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Research Article

Diagnostic accuracy of the combination of fecal calprotectin and occult blood tests in inflammatory bowel disease

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Abstract

Objectives: This study aimed to assess the diagnostic accuracy of the fecal occult blood test (FOBT), fecal calprotectin (FC), and the combination of these markers in patients with suspected inflammatory bowel disease (IBD). Additionally, FC levels were compared between patients monitored for IBD and those newly diagnosed with IBD.

Methods: Conducted at Gazi University Application and Research Hospital, this retrospective study reviewed demographic, clinical, colonoscopy reports, and laboratory data (FC and FOBT) of IBD patients. The final analysis included 153 patients with suspected IBD to evaluate the diagnostic accuracy of FOBT, FC, and their combination. FC was analyzed using the Quantum Blue® fCAL extended test. The ROC curve was drawn to determine the diagnostic ability of FC, and the area under the curve (AUC) was calculated. Sensitivity, specificity, and predictive values were determined for FC and FOBT.

Results: The AUC was determined as 0.827 (95% CI:0.742–0.913) for FC ($p<0.001$). FC showed a sensitivity of 85.7%, specificity of 62.4%, positive predictive value (PPV) of 30.6%, and negative predictive value (NPV) of 95.8%. FOBT had a sensitivity of 81.3%, specificity of 78.1%, PPV of 30.2%, and NPV of 97.3%. The combination of FOBT and FC, with positivity in at least one of the tests, had a sensitivity of 93.8%, specificity of 63.5%, PPV of 23.1%, and NPV of 98.9%. The combined use of FOBT and FC demonstrated higher diagnostic accuracy than either test alone.

Conclusion: The combination of FOBT and FC provides superior diagnostic accuracy for identifying suspected IBD patients compared to each test alone. This combined approach could serve as a cost-effective strategy to avoid unnecessary invasive procedures.

Keywords: Diagnostic accuracy, fecal calprotectin, fecal occult blood test, inflammatory bowel diseases

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Abdominal pain, changes in bowel habits, rectal bleeding, and iron-deficiency anemia are indicative of gastrointestinal system (GIS) disorders. However, most patients presenting with these symptoms do not have any pathological condition [1]. Nevertheless, to accurately diagnose patients and avoid missing serious GIS pathologies such as cancer, some of these patients undergo further investigations [2].

Although colonoscopy is one of the methods most commonly used for many GIS disorders, it is an expensive and invasive method. Using simpler, cheaper, and non-invasive tests is an increasingly popular approach to distinguish between GIS disorders [3]. The fecal occult blood test (FOBT) is the most essential primary screening test for colorectal cancer. However, the prevalence of GIS bleeding is high in patients with inflammatory bowel disease (IBD). In these patients, FOBT positivity may be a late sign of inflammatory tissue damage [4]. On the other hand, the fecal calprotectin (FC) test, a relatively new tool in clinical laboratories, assists in diagnosing GIS disorders [2]. FC is a crucial biomarker for differentiating between inflammatory and non-inflammatory GIS disorders and evaluating intestinal mucosal inflammation in human stool samples. Increased FC concentrations in the intestinal

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lumen indicate the migration of neutrophils to the mucosa and the severity of inflammation [5]. The concentration of FC in the stool is higher than in the plasma of patients with IBD. FC is widely used to diagnose IBD, monitor patients with IBD, and predict relapse in IBD patients [6].

IBD is a chronic inflammatory disease that can affect any part of the GIS tract and has a course of remission and flare-ups. Studies on disease activity and treatment monitoring in IBD show that biomarkers such as FC, C-reactive protein (CRP), albumin, and white blood cell counts are commonly used [7]. However, it has been observed that the FC test is more consistent with colonoscopy results than the other tests [8].

Literature review indicates that different studies have been conducted on the effectiveness of biomarker use in IBD diagnosis. The studies show that combining FC and FOBT tests is a valuable strategy for determining the need for a colonoscopic examination [9, 10]. However, other studies have suggested that combining these two tests does not provide additional information for evaluating GIS pathologies [11, 12].

Examining the effects of the combined use of these tests could provide essential insights into the diagnosis, follow-up, and exclusion of IBD. The combination could also serve as a predictor prior to diagnostic colonoscopy in patients with IBD symptoms. Therefore, this study aimed to investigate the diagnostic accuracy of FOBT, FC, and the combination of these markers (FOBT and FC) in patients with suspected IBD. Furthermore, this study aimed to compare FC levels between patients monitored for IBD and those newly diagnosed with IBD.

Materials and Methods

Study design and population

The study was approved by the Gazi University Clinical Research Ethics Committee (decision number: 847) on November 21, 2022. Since there was no direct patient participation, patient consent was not deemed necessary by the Ethics Committee. This study was conducted in accordance with the principles of the Helsinki Declaration.

The medical records of patients admitted to the gastroenterology outpatient clinic of Gazi University Medical Faculty Hospital between June 2021 and November 2022 were retrospectively reviewed. FOBT and FC tests were performed during the follow-up period in patients previously diagnosed with IBD, including ulcerative colitis and Crohn's disease, to assess disease severity. Tests were also performed on patients with suspected IBD who had symptoms such as persistent diarrhea, abdominal pain, rectal bleeding/bloody stool, weight loss, and fatigue, to diagnose the disease.

Colon examinations were performed when necessary. Diagnosis of IBD was confirmed by colonoscopy and by histologists. Patients' demographic and clinical information, colonoscopy reports, and laboratory data (FC and FOBT) were retrieved from the Laboratory Information Operation System (L.I.O.S.) and electronic patient records were retrospectively reviewed.

A total of 440 patients met the inclusion criteria; patients with IBD were followed up with a diagnosis of IBD, and patients with suspected IBD were treated at the outpatient clinic to confirm the diagnosis.

Exclusion criteria included patients under 18, pregnant women, and those missing colon examination results (colonoscopy or radiological imaging). Additionally, FC test requests from clinics other than gastroenterology were excluded from the study.

Patients with a confirmed final diagnosis via colon examination and whose specialist physician requested an FC test from the outpatient clinic during this process were included in the study.

Laboratory methods

FOBT and FC analyses of the stool samples were performed at the Gazi University Hospital Medical Biochemistry Laboratory.

Immunochemical-based FOBT is commonly used to detect human hemoglobin in feces. There are two types of FOBT available: qualitative (based on immunochromatography, yielding a positive or negative result) or quantitative (based on latex agglutination immunoturbidimetry, yielding a fecal hemoglobin concentration-dependent result) [13]. This study analyzed FOBT using the Toyo cassette test (Türklab, Turkiye), a qualitative immunochromatographic method. Any sample reported by the analytical system as a positive result above 10 ng hHb/mL was considered as a "detectable FHb." The specificity and sensitivity of FOBT were 99.9% and 97%, respectively.

FC was analyzed using the Quantum Blue® fCAL extended test (Buhlmann Laboratories AG, Schonenbuch, Switzerland).

BÜHLMANN Quantum Blue® fCAL is an *in vitro* diagnostic test for quantitatively determining FC extended to human stool specimens. The test was designed to measure FC antigens selectively using a sandwich immunoassay. The FC concentration was measured using a semi-quantitative lateral flow assay (Quantum Blue Reader®, Bühlmann Laboratories, Switzerland). Different manufacturers and laboratories may use varying cut-off values, such as 50 µg/g [9]. However, we adhered to the manufacturer's cut-off values for the BÜHLMANN Quantum Blue® fCAL assay: normal ≤80 µg/g, borderline 80–160 µg/g, and abnormal ≥160 µg/g [14]. The specificity and sensitivity of FC were 91.9% and 64.9%, respectively.

For patients with suspected IBD, FC concentrations of <80 µg/g feces were considered normal, and IBD was ruled out. In these patients, the risk of IBD is less than 1%. Patients with low FC levels are unlikely to require invasive procedures to determine the cause of inflammation. FC concentrations between 80 and 160 µg/g are considered borderline, also called gray-zone levels. Mid-range FC levels do not directly indicate active inflammation and require immediate follow-up and invasive testing; however, inflammation cannot be ruled out. Re-evaluation of FC levels after 4–6 weeks is recommended at gray-zone levels to assess the inflammatory status. FC values of >160 µg/g indicate neutrophil infiltration in the GIS tract, which may indicate the presence of active inflammatory disease. These concentrations require more precise interven-

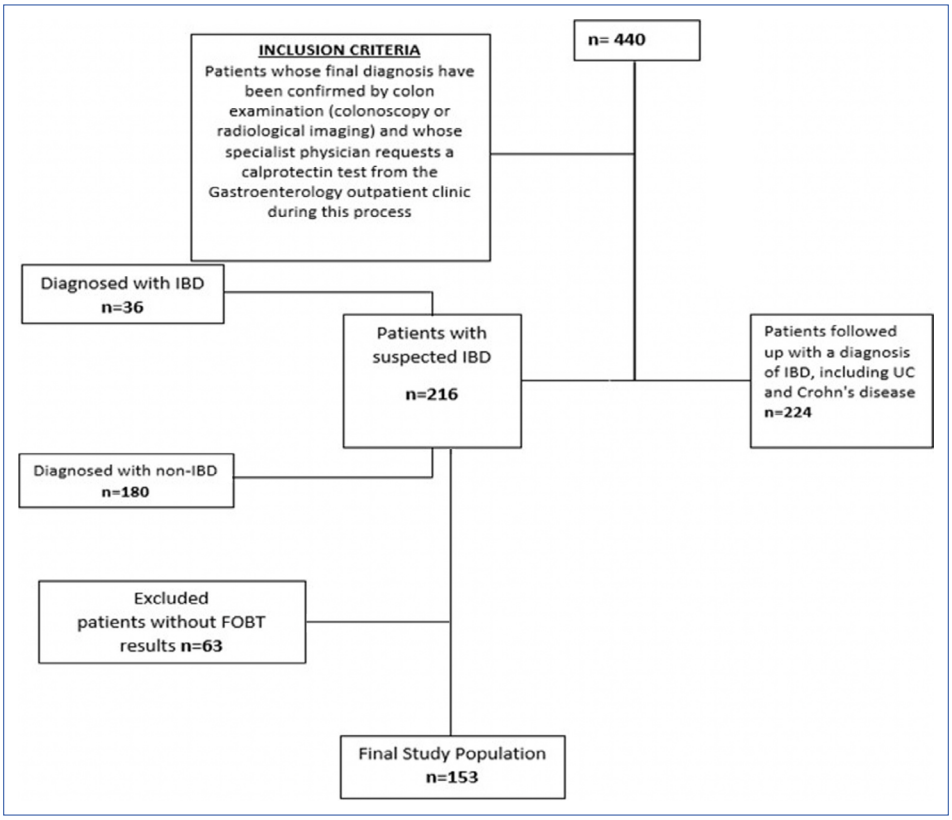

Figure 1. Study flow diagram of inclusion and exclusion.

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; FOBT: Fecal occult blood test.

tions and deeper clinical workup. Further investigations, such as colonoscopy or radiological imaging procedures, are suggested to achieve an overall clinical diagnosis.

Statistical analysis

When calculating the sample size, relevant literature and reference studies were taken into consideration. The Power Statistics Program was used for sample size calculation, with relevant literature as a reference. The research data were evaluated using the SPSS 28.0 statistical package. The Shapiro–Wilk test was used to determine whether the data were normally distributed. Descriptive statistics are presented as median (IQR 25–75), frequency distribution, and percentage. The chi-square test was used for categorical variables. The Kruskal–Wallis and Mann–Whitney U tests were employed, as the data for continuous variables did not meet parametric test conditions (normal distribution and homogeneity of variances). To assess the diagnostic utility of FC in diagnosing IBD, the area under the curve (AUC) and threshold values were determined using receiver operating characteristic (ROC) curve analysis. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated for FC and FOBT. Statistical significance was accepted at $p<0.05$.

Results

A total of 440 patients, whose final diagnosis was confirmed by colon examination (colonoscopy or radiological imaging) and whose specialist physician requested FC testing from the gastroenterology outpatient clinic, were included in this study.

Of the 440 patients, 224 were followed up with a diagnosis of IBD, including ulcerative colitis (UC) and Crohn's disease, while 216 patients were suspected of having IBD. After further examinations, 36 of the 216 patients were diagnosed with IBD, while the remaining 180 patients received non-IBD diagnoses, such as cancer, polyp, and aneurysm. A total of 153 of the 216 patients were included in the final analysis to evaluate the diagnostic accuracy of FOBT, FC, and their combination for diagnosing patients with suspected IBD. 63 patients without FOBT results were excluded from the study; the study flow diagram for inclusion and exclusion is shown in Figure 1.

In this study, a similar proportion of both genders participated, and there were no significant differences in gender and age between groups. The groups in the study were classified as follows: Group I = Patients followed up with IBD, Group II = Diagnosed with IBD, Group III = Diagnosed with non-IBD. The FC median value of patients followed up with IBD (Group I) was 198 µg/g (IQR 25–75: 57–809), while the FC median value of patients diagnosed with IBD (Group II) was 708 µg/g (IQR 25–75: 114–1000). The FC median value of patients with non-IBD (Group III) was 36 µg/g (IQR 25–75: 30–178). There was a significant difference in FC levels between the groups ($p<0.001$). The demographic data and FC levels in the groups are shown in Table 1.

Table 1. Demographic data and FC levels (µg/g) changes in the studied groups.

	Group I (n=224)	Group II (n=36)	Group III (n=180)	p
Age, median (IQR 25–75)	41 (31–55)	39 (27–51)	44 (28.5–58)	0.345
Gender, n (%)				
Female	114 (48.7)	20 (8.5)	100 (42.7)	0.606
Male	110 (53.4)	15 (7.3)	81 (39.3)	
FC (µg/g), median (IQR 25–75)	198 (57–809)	708 (114–1000)	36 (30–178)	**<0.001**

FC: Fecal calprotectin; IQR: Interquartile range.

FC levels (µg/g) were significantly higher in Group I compared to Group II and Group III (p=0.013, p<0.001, respectively). FC levels were statistically significantly lower in Group III than in the other two groups. The distribution of FC levels (µg/g) across groups is shown in Figure 2.

Based on the ROC curve analysis, the AUC was determined as 0.827 (95% CI: 0.742–0.913) for FC (p<0.001). The ROC analysis for FC is visually represented in Figure 3.

For detecting IBD, FC returned a sensitivity of 85.7%, specificity of 62.4%, PPV of 30.6%, and NPV of 95.8%. FOBT had a sensitivity of 81.3%, specificity of 78.1%, PPV of 30.2%, and NPV of 97.3%. The combination of FOBT and FC, with positivity in at least one of the two tests, was associated with a sensitivity of 93.8%, specificity of 63.5%, PPV of 23.1%, and NPV of 98.9%. Diagnostic accuracy performance (sensitivity (%), specificity (%), NPV (%), and PPV (%)) for FOBT, FC, and the combination of tests for detecting IBD are presented in Table 2. Cut-off values for FOBT and FC were determined as "positive" and 80 µg/g, respectively, for this study.

Discussion

IBD is a chronic, progressive, and highly heterogeneous disease that affects both adults and children, with severity and symptoms ranging from mild to severe. Delays in diagnosing IBD are common, correlating with adverse outcomes and potentially leading to significant morbidity and complications, including fissures, fistulas, systemic inflammation, and cancer [15]. The initial goal in diagnosing the disease is to evaluate disease activity and relieve symptoms, while long-term objectives aim to prevent disease progression and reduce complications. Early diagnosis of IBD and prompt treatment are essential for improving outcomes and maximizing health [16]. There is no gold standard diagnostic method for IBD; instead, clinical assessment, endoscopic examination, histopathological analysis, and laboratory tests are utilized. FC levels emerge as a valuable biomarker, strongly correlating with endoscopic activation [17]. The Food and Drug Administration has approved FC as a biomarker of intestinal inflammation, with potential clinical applications as a diag-

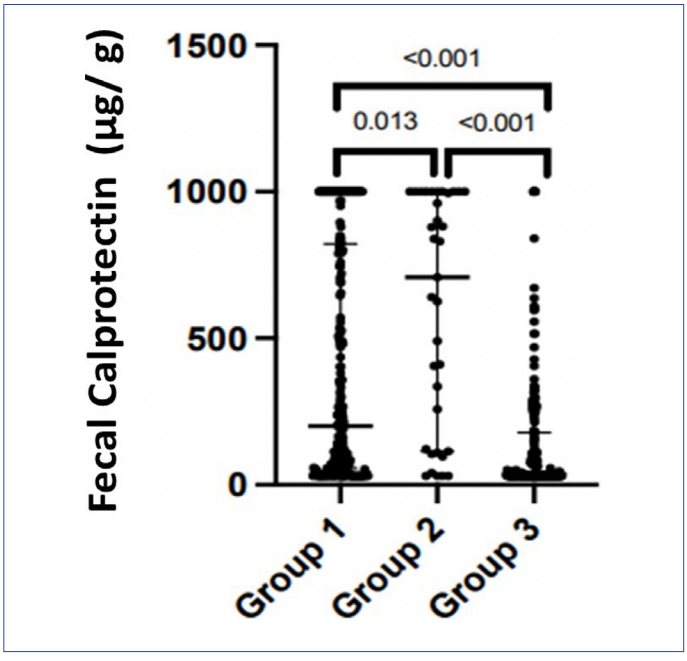

Figure 2. Distribution of FC levels in groups.
FC: Fecal calprotectin.

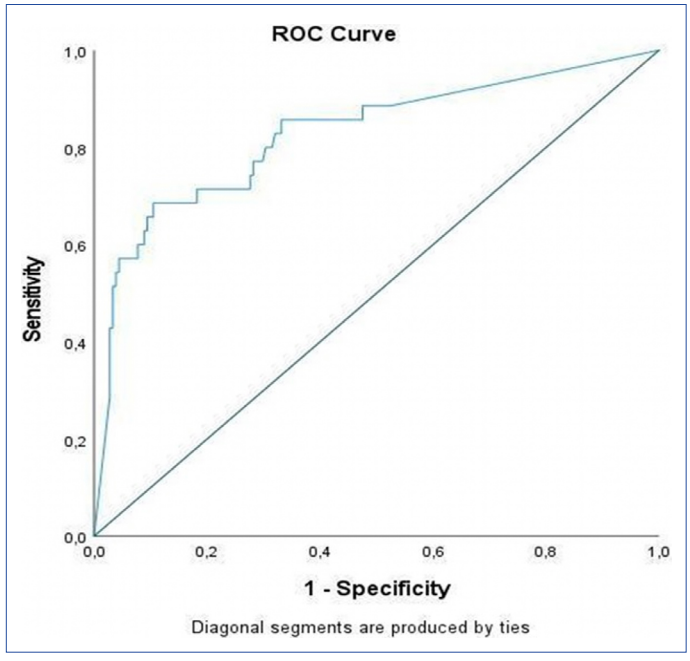

Figure 3. ROC analysis for FC.
ROC: Receiver operating characteristic; FC: Fecal calprotectin.

Table 2. Diagnostic accuracy performance of FOBT, FC and the combination of both these markers

	FC	FOBT	FOBT and/or FC
Total number of cases	216	153	153
True positives (n)	30	13	15
True negatives (n)	113	107	87
False positives (n)	68	30	50
False negatives (n)	5	3	1
NPV (%)	95.8	97.3	98.9
PPV (%)	30.6	30.2	23.1
Sensitivity (%)	85.7	81.3	93.8
Specificity (%)	62.4	78.1	63.5

FOBT: Fecal occult blood test; FC: Fecal calprotectin; NPV: Negative predictive value; PPV: Positive predictive value.

nostic and follow-up adjunct for IBD [18, 19]. Therefore, it is crucial for monitoring disease activity, assessing treatment efficacy, and detecting postoperative recurrences.

In our retrospective study, we observed a significant difference in FC levels between groups, including patients followed up with IBD and patients diagnosed with IBD and non-IBD. Furthermore, it was determined that FC levels were higher in patients diagnosed with IBD than in patients who were followed up with IBD. Studies evaluating disease progression using FC levels have been reported in the literature. In one study, FC levels were higher in patients newly diagnosed with IBD than in those under follow-up, consistent with our findings [20]. A study by Zhu et al. [21] found that FC levels in the active IBD group were significantly higher than those in the standard group, while no difference was observed between the inactive IBD and control groups. A decrease in FC levels is expected during the IBD follow-up period, corresponding with disease treatment. It should be noted that high FC levels during follow-up indicate disease relapses [22].

Diagnostic accuracy is crucial for tests and markers used to evaluate IBD [23]. This study investigates the diagnostic accuracy of FOBT, FC, and the combination of these markers in patients with suspected IBD.

Before the routine clinical use of FC in diagnosing and monitoring IBD, numerous studies have been conducted on appropriate cut-off values for IBD diagnosis and the diagnostic accuracy of FC [18, 24, 25]. Although many studies have demonstrated the diagnostic accuracy of FOBT for colorectal cancer, studies have also examined FOBT's diagnostic accuracy for IBD [10, 26].

The diagnostic accuracy of combining FOBT and FC for various GIS pathologies, including IBD, has been evaluated in previous studies [9, 27]. This study is the first retrospective investigation into the role of combining FOBT and FC specifically for predicting IBD diagnosis. Our literature review reveals limited data on the diagnostic accuracy for patients with IBD.

In our study, FC had a sensitivity of 85.7%, specificity of 62.4%, and NPV of 95.8%. When combined with FOBT, the sensitivity, specificity, and NPV were 93.8%, 63.5%, and 98.9%, respectively. Sensitivity, specificity, and NPV increased with this combination. These results indicate that combining FOBT and FC had better diagnostic accuracy than each test used alone in our study. Lué et al. [9] showed that the combination of FOBT and FC had a sensitivity of 89.7% and NPV of 100% for diagnosing IBD, which was higher than when either test was used alone, similar to our findings. A study by Mowat et al. [11] found that combining FOBT and FC achieved a sensitivity of 99.3% and NPV of 97.1% for diagnosing IBD when using an FC cut-off value of 50 µg/g. Although different FC cut-off values were used in that study, the combination outperformed both tests used alone, in line with our findings.

Högberg et al. [28] demonstrated that the combination of FOBT and FC had a sensitivity of 90% and an NPV of 99.6% when using a cut-off value of 100 µg/g for FC. Additionally, when the cut-off value was 20 µg/g, they found that the combination of both tests did not provide additional diagnostic information for IBD. Our findings differ from the conclusions reached in other studies, where the combination of both tests did not appear to provide additional information. In a study by Widlak et al. [12], the tests demonstrated a sensitivity of 86% and an NPV of 100% for diagnosing IBD, both when assessed individually and in combination. When these studies are examined, the results are broadly similar, showing that the combination offers better diagnostic accuracy than the tests used alone. However, sensitivity and NPV percentages vary, potentially due to population characteristics, whether the FOBT is qualitative or quantitative, and the chosen cut-off values.

Our study observed that the combined utilization of FOBT and FC demonstrated superior diagnostic accuracy in identifying patients with suspected IBD compared to individual tests alone. This finding suggests that implementing a combination of FOBT and FC before colon examination (colonoscopy or radiological imaging) is a cost-effective strategy to mitigate unnecessary procedures and reduce potentially associated complications.

Limitations

This study has some limitations, including the short data collection period and the fact that not all patients had both FOBT and FC results. In our study, we used data from 216 patients to assess the diagnostic accuracy of FC in suspected IBD, with FC results available in our hospital registry. However, not all of these patients had FOBT results. To ensure data consistency and completeness in our analysis, we excluded patients without an FOBT result when evaluating the diagnostic accuracy of the combination. Additionally, using quantitative methods in evaluating FOBT prevented us from obtaining AUC values for both FOBT alone and in combination with FC. Despite this, our approach allows for a comprehensive evaluation of the diagnostic utility of the combined tests in suspected cases of IBD and adds valuable information to clinical practice.

Conclusion

In conclusion, the sensitivity and NPV of the FC and FOBT combination are notably high compared to using them alone. We believe that this combination can be a valuable strategy for identifying patients with suspected IBD and for accurately identifying truly negative cases. These findings suggest that FC testing combined with FOBT could help clinicians identify patients who may benefit from further diagnostic evaluations for IBD, ultimately facilitating timely and appropriate management strategies. Well-designed studies are needed to confirm whether a positive FOBT and/or elevated FC test is a reliable predictor of IBD and therefore an indication for colonoscopy. For this reason, we designed this study. However, larger-scale studies are needed to confirm these findings, and research on the effectiveness of this testing approach for different types of IBD and varying disease activity levels is required.

Ethics Committee Approval: The study was approved by The Gazi University Clinical Research Ethics Committee (No: 847, Date: 21/11/2022).

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