Hend Mostafa Ahmed: laboratory procedures, data analysis, and approved final draft; Kamal Abdel Rahman El-Atrebi: Clinical investigations.

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