

Clinical implications of fecal calprotectin and fecal immunochemical test on mucosal status in patients with ulcerative colitis

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Abstract

Although fecal calprotectin (Fcal) and the fecal immunochemical test (FIT) have been associated with endoscopic activity in ulcerative colitis (UC), the clinical implications of each marker depending on the mucosal status are not well known.

A total of 174 results obtained from 128 patients with UC who simultaneously underwent colonoscopy and fecal tests were retrospectively evaluated from March 2015 to February 2018. The correlation and predictability of fecal markers as a surrogate marker of endoscopic activity, and the sensitivity, specificity, and predictive value of fecal tests for mucosal healing were statistically evaluated.

Both fecal tests showed a statistically significant correlation with Mayo Endoscopic Subscore (MES) (Fcal: $r=0.678$, $P<.001$ and FIT: $r=0.635$, $P<.001$) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (Fcal: $r=0.711$, $P<.001$ and FIT: $r=0.657$, $P<.001$). Fcal was statistically superior to FIT in predictive accuracy for endoscopic activity (area under the curve [AUC]: 0.863 vs 0.765 with MES, $P<.001$ and AUC; 0.847 vs 0.757 with UCEIS, $P<.001$). FIT was superior to Fcal in sensitivity for mucosal healing (98.0% vs 78.4% with MES, 94.9% vs 74.6% with UCEIS).

Fcal and FIT were well correlated with endoscopic activity in UC and can be surrogate markers of mucosal inflammation. Depending on mucosal status, Fcal was more accurate in predicting the endoscopic activity in active inflammation, whereas FIT was more sensitive in predicting the achievement of mucosal healing.

Abbreviations: AUC = area under the curve, Fcal = fecal calprotectin, FIT = fecal immunochemical test, MES = Mayo endoscopic subscore, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristic, UC = ulcerative colitis, UCEIS = Ulcerative Colitis Endoscopic Index of Severity.

Keywords: fecal calprotectin, fecal immunochemical test, ulcerative colitis

1. Introduction

Ulcerative colitis (UC), a type of inflammatory bowel disease, is a chronic inflammatory disorder that repeatedly worsens and improves in the large intestine. Recently, mucosal healing has been highlighted as the most important target in the treatment of UC, because it is associated with a reduced risk of relapse and improved

clinical outcomes, which reduces the risk of surgery,^[1,2] steroid dependency,^[2] and hospitalization.^[1,2] Therefore, it is essential to modify the medication after periodic inspection of the mucosal status for achievement of mucosal healing. However, endoscopic assessment, an essential method for evaluating mucosal status, is not only an invasive and inconvenient test, but it can also aggravate symptoms in patients with UC.^[3] Thus, a reliable, noninvasive surrogate marker to replace the endoscopic assessment is needed.

Among surrogate markers for mucosal inflammation, both fecal calprotectin (Fcal) and the fecal immunochemical test (FIT) have been shown to be well correlated with endoscopic activity^[4-7] and have predictability for recurrence in patients with UC.^[8-11] However, both tests are used to assess the mucosal status in different ways; that is, Fcal is a surrogate marker for detecting a cytosolic granulocyte protein associated with neutrophil migration to the intestinal tract, and FIT is a surrogate marker for detecting stool hemoglobin derived from occult blood loss in mucosal ulceration.^[12] Thus, the results of both tests for mucosal inflammation or healing may have different clinical implications.

In the present study, we aimed to evaluate the correlation among endoscopic activity and fecal tests, and to determine the clinical implications of each test on the mucosal status for proper application of both fecal tests in patients with UC.

2. Methods

2.1. Patients

From March 2015 to February 2018, the medical records of patients with UC at the Pusan National University Yangsan

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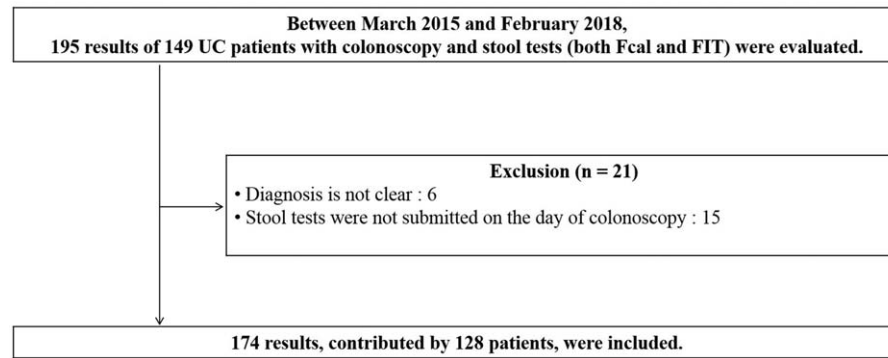


Figure 1. Flow chart of the enrolled patients. Fcal=fecal calprotectin, FIT=fecal immunochemical test, UC=ulcerative colitis.

Hospital (PNUYH) in the Republic of Korea were retrospectively reviewed. During the study period, 195 results of 149 patients with UC who underwent colonoscopy, Fcal, and FIT were evaluated. Among them, 6 patients whose diagnosis was not clear and 15 patients whose stool tests were not submitted on the day of endoscopy day were excluded. Finally, 174 results, contributed by 128 patients, were included (Fig. 1). This study was approved by the Institutional Review Board (IRB) of PNUYH (IRB number: 05–2018–070). Informed consent was obtained from each patient. There are no conflicts of interest or sponsors for this study.

2.2. Fecal sampling and analysis

All fecal samples were collected in two separate stool containers at 1 or 2 days before bowel preparation and submitted on the day of colonoscopy.

Samples submitted for calprotectin analysis were stored at -70°C until they were transported to the laboratory (Green Cross Laboratories, GC Labs, Korea). Calprotectin was measured using the EliA™ Calprotectin enzyme-linked immunosorbent assay kit (Thermo Fisher Scientific, Bremen, Germany). The quantitative range was between 11.5 and 2000 $\mu\text{g/g}$ for calprotectin, after an appropriate 1:100 dilution of the fecal samples.

Samples submitted to FIT analysis were immediately processed using the HM-JACK system (Kyowa Medex, Shizuoka, Japan), a fully automated quantitative FIT system. The HM-JACK system can accurately measure the fecal hemoglobin concentration within a range of 7 to 1200 ng/mL.

2.3. Assessment of endoscopic activity

Endoscopic activity was evaluated using the Mayo Endoscopic Subscore (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS).^[13,14] All endoscopic examinations were performed by experienced endoscopists. Endoscopic mucosal healing was defined as MES of 0 and UCEIS of 0–1 in this study.

2.4. Statistical analysis

Spearman's rank correlation was used to determine the correlation among fecal tests and instruments to assess the endoscopic severity of UC. The comparison between the area under the receiver operating characteristic (ROC) curve was analyzed using DeLong's test. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), with associated 95% confidence intervals, of fecal tests for mucosal healing were evaluated. A P -value $< .05$ was considered statistically significant.

Statistical calculations were performed with SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patients' characteristics

One hundred seventy-four results contributed by 128 patients (87 men and 41 women; median age, 47.2 years) were included in this study. Baseline characteristics of the enrolled patients are shown in Table 1. Mean disease duration was 48.9 months (range, 0–240

Table 1

Baseline characteristics of 128 patients and 174 cases.

Patients (n = 128)	
Male/female, n (%)	87/41 (68.0/32.0)
Age, mean \pm SD (range) years	47.2 (16–78) \pm 13.8
Disease duration, mean \pm SD (range) months	48.9 (0–240) \pm 50.8
Smoking, n (%)	
Current	4 (3.1)
Former	32 (25.0)
Never	92 (71.9)
Disease extent, n (%)	
Extensive colitis	48 (37.5)
Left sided colitis	50 (39.1)
Proctitis	30 (23.4)
Endoscopies and other values (n = 174)	
Mayo endoscopic subscore, n (%)	
'0'	51 (29.3)
'1'	54 (31.0)
'2'	41 (23.6)
'3'	28 (16.1)
UCEIS, n (%)	
'0–1'	59 (33.9)
'2–4'	55 (31.6)
'5–6'	47 (27.0)
'7–8'	13 (7.5)
Drug at study entry, n (%)	
Oral or topical 5-ASA	158 (90.8)/14 (8.0)
Systemic steroids	31 (17.8)
Azathioprine	32 (18.4)
anti-TNF alpha	22 (12.6)
Fecal calprotectin level ($\mu\text{g/g}$), mean (range)	699.13 (< 11.5 –2000)
Fecal hemoglobin concentrations (ng/mL), mean (range)	132.03 (< 7 –1200)
Hemoglobin level ($\times 10^6/\mu\text{L}$), mean (range)	13.2 (8–17.8)
White blood cell count ($\times 10^3/\mu$), mean (range)	7.33 (2.88–21.75)
Erythrocyte sedimentation rate (mm/h), mean (range)	18 (2–93)
C-reactive protein level (mg/L), mean (range)	0.91 (0.01–12.9)
Serum albumin level (g/dL), mean (range)	4.2 (2.0–5.1)

*5-ASA = 5 aminosalicylic acids, SD = standard deviation, TNF = tumor necrosis factor, UCEIS = ulcerative colitis endoscopic index of severity.

months). In most cases (98.8%), treatment was a suppository or oral 5-aminosalicylate, and in 85 cases (48.9%), the following additional medications were administered as treatment: systemic steroids in 31 (17.8%), azathioprine in 32 (18.4%), and antitumor necrosis factor- α therapy in 22 (2.6%) cases. During the study period, 39 patients were hospitalized for severe UC. Three patients underwent surgery for severe UC refractory to medical therapy. One patient underwent surgery for advanced colon cancer. Three patients were hospitalized for reasons other than UC itself, and one of them died of acute myocardial infarction.

3.2. Correlation between endoscopic activity and the fecal tests

Colonoscopy was performed in all patients. Sixty-six patients (38.0%) had extensive colitis, 74 (42.5%) had left-sided colitis, and 34 (19.5%) had proctitis. Endoscopic activity assessed by MES was as follows: mucosal healing (0) in 51 cases (29.3%), mild activity (1) in 54 cases (31.0%), moderate activity (2) in 41 cases (23.6%), and severe activity (3) in 28 cases (16.1%). Endoscopic activity assessed by UCEIS was as follows: mucosal healing (0–1) in 59 cases (33.9%), mild activity (2–4) in 55 cases (31.6%), moderate activity (5–6) in 47 cases (27%), and severe activity (7–8) in 13 cases (7.5%).

Fcal was measured with an average value of 699.1 $\mu\text{g/g}$ (range, negative to 2000 $\mu\text{g/g}$), and FIT was measured with an average value of 132.0 ng/mL (range, negative to 1200 ng/mL) in the enrolled patients. Both Fcal and FIT results were significantly

correlated with MES and UCEIS. Fcal was positively correlated with endoscopic activity; Spearman’s rho correlation coefficients were 0.678 with MES ($P < .001$) and 0.711 with UCEIS ($P < .001$). FIT was also positively correlated with endoscopic activity; Spearman’s rho correlation coefficients were 0.635 with MES ($P < .001$) and 0.657 with UCEIS ($P < .001$). The correlation between endoscopic activity and the fecal tests is shown in Figure 2.

3.3. Comparison of predictability of endoscopic activity between Fcal and FIT

As a negative cut-off value in this study, FIT was based on 100 ng/mL, which is used for colorectal cancer screening in most studies, and Fcal was set at 170 $\mu\text{g/g}$ based on the ROC curve for mucosal inflammation (Fig. 3). The predictive accuracy of Fcal for MES was statistically better than that of FIT (AUC, 0.863 vs 0.765, $z = 3.429$, $P < .001$). The predictive accuracy of Fcal for UCEIS was also statistically better than that of FIT (AUC, 0.847 vs 0.757, $z = 2.988$, $P < .001$). The comparison between two fecal tests is shown in Figure 4.

3.4. Sensitivity, specificity, and predictive value of the fecal tests for mucosal healing

The sensitivity, specificity, PPV, NPV, and accuracy of the two fecal tests for mucosal healing are summarized in Table 2. When the values indicative of mucosal healing were applied, Fcal

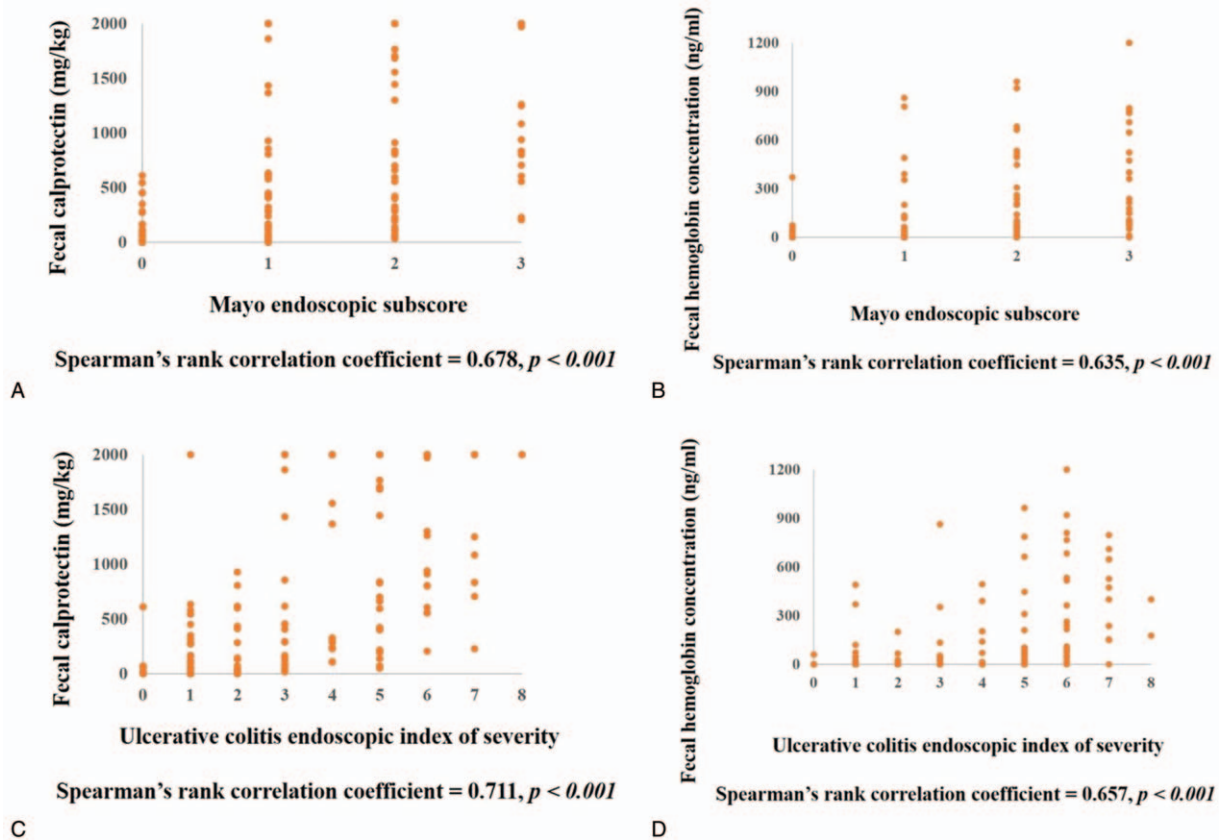


Figure 2. Correlation between fecal tests and endoscopic activity. (A) Fecal calprotectin and Mayo endoscopic subscore, (B) fecal immunochemical test and Mayo endoscopic subscore, (C) fecal calprotectin and Ulcerative colitis endoscopic index of severity, and (D) fecal immunochemical test and Ulcerative colitis endoscopic index of severity.

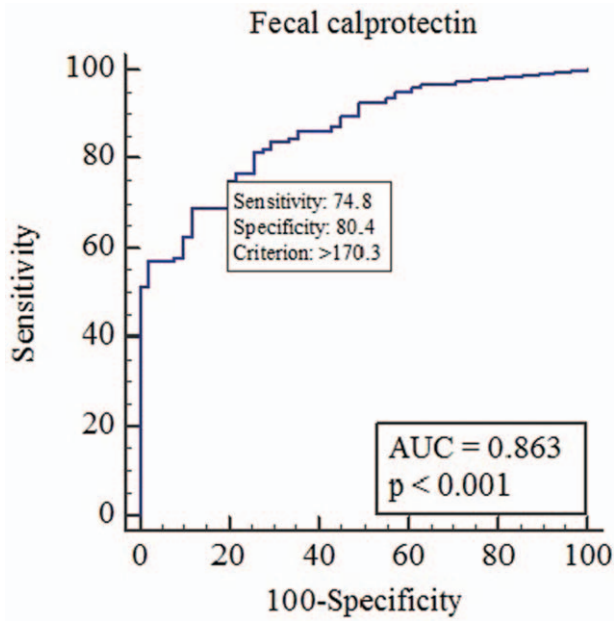


Figure 3. The receiver-operator characteristics curve of fecal calprotectin for predicting mucosal inflammation, MES 1-3. AUC=area under curve, MES= Mayo endoscopic subscore.

showed a sensitivity of 78.4%, specificity of 74.8%, PPV of 56.3%, NPV of 89.3%, and accuracy of 75.9%; and FIT showed a sensitivity of 98.0%, specificity of 37.4%, PPV of 39.4%, NPV of 97.9%, and accuracy of 55.2% in identifying patients with MES of 0 (Table 2A). Similar results were obtained for UCEIS. Fcal showed a sensitivity of 74.6%, specificity of 76.5%, PPV of 62.0%, NPV of 85.4%, and accuracy of 75.9%; and FIT showed a sensitivity of 94.9%, specificity of 38.3%, PPV of 44.1%, NPV of 93.6%, and accuracy of 57.5% in identifying patients with UCEIS of 0–1 (Table 2B).

4. Discussion

In this study, we confirmed a positive correlation between endoscopic activity and the fecal tests, and different predictability between the fecal tests depending on the mucosal status in patients with UC. Although several studies suggested that Fcal and FIT were well correlated with endoscopic activity and mucosal healing^[6,15–19] and that a negative FIT has a high sensitivity to mucosal healing in patients with UC,^[6,17–19] there has been no conclusion as to which of the two tests is superior. This study showed that Fcal was statistically more relevant to endoscopic activity with MES and UCEIS, and FIT was superior to Fcal in sensitivity for mucosal healing with MES and UCEIS.

Regarding the clinical application of our results, a conclusion similar to that in a recent study can be made. Hiraoka et al suggested that FIT confirms mucosal healing and is favorable for subsequent relapse prediction, suggesting that Fcal is more effective in monitoring patients with active inflammation.^[11] In this study, Fcal was more superior to FIT in predictability of endoscopy activity and had a low sensitivity for mucosal healing, so it could be used for monitoring UC patients with active inflammation. However, FIT had a high sensitivity for mucosal healing, and thus, could be used to monitor relapse in UC patients with mucosal healing. Based on these results, the strategy to use one of the two fecal tests depending on the mucosal status may be more economical rather than only using Fcal regardless of the mucosal status because FIT is inexpensive. On the basis of these results, we created a simple algorithm for managing patients with UC by using the two fecal tests (Fig. 5). After induction treatment, patients with UC should undergo endoscopy to confirm mucosal healing. If patients have mucosal healing and no symptoms, FIT should be used to regularly monitor them every 6–12 months. However, an endoscopic evaluation should be performed when FIT result is elevated to 100 ng/mL in these patients. If patients failed to show mucosal healing after induction treatment, Fcal level should be assessed after 3–6 months. According to Fcal level, an endoscopy to confirm mucosal healing should be performed in patients with Fcal level <170 μg/g and no symptoms, or re-

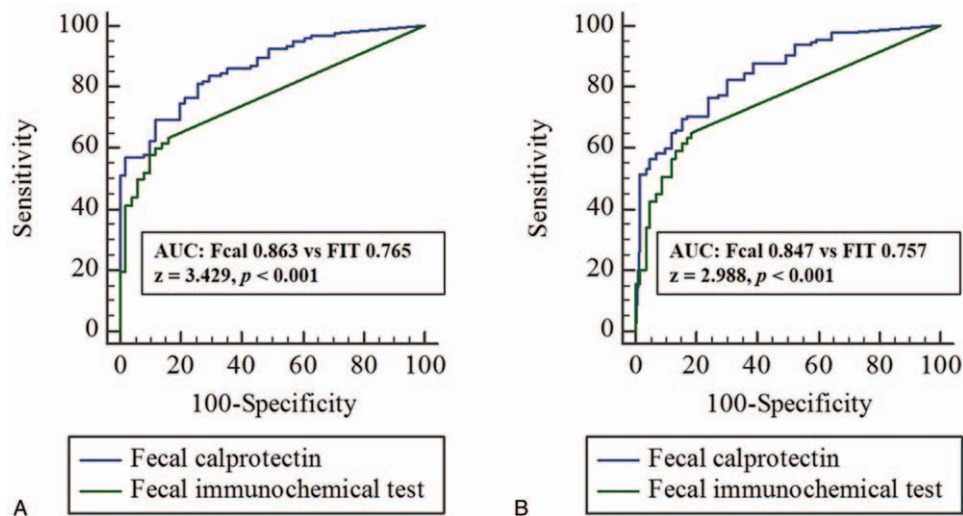


Figure 4. Comparison between fecal calprotectin and fecal immunochemical test for mucosal inflammation. AUC=area under curve, Fcal=fecal calprotectin, FIT=fecal immunochemical test, MES=Mayo endoscopic subscore, ROC=receiver-operator characteristics, UCEIS=ulcerative colitis endoscopic index of severity.

Table 2
The sensitivity, specificity, and predictive values of the two fecal tests for mucosal healing.

A. Fecal calprotectin vs fecal immunochemical test in Mayo endoscopic subscore 0		
Statistic	Fecal calprotectin (cut-off value < 170 µg/g) (%)	Fecal immunochemical test (cut-off value < 100 ng/mL) (%)
Sensitivity	78.4	98.0
Specificity	74.8	37.4
Positive predictive value	56.3	39.4
Negative predictive value	89.3	97.9
Accuracy	75.9	55.2
B. Fecal calprotectin vs fecal immunochemical test in ulcerative colitis endoscopic index of severity 0-1		
Statistic	Fecal calprotectin (cut-off value < 170 µg/g) (%)	Fecal immunochemical test (cut-off value < 100 ng/mL) (%)
Sensitivity	74.6	94.9
Specificity	76.5	38.3
Positive predictive value	62.0	44.1
Negative predictive value	85.4	93.6
Accuracy	75.9	57.5

monitoring of Fcal level should be performed after 3–6 months in patients with Fcal level $\geq 170 \mu\text{g/g}$.

Recently, simple and noninvasive tests that replace endoscopy have been studied in the evaluation of UC. Among several tests, Fcal is most frequently used. Fcal is a neutrophil-derived protein released in stool in response to mucosal inflammation, and it indicates the amount of inflammatory cells.^[20] Fcal has been reported to be associated with various conditions of UC. The level of Fcal is related to endoscopic severity,^[15] prediction of mucosal healing,^[16] and prediction of relapse,^[21] and it is useful in monitoring patients' response to treatment.^[22,23] Conversely, FIT indicates the amount of blood coming from the damaged mucosa, and it is used for colorectal cancer screening.^[24] There are a relatively small number of studies about FIT compared to Fcal in UC, and there are few reports related to mucosal healing.^[17–19] A recent meta-analysis reported that the sensitivity and specificity of the FIT result for predicting mucosal healing in UC were 0.77 and 0.81, respectively.^[25] In our study, the sensitivity and specificity of FIT for predicting mucosal healing in UC were 0.98 and 0.38,

respectively. The lower specificity of FIT for predicting mucosal healing in UC in this study than in the meta-analysis may be caused by the strict definition of mucosal healing and cut-off values of the present study. Actually, the definition of mucosal healing and the cut-off value were MES of 0 and 100 ng/mL in the present study, respectively, whereas those were MES of 0–1 and 50–280 ng/mL in studies included in the meta-analysis, respectively.

Several scoring systems are used for evaluating endoscopic activity of UC, among which MES is the most representative.^[13] More recently, UCEIS has been introduced^[14] and is known to reflect clinical outcomes and long-term prognosis.^[26,27] Ikeya et al suggested that UCEIS more accurately reflects clinical outcomes and long-term prognosis than MES.^[26] In this study, both scoring systems were useful because MES and UCEIS were statistically significantly correlated ($r=0.923$, $P<.001$). The definition of mucosal healing is not clearly defined, but recent studies have defined mucosal healing as only MES of 0.^[17,28,29] UCEIS does not yet have a standard value for mucosal healing.

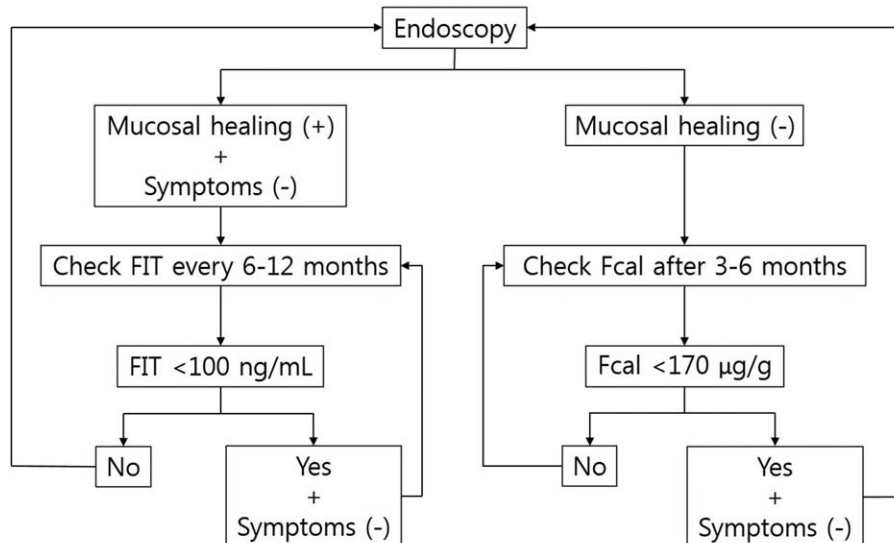


Figure 5. Algorithm for managing patients with UC using fecal tests. Fcal=fecal calprotectin, FIT=fecal immunochemical test, UC=ulcerative colitis.

Herein, endoscopic activity was evaluated by both MES and UCEIS, and mucosal healing was defined as MES of 0 and UCEIS of 0–1.

In the present study, FIT had a better sensitivity for mucosal healing than Fcal. However, the sensitivity may change depending on the determined cut-off value. For the FIT, usually a cut-off value of 100 ng/mL is used for screening for colorectal cancer. However, Fcal does not have a defined cut-off value. Therefore, most studies have used cut-off values of Fcal based on ROC curves. The cut-off value of Fcal for mucosal healing (MES 0) varied in each study: 180 µg/g in Hiraoka et al,^[11] 187 µg/g in Lee et al,^[30] and 194 µg/g in Yamaguchi et al.^[7] In these studies, the sensitivity and specificity were reported as 71% to 85% and 58% to 89%, respectively.^[7,11,30] In our study, the cut-off value was also determined based on the ROC curve, and the cut-off value of Fcal for MES of 0 could be set to 170 µg/g. Additionally, the sensitivity and specificity in our study were not significantly different from those in other studies.

There are some limitations to this study. First, there are inaccuracies and limitations of the fecal tests. FIT can be positive in different situations unrelated with UC, such as anal bleeding. Fcal has no standard cut-off value and produces different results depending on measurement kits and diurnal variation.^[31] Second, the sensitivity of FIT to mucosal healing was significantly higher but the specificity was lower than that reported in other studies, and FIT can show high false-positive results. However, FIT is an inexpensive and fast test, so we can perform it easily and frequently. Third, this study had a single-center, retrospective design with a small sample size. Nevertheless, when compared with other studies confirming the usefulness of fecal tests in patients with UC, the number of participating patients was relatively high, and only those patients who submitted a stool test on the day of colonoscopy were included in this study.

In conclusion, this study revealed that both Fcal and FIT were well correlated with endoscopic activity in patients with UC. Between the two tests, Fcal was statistically more correlated and had better predictive accuracy with endoscopic activity. On the other hand, FIT was more sensitive for predicting mucosal healing with MES and UCEIS. Therefore, we suggest that Fcal may be used to evaluate disease activity and treatment response in active UC patients with mucosal inflammation, and FIT may be used to monitor recurrence in patients with UC with mucosal healing. Further well-designed prospective, randomized, large-volume trials are required to determine proper application of the two fecal tests in patients with UC.

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Visualization: Dae Gon Ryu, Su Bum Park.

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Writing – review & editing: Dae Gon Ryu, Hyung Wook Kim.

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