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# Fecal calprotectin from ileostomy output in patients with Crohn's disease

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## Abstract

**Background** Fecal calprotectin (FC) is a reliable biomarker widely used for assessing disease activity and postoperative monitoring in patients with Crohn's disease (CD); however, its efficacy in patients with an ileostomy is poorly understood. Our study evaluated whether FC from the ileostomy output can be used to predict postoperative small bowel inflammation in patients with CD.

**Methods** Data from patients with CD and an ileostomy who had undergone FC measurement between January 1, 2015, and December 30, 2022, were analyzed retrospectively. Patients were enrolled in the study if they had undergone FC tests with concurrent imaging and/or endoscopic studies, facilitating comparison between FC tests and imaging and/or endoscopic examinations. FC measured with the point-of care (POC) test was denoted as FC-POCT, and that measured using the enzyme-linked immunosorbent assay (ELISA) was denoted as FC-ELISA.

**Results** This study analyzed 101 patients and 224 FC test results. FC concentration differed significantly in patients with signs of small bowel inflammation on imaging and/or ileoscopy compared with those in remission (FC-POCT: median 191.0 μg/g; interquartile range [IQR], 94.6–499.0 μg/g vs. 29.9 μg/g; IQR, 29.9–50.0 μg/g; $P<0.001$; FC-ELISA: median 252.5 μg/g; IQR, 118.5–911.0 μg/g vs. 16.8 μg/g, IQR, 8.2–33.0 μg/g; $P<0.001$). The optimal cutoff value for FC-POCT and FC-ELISA to distinguish between small bowel inflammation and remission was 63.3 μg/g (area under the curve [AUC], 0.90; 95% confidence interval [CI], 0.88–0.97) and 40.1 μg/g (AUC, 0.89; 95% CI, 0.79–0.99), respectively. We also compared the diagnostic accuracy between the POC and ELISA testing methods and found no statistically significant difference ($P=0.692$).

**Conclusions** FC from the ileostomy output is a valuable biomarker with high sensitivity and specificity for monitoring small bowel inflammation in postoperative patients with CD and an ileostomy.

**Keywords** Crohn disease, Calprotectin, Ileostomy, Postoperative

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## Introduction

Crohn's disease (CD) is a chronic relapsing inflammatory disorder that affects the gastrointestinal tract [1]. Most patients present with the inflammatory phenotype at diagnosis, but complications such as strictures, fistulas, and perforations develop over time in half of the patients, often necessitating surgery [2]. Approximately 25% of patients require a second surgery during follow-up after the initial surgical intervention [3]. Recurrent mucosal damage can progress even before symptom onset, leading to endoscopic recurrence in 90% of cases within one year of surgery [4]. Therefore, studies have emphasized the importance of monitoring post-surgical intestinal inflammation using early colonoscopy and considering treatment step-ups for preventing postoperative CD recurrence [5, 6]. However, these strategies are primarily recommended for patients with ileocolonic anastomosis, where recurrence is most frequently observed [6, 7]. In contrast, approaches for detecting postoperative recurrence in patients with permanent ileostomy remain poorly established.

Recent studies have reported utilizing fecal calprotectin (FC), a non-invasive and cost-effective biomarker for evaluating intestinal mucosal inflammation and predicting relapse of inflammatory bowel disease (IBD) [8–10]. The Selecting Therapeutic Targets in IBD (STRIDE-II) update has established normalization of the FC level (to 100–250 μg/g) as a treatment target because of its usefulness [11]. However, studies investigating the utility of FC for disease monitoring in patients with CD who have an ileostomy are lacking [12]. Owing to technical challenges in performing ileoscopy via the stoma and the lack of validated studies, literature on the role of ileoscopy is also limited in patients with CD and an ileostomy [7, 13]. Instead, other imaging modalities such as abdominal and pelvic computed tomography (APCT) or abdominal magnetic resonance imaging (MRI) have been widely utilized in clinical practice to assess small bowel inflammation [14–16]. This unique circumstance has made it difficult to evaluate the utility of FC in patients with CD and an ileostomy. To date, only one study reported the utility of FC in 51 patients with CD and an ileostomy, most of whom were Caucasian, suggesting a cutoff value of 60 μg/g for monitoring small bowel inflammation and disease recurrence [12].

Two well-established methods: enzyme-linked immunosorbent assay (ELISA) and point-of-care (POC) tests are used most commonly for measuring FC [17]. ELISA is a gold standard quantitative test most widely utilized for measuring FC [18]. However, due to its time-consuming nature and limited analysis capability of only 35–40 samples simultaneously, various automated ELISA tests based on fluorescence, chemiluminescence, or immune-turbidimetry have been developed [18]. These new methods provide flexibility in the number of tests that can be performed simultaneously, yielding faster results [18]. Rapid POC tests using lateral flow immunochromatography have been developed to provide the quantitative or semi-quantitative value of calprotectin within 30 min [9, 17–19]. There is good agreement between the results of the POC tests and ELISA, suggesting that the former can be employed when a prompt FC value is needed [17, 19]. POC tests may offer advantages in primary care if a rapid processing time is essential for improving patient care, and only a small number of specimens need to be evaluated at any given time [20].

Therefore, the present study evaluated the utility of FC measurement through the ileostomy output in patients with CD who have an ileostomy, to predict small bowel inflammation, in addition to imaging and/or endoscopic examinations. We also compared the performance of the ELISA and POC tests for FC measurement.

## Methods

### Study population

We maintained an IBD registry since 1997 at Asan Medical Center, a tertiary university hospital in Korea, which has been previously described in detail [21]. IBD was diagnosed based on conventional clinical, endoscopic/radiologic, and histologic criteria. From the IBD registry, this study enrolled patients with CD who had an ileostomy after bowel resection. Among them, patients who underwent FC measurement from an ileostomy between January 1, 2015, and December 30, 2022, were enrolled, and only FC tests with corresponding imaging and/or endoscopic studies performed within 30 days were included in the analysis. The median interval between the day of FC examination and the day of imaging or ileoscopy examination was 3 days (interquartile range [IQR], 0–21 days). Of 101 patients, 64 (63.4%) underwent multiple FC measurements, each accompanied by corresponding imaging or ileoscopy studies. The median interval between FC tests in each patient was 674 days (IQR, 417.8–896.5 days). The current study was approved by the institutional review board of Asan Medical Center (approval number: 2022 – 1146).

### Data collection and definition of imaging/endoscopic inflammation

Once eligible patients were identified, the electronic medical records from the IBD registry, including their demographic characteristics, laboratory test results, surgical records, imaging tests, and ileoscopy results, were thoroughly reviewed. Demographic characteristics such as sex, age at diagnosis, smoking status, Montreal classification, duration of CD, type of ileostomy, age at surgery, and the time interval between surgery and the FC test were investigated. Laboratory tests included albumin,

C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR), which were conducted concurrently with FC.

Imaging tests such as APCT, CT enterography (CTE), abdominal MRI, and MR enterography (MRE) were performed to assess the presence of inflammation in the small intestine. All imaging tests were interpreted by board-certified gastrointestinal radiologists with adequate experience evaluating CTE and MRE images for CD [16, 22, 23]. The presence of mural enhancement with wall thickening (≥ 3 mm), ulcers, perienteric edema/infiltration, pseudo-sacculation of the bowel due to shortening of the mesenteric border, and engorged vasa recta on radiological imaging were considered indicative of small intestinal inflammation [14, 16]. All ileoscopies via the stoma were performed by certified gastroenterologists specializing in IBD, and all endoscopic images were independently reviewed by an IBD specialist with > 10 years' experience (SWH). The presence of erosions, aphthous ulcers, inflammatory strictures, edema, erythema, and friability on ileoscopy were considered indicative of inflammation [24]. For statistical analysis, participants were divided into two groups: those with and those without small intestinal inflammation (active or in remission), based on the findings of imaging tests and/or ileoscopy.

### Fecal biomarker assays

The concentration of calprotectin was analyzed using high-range FC quantitative POC tests (Quantum Blue, Bühlmann Laboratories, Schönenbuch, Switzerland) and the EliA Calprotectin 2 reagent (Phadia GmbH, Freiburg, Germany) based on fluorescence enzyme immunoassay principles. FC testing at Asan Medical Center transitioned from POC tests to ELISA in December 2020. From January 2015 to November 2020, FC was measured using POC tests and was measured using the ELISA from December 2020 to December 2022. FC measured with the POC test was denoted as FC-POCT and that measured using the ELISA was denoted as FC-ELISA.

### Statistical analysis

Continuous variables were presented as medians with interquartile ranges, and categorical variables were presented as numbers with percentages. The chi-squared or Fisher's exact test was used to compare categorical variables. Student's t-test or the Mann-Whitney U-test was used to compare continuous variables. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the FC test were calculated for FC-POCT and FC-ELISA. A receiver operating characteristic (ROC) curve plotted all FC cutoffs and their sensitivities versus 1-specificity. The area under the curve (AUC) was calculated to determine the cutoff value. To compare the utility of FC-POCT and FC-ELISA, the AUCs were compared using DeLong's test, which accounts for the correlation between the AUCs. All $p$-values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA) or R version 4.2.1 (R Foundation for Statistical Computing, Vienna Austria).

## Results

### Baseline characteristics

We identified 4,129 patients with CD who underwent FC measurement between January 1, 2015, and December 30, 2022, of which 226 patients underwent ostomy. Forty patients with colostomy, 58 patients who underwent FC measurement after takedown surgery, and 27 patients without corresponding imaging and ileoscopy were excluded. Finally, 101 patients with 224 FC tests met our inclusion criteria and had confirmatory imaging in the form of CT, MR, and/or ileoscopy within 30 days of FC measurement (Fig. 1).

The patients' baseline demographic and clinical characteristics are shown in Table 1. The median age at the diagnosis of CD was 19.3 years (IQR, 16.0–25.3 years) and the median age at surgery for ileostomy was 29.2 years (IQR, 24.6–34.5 years). Fifty-five (54.5%) of the 101 patients were men. The median disease duration, defined as the interval between diagnosis and last follow-up, was 20 years (IQR, 16–24 years).

### Evaluation of imaging/endoscopic inflammation

In the 224 FC cases, the median interval between the day of FC examination and the day of imaging or ileoscopy examination was 3 days (IQR, 0–21 days). Only APCT or CTE was performed in 151 cases (67.4%), only abdominal MRI or MRE was performed in 29 cases (12.9%), and only ileoscopy was performed in 3 cases (1.3%). In 25 cases (11.2%), APCT or CTE was performed along with ileoscopy, and abdominal MRI or MRE was performed along with ileoscopy in 16 cases (7.1%). The number of radiological imaging and ileoscopy examinations are summarized in Table 2.

Analysis of 41 FC tests with both imaging and ileoscopy examinations revealed a lack of concordance between the imaging and ileoscopy in 6 cases (14.6%). In 3 cases, there was no evidence of inflammation on CTE, but ileoscopy revealed inflammation in the small intestine. Upon analysis of the ileoscopy findings, aphthous ulcers or small ulcers were observed around the ileostomy, suggesting that superficial mucosal inflammation was not visible on CTE (Fig. 2A). The remaining 3 cases showed evidence of inflammation on CTE or MRE, but no inflammation was observed on ileoscopy. In these cases, there was no inflammation around the ileostomy on imaging, and inflammation was only observed in the small bowel

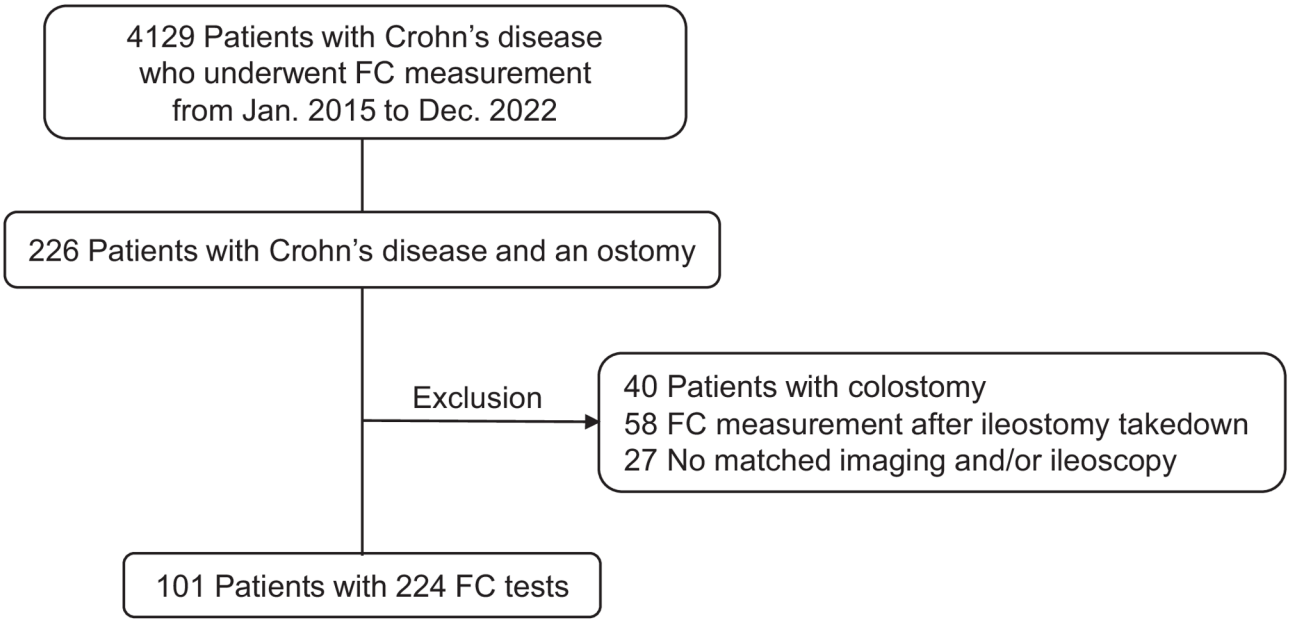


**Fig. 1** Inclusion criteria
*FC* fecal calprotectin

far from the ileostomy, which could not be visualized by ileoscopy (Fig. 2B). We classified these six cases into the active inflammation group.

#### Comparison between active and remission group

To analyze the characteristics of the 224 stool tests based on the presence or absence of inflammation, they were divided into the active group with inflammation confirmed by imaging and/or ileoscopy and the remission group without inflammation (Table 3). Steroids were administered in 11 cases out of 151 in the active group, whereas no patient in the remission group used steroids ($P = 0.042$). There was no statistically significant difference in the use of other medications, such as immunomodulators or biologics, or small bowel length between the two groups. The analysis of all tests included 224 FC test results. The median FC concentration was significantly higher in 151 tests showing the presence of small bowel inflammation on imaging and/or ileoscopy compared to 73 tests indicating remission (202.0 μg/g; IQR, 98.2–584.0 μg/g vs. 29.9 μg/g; IQR, 29.9–43.7 μg/g; $P < 0.001$). An evaluation of the impact of factors such as age, remnant bowel length, and medication use, including biologics and immunomodulators, on FC levels revealed that none had a significant effect (data not shown). Statistically significant differences were also found in the CRP, ESR, and albumin levels between the active and remission groups. However, the CRP and albumin levels were within the normal range in both groups, indicating that these laboratory parameters had little clinical significance.

#### Optimal FC cutoff in discriminating small bowel inflammation from remission

The concentrations of FC, sensitivity, specificity, positive predictive value, and negative predictive value for predicting small bowel inflammation are summarized in Table 4. Of the 224 FC tests, 163 samples were analyzed using POC tests (FC-POCT) and 61 using the ELISA (FC-ELISA). The FC values obtained with the POC test and ELISA differed significantly between the active and remission groups ($P < 0.001$) (Table 4; Fig. 3). The median FC-POCT concentration indicating the small bowel inflammation and remission on imaging and/or ileoscopy was 191.0 μg/g (IQR, 94.6–499.0 μg/g) and 29.9 μg/g (IQR, 29.9–50.0 μg/g), respectively ($P < 0.001$). The median FC-ELISA concentration was 252.5 μg/g (IQR, 118.5–911.0 μg/g) for active inflammation group and 16.8 μg/g (IQR, 8.2–33.0 μg/g) for remission group ($P < 0.001$). ROC analysis revealed a cutoff level of 63.3 μg/g (AUC, 0.92; 95% CI, 0.88–0.97) for FC obtained by the POC tests (Fig. 4A) and 40.1 μg/g (AUC, 0.89; 95% CI, 0.79–0.99) by the ELISA (Fig. 4B) for predicting remission of small bowel inflammation. Although the POC tests had a slightly higher AUC, according to the DeLong's test, there was no statistically significant difference in the AUCs between the two methods ($P = 0.692$).

Of the 224 cases, 180 underwent imaging tests alone. In this set, the median FC concentration was 217.0 μg/g (IQR, 98.0–610.0 μg/g) for the active inflammation group and 29.9 μg/g (IQR, 29.9–48.8 μg/g) for the remission group ($P < 0.001$), with a cutoff value of 58.2 μg/g.

**Table 1** Baseline characteristics of the study population ($n = 101$)

| | **Total ($n = 101$)** |
|---|---|
| **Sex (M/F)** | 55/46 |
| **Age at diagnosis, median (IQR), years** | 19.3 (16.0–25.3) |
| **Age at surgery for ileostomy, median (IQR), years** | 29.2 (24.6–34.5) |
| **Indication for ileostomy** | |
| Obstruction | 44 (43.6) |
| Perforation | 18 (17.8) |
| Abscess or enteroenteric fistula | 28 (27.7) |
| Perianal or rectal fistula | 7 (6.9) |
| Colorectal cancer | 4 (4.0) |
| **Smoking at diagnosis** | 69 (68.3) |
| Never-smoker | 4 (4.0) |
| Current smoker | 28 (27.7) |
| Ex-smoker | |
| **Age at diagnosis** | 28 (27.7) |
| A1: less than 17 years | 72 (71.3) |
| A2: 17–40 years | 1 (1.0) |
| A3: above 40 years | |
| **Disease location at diagnosis** | 3 (3.0) |
| L1: Ileal | 7 (6.9) |
| L2: Colonic | 91 (90.1) |
| L3: Ileo-colonic | 14 (14.1) |
| L4: Upper GI involvement | |
| **Disease behavior at diagnosis** | 75 (74.3) |
| B1: non-stricturing, non-penetrating | 10 (9.9) |
| B2: stricturing | 16 (15.9) |
| B3: penetrating | 44 (43.6) |
| p: perianal disease | |
| **Type of ileostomy** | 94 (92.6) |
| End ileostomy | 7 (7.4) |
| Temporary loop ileostomy | |
| **Time from ileostomy to first FC measurement, median (IQR), years** | 5.0 (2.0–9.0) |
| **Duration from diagnosis to last follow-up, median (IQR), years** | 20.0 (16.0–24.0) |

Data are presented as numbers (%) unless otherwise indicated

*F* female, *M* male, *IQR* interquartile range, *FC* fecal calprotectin, *GI* gastrointestinal

**Table 2** Number of radiological imaging or ileoscopy examinations used in this study ($n = 224$)

| | **Total ($n = 224$)** |
|---|---|
| **APCT or CTE only** | 151 (67.4) |
| **MRI or MRE only** | 29 (12.9) |
| **Ileoscopy only** | 3 (1.3) |
| **APCT and ileoscopy** | 25 (11.2) |
| **MRI and ileoscopy** | 16 (7.1) |
| **Time between FC and imaging/ileoscopy, median (IQR), days** | 3.0 (0–21.0) |

Data are presented as numbers (%) unless otherwise indicated

*APCT* abdominal and pelvic computed tomography, *CTE* computed tomography enterography, *MRI* magnetic resonance imaging, *MRE* magnetic resonance enterography, *FC* fecal calprotectin, *IQR* interquartile range

## Discussion

This study evaluated the utility of FC in predicting relapse in patients with CD who had an ileostomy due to bowel resection. A total of 101 patients with an ileostomy were included, and 224 FC samples and the corresponding imaging and/or ileoscopy examinations were analyzed. The median concentration of FC differed significantly in patients with small bowel inflammation compared with those in remission ($P < 0.001$). The most appropriate FC cutoff value for distinguishing between the presence and absence of bowel inflammation through imaging tests and/or ileoscopy was determined to be 63.3 μg/g by the POC tests and 40.1 μg/g by the ELISA, with high sensitivity and specificity. Thus, simple and non-invasive measurement of FC could potentially replace the need for frequent imaging and/or endoscopic evaluations. Furthermore, we evaluated the POC test and ELISA methods and found no statistically significant difference between them.

CD is associated with a high rate of reoperation, and repeated surgeries can significantly impact the quality of life [25]. Early monitoring is crucial for preventing relapse, but indicators, such as the CD activity index, do not always correlate well with endoscopic evidence of recurrence after surgery [26]. Therefore, postoperative endoscopic evaluation is of paramount importance, and regular endoscopic examinations are recommended 6 months post-surgery and then every 1–2 years thereafter [5, 6]. However, as endoscopy is an invasive procedure with attendant risks such as bleeding and perforation, and frequent examinations can cause discomfort to patients, previous and ongoing research has focused on non-invasive monitoring methods, including FC [27–29]. A prospective, randomized controlled trial conducted in 2015 that enrolled 135 patients who underwent surgery for CD investigated whether monitoring FC levels could serve as a substitute for endoscopic analysis [27]. They found that FC values greater than 100 μg/g had a sensitivity of 89%, specificity of 58%, and negative predictive value of 91% for predicting endoscopic recurrence, meaning that colonoscopy could have been avoided in 47% of patients [27]. Finally, a meta-analysis of 9 studies in postoperative patients with CD reported a combined sensitivity of 70% (95% CI, 59–81%) and specificity of 69% (95% CI, 61–77%) for an FC threshold of 150 μg/g [10]. However, research evidence targeting patients with an ileostomy is limited [30], and as a result, routine ileoscopy through the stoma has not reached a consensus [7].

Patients with CD and an ileostomy have generally undergone total proctocolectomy due to refractory colonic and perianal disease, with up to one-third of this

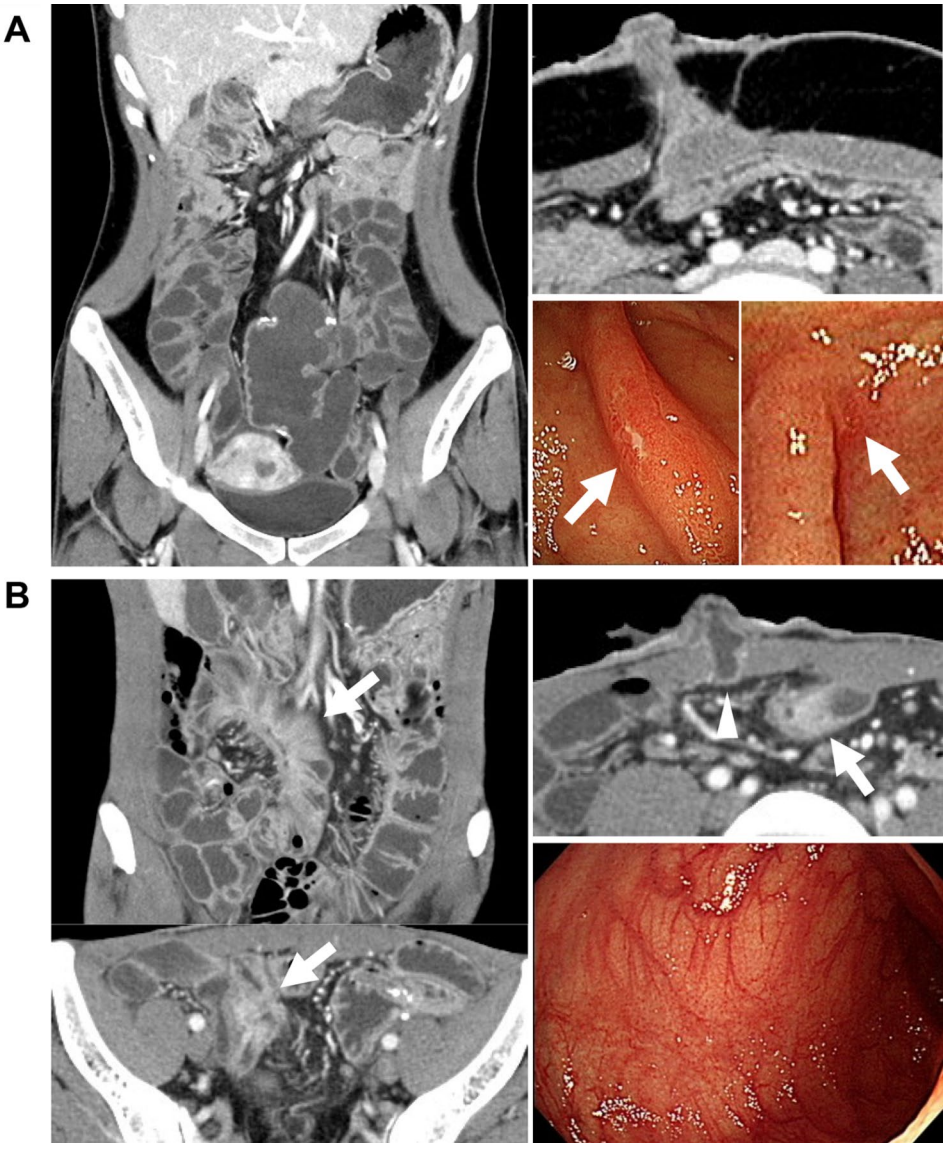


**Fig. 2** Two representative cases of discordance. **A**: A 28-year-old woman with CD and an ileostomy, with FC elevated to 102 µg/g. Coronal and axial view of CTE show no definite ileal inflammation, including at the ileostomy site, but ileoscopy revealed several small ulcers (*white arrow*) in the ileum. **B**: A 50-year-old man with CD and an ileostomy, with FC elevated to 474 µg/g. Coronal and axial views on CTE show the comb sign with bowel wall thickening and enhancement in the ileum (*top left and bottom left*, *white arrow*). Axial view of CTE demonstrates no definite inflammation near the ileostomy site (*top right*, *white arrowhead*) but reveals ileal inflammation (*top right*, *white arrow*). Ileoscopy via the stoma (*bottom right*), limited to 24 cm due to fixed adhesive bowel, shows no definite mucosal inflammation

*CTE* computed tomography enterography, *CD* Crohn's disease, *FC* fecal calprotectin

population experiencing overall disease recurrence [31, 32]. Monitoring inflammation in the remaining small bowel of these patients is an important consideration [33]. CTE and MRE are widely used in the management of postoperative CD, as they show comparable accuracy in detecting small bowel inflammation and associated complications [14–16, 34]. However, previous studies focused primarily on patients who underwent ileocolonic resection and anastomosis to compare findings from ileocolonic anastomosis and the neoterminal ileum observed on colonoscopy with those on CT or MRI, rather than providing a comprehensive assessment of small bowel inflammation [35, 36]. Research on the most effective and practical modality for evaluating the whole remaining small bowel in postoperative patients with CD is limited [37]. In patients with CD and an ileostomy, performing ileoscopy via the stoma can be technically challenging, making it difficult to achieve deep visualization. Moreover, CTE and MRE have certain limitations, including concerns about radiation exposure, discomfort associated with the use of luminal contrast agents, and high cost [38]. This highlights the need to study FC, a non-invasive

**Table 3** Comparison between the active and remission groups*

| | Active ($n=151$) | Remission ($n=73$) | *P*-value |
|---|---|---|---|
| **Fecal calprotectin, median (IQR), μg/g** | 202.0 (98.2–584.0) | 29.9 (29.9–43.7) | **< 0.001** |
| **Age at FC measurement, median (IQR), years** | 38.5 (32.4–45.0) | 36.6 (32.7–43.8) | 0.497 |
| **Time from ileostomy to FC measurement, median (IQR), years** | 6.0 (3.0–10.0) | 7.0 (3.0–10.0) | 0.874 |
| **Remnant small bowel length, median (IQR), cm** | 280.0 (205.0–360.0) | 332.5 (220.0–370.0) | 0.303 |
| **Medication at FC measurement** | 71 (47.0) | 44 (60.3) | 0.086 |
| 5-ASA | 11 (7.3) | 0 (0) | **0.042** |
| Steroid | 98 (64.9) | 37 (50.7) | 0.058 |
| Immunomodulator | 93 (61.6) | 44 (60.3) | 0.966 |
| Biologics | | | |
| **ESR, median (IQR), mm/hr** | 21.0 (10.5–41.0) | 12.0 (7.0–21.0) | **< 0.001** |
| **CRP, median (IQR), mg/dL** | 0.3 (0.1–1.1) | 0.1 (0.1–0.2) | **< 0.001** |
| **Albumin, median (IQR), g/dL** | 3.7 (3.3–4.0) | 4.1 (3.8–4.2) | **< 0.001** |

Data are presented as numbers (%) unless otherwise indicated

*Active group means the presence of small bowel inflammation in imaging and/or ileoscopy, while the remission group means the absence of small bowel inflammation in imaging and/or ileoscopy

*IQR* interquartile range, *FC* fecal calprotectin, *5-ASA* 5-aminosalicylic acid, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

**Table 4** Concentrations of FC, sensitivity, specificity, positive predictive value, and negative predictive value for FC for predicting small bowel inflammation in patients with CD who have an ileostomy

| | Active* | Remission* | *P*-value | Cutoff (μg/g) | Sen (%) | Spe (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|---|
| FC-POCT ($n=163$) | $n=111$ 191.0 (94.6–499.0) | $n=52$ 29.9 (29.9–50.0) | **< 0.001** | 63.3 | 88.3 | 88.5 | 94.3 | 78.2 |
| FC-ELISA ($n=61$) | $n=40$ 252.5 (118.5–911.0) | $n=21$ 16.8 (8.2–33.0) | **< 0.001** | 40.1 | 95.0 | 85.7 | 92.7 | 90.5 |

* Data are presented as the median (μg/g) and interquartile range

*FC-POCT* fecal calprotectin point-of-care tests, *FC-ELISA* fecal calprotectin enzyme-linked immunosorbent assay, *Sen* sensitivity, *Spe* specificity, *PPV* positive predictive value, *NPV* negative predictive value, *CD* Crohn's disease

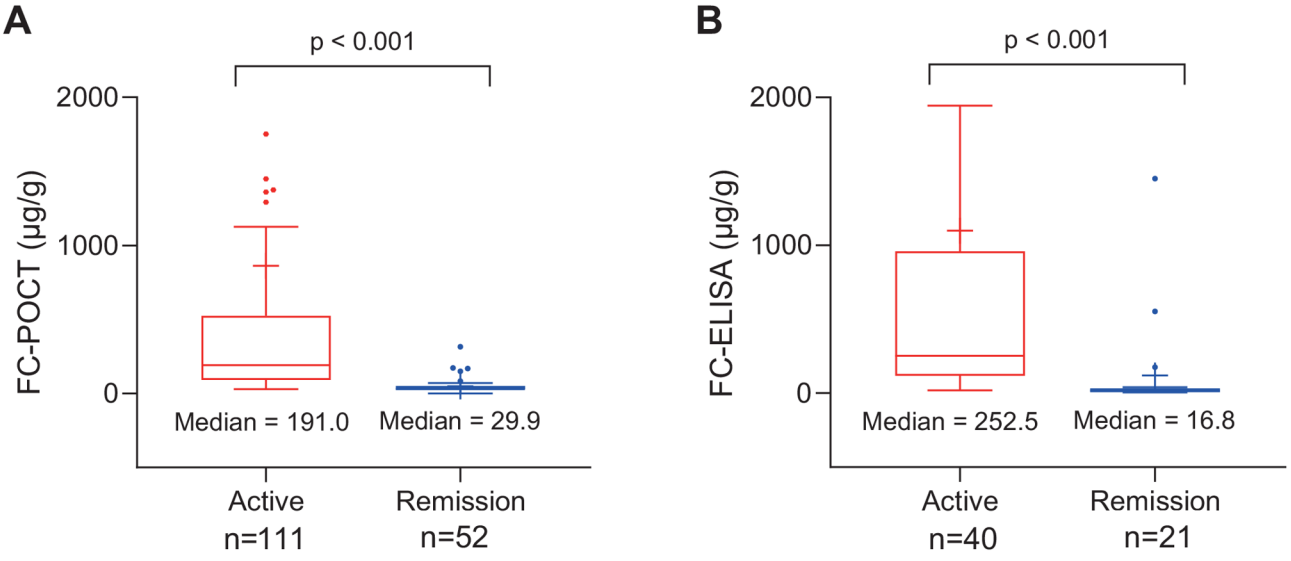


**Fig. 3** Concentrations of **A** FC-POCT and **B** FC-ELISA in cases with radiologic/endoscopic active inflammation vs. remission
*FC-POCT* fecal calprotectin point-of-care tests, *FC-ELISA* fecal calprotectin enzyme-linked immunosorbent assay

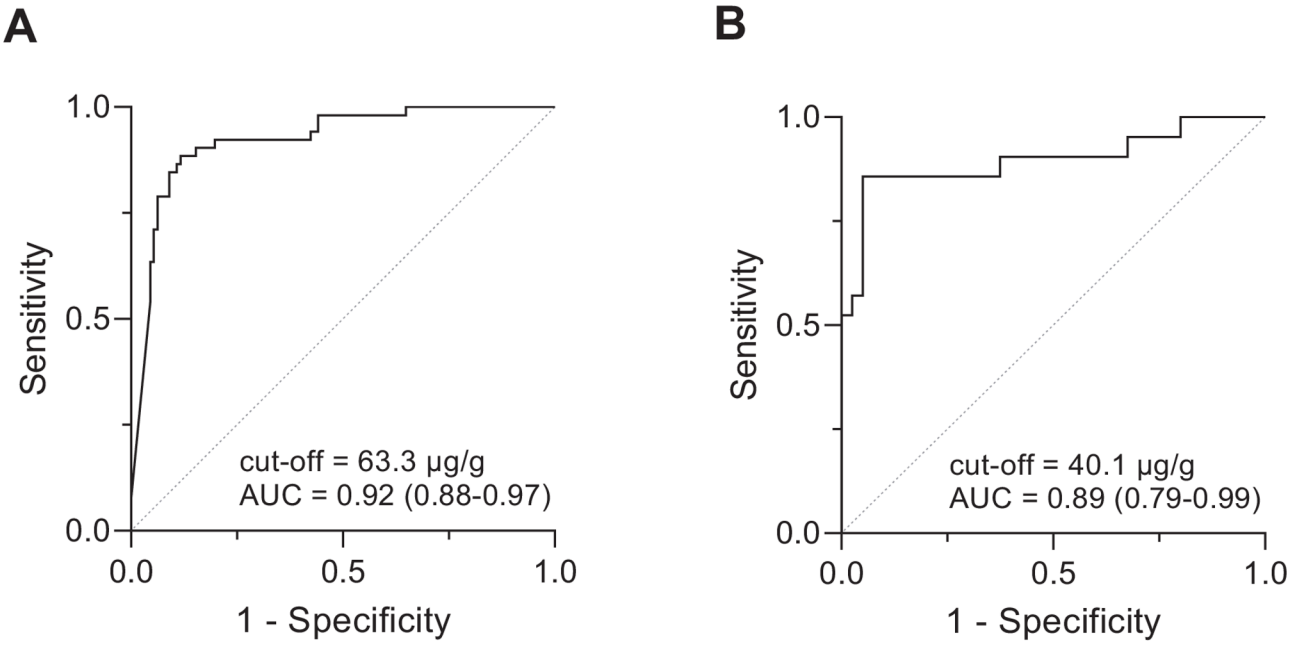


**Fig. 4** Receiver operating characteristic (ROC) curve for **A** FC-POCT and **B** FC-ELISA for predicting small bowel inflammation in patients with CD who have an ileostomy

*FC-POCT* fecal calprotectin point-of-care tests, *FC-ELISA* fecal calprotectin enzyme-linked immunosorbent assay, *CD* Crohn's disease, *AUC* area under the curve

and accessible test, for monitoring small bowel inflammation in patients with CD and an ileostomy.

Notably, to date, only one study has focused on the utility of FC in postoperative patients with CD and an ileostomy. The study was conducted at the Mayo Clinic and evaluated the efficacy of FC in 51 patients with CD who had an ileostomy [12]. In that study, 46 patients had small bowel inflammation confirmed by imaging and/or ileoscopy, and the remaining 5 patients did not have small bowel inflammation; thus, the sample size was relatively smaller than that of our study. When the FC cutoff was 60 μg/g (AUC, 0.90; 95% CI, 0.80–1.00), the sensitivity, specificity, and positive and negative predictive values were 87.5%, 91.4%, 82.3%, and 94.1%, respectively [12]. The cutoff value in our study was similar to that study, highlighting consistency in the findings. The majority of patients (41/51, 80%) had an end-ileostomy, with a median interval of 7 years between the ileostomy and FC measurement [12]. In our study, 94 of 101 (93%) patients had an end-ileostomy, with a median interval of 5 years from the day of ileostomy creation to the FC tests. While the study conducted at Mayo Clinic predominantly included Caucasian patients [12], our study population comprised Asian patients. Additionally, we calculated the median age at the time of ileostomy, which revealed that the patients underwent surgery at a relatively young age of 29.2 years (IQR, 24.6–34.5 years).

Although multiple studies have evaluated the ability of FC to detect postoperative recurrence in CD [8, 10, 27–29], the optimal frequency for FC testing in clinical practice remains undefined [39]. Nevertheless, FC can be performed more frequently than CT, MRI, or ileoscopy, which have limitations and are less practical modalities for frequent monitoring [11, 40]. Two consecutively elevated FC measurements within 2–3 months in asymptomatic patients with IBD suggest subclinical inflammation [41], thereby enabling proactive interventions to prevent disease exacerbation [10, 22]. Similarly, evaluating FC levels after a medication change might be helpful for predicting the treatment response [42]. However, these findings are not well studied in patients with CD and an ileostomy. Future prospective studies are needed to establish the ability of FC testing to meet STRIDE II guidelines and facilitate the implementation of tight control strategies, particularly in these subgroups.

We compared the diagnostic accuracy between the POC test and ELISA, which are the most widely used methods [17] for FC measurement and found no statistically significant difference ($P=0.692$). This finding is consistent with previous studies suggesting that POC tests can be adopted when rapid FC measurement is desired without compromising accuracy [19, 43]. Fukunaga et al. [19] have reported a high level of correlation between the two techniques for patients with ulcerative colitis ($r=0.78$, $P<0.0001$) and those with CD ($r=0.88$, $P<0.0001$).

There are several limitations to this study. First, the current sample size was small, although it incorporated

a larger sample size compared to the previous study targeting patients with an ileostomy [12]. This limitation reflects the low incidence of permanent ileostomy among patients with CD and the lack of standardized methods for assessing small bowel inflammation in patients with CD and an ileostomy [7, 13, 44, 45]. Moreover, the small sample size may have influenced the lack of significant results in the subgroup analyses of factors such as age and medication use. Second, we intended to compare the median FC values before and after ileostomy; however, since FC testing was instituted only after 2015, most patients underwent surgery several years before 2015, making it impossible to compare the values directly. Third, the median interval between FC testing and imaging/ileoscopy in our study was 3 days (IQR, 0–21 days). Although this interval is comparable to those of previous studies [12, 22], its variability might have affected the accuracy of FC in predicting inflammation. Further research with shorter FC testing intervals is needed to enhance diagnostic accuracy. And finally, we could not evaluate the correlation between FC levels and the degree or location of inflammation owing to several factors, such as study population heterogeneity, imaging modality variability, and the lack of a standardized scoring system; instead, we could only compare the presence or absence of inflammation.

## Conclusions

In conclusion, our study proves that FC is a valuable biomarker for discriminating small bowel inflammation from remission in postoperative patients with CD and an ileostomy, although prospective studies are warranted to confirm the relationships with the severity of inflammation.

#### Abbreviations

| | |
|---|---|
| CD | Crohn's disease |
| IBD | Inflammatory bowel disease |
| FC | Fecal calprotectin |
| ELISA | Enzyme-linked immunosorbent assay |
| POC | Point-of-care |
| CRP | C-reactive protein |
| ESR | Erythrocyte sedimentation rate |
| CTE | Computed tomography enterography |
| MRE | Magnetic resonance enterography |
| IQR | Interquartile range |
| ROC | Receiver operating characteristic |
| AUC | Area under the curve |

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#### Author contributions

Conceptualization, S.W.H. and J.B.P.; Data acquisition, J.K.S., J.E.B., J.H.B., S.W.H., S.H.P., D.H.Y., B.D.Y., J.S.B., S.J.M., and S.K.Y.; Data analysis and interpretation, J.B.P. and S.W.H.; Statistical analysis, J.B.P.; Drafting of the manuscript, J.B.P.; Critical revision of the manuscript for important intellectual content, S.W.H.; Study supervision, S.W.H. All the authors approved the final manuscript.

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#### Data availability

All necessary data to support the conclusions of this paper are included within the article. The datasets used in this study are available from the corresponding author upon reasonable request.

## Declarations

#### Ethics approval and consent to participate

The entire study was carried out in compliance with the Declaration of Helsinki. It was approved by the Institutional Review Board of Asan Medical Center (2022 – 1146). The requirement for informed consent was waived by the Institutional Review Board of Asan Medical Center (2022 – 1146) in view of the retrospective nature of this study.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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