Evaluation of mucosal healing of ulcerative colitis by a quantitative fecal immunochemical test

Short Title: Evaluation of mucosal healing by FIT

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CONFLICT OF INTEREST

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Abbreviations:

UC, ulcerative colitis; FIT, fecal immunochemical test; CRC, colorectal cancer; IBD, inflammatory bowel disease; CD, Crohn’s disease

Abstract

OBJECTIVES: Accumulating evidence has underlined the importance of mucosal healing as a treatment goal for ulcerative colitis (UC). Quantitative fecal immunochemical tests (FITs), which can rapidly quantify fecal blood with automated equipment, have been used recently to screen for colorectal neoplasia. The aim of this study is to determine whether an FIT can evaluate mucosal healing in UC.

METHODS: Feces collected from UC patients who underwent colonoscopy were examined by FITs, and results were compared with colonoscopic findings. Mucosal status was assessed using the Mayo endoscopic subscore classification. Maximum score for the colorectum in each patient was recorded.

RESULTS: Evaluated were FIT results in conjunction with 310 colonoscopies that were performed in 152 UC patients. A large majority of patients with a Mayo 0 endoscopic score had negative FIT (< 100 ng/ml) results (92%), and the proportion of negative FIT results decreased with increases in the Mayo score (Mayo 1: 47%, Mayo 2: 13%, Mayo 3: 12%, $p < 0.0001$, Cochran-Armitage trend test). When the negative FIT was defined as < 100 ng/ml, the sensitivity and specificity of a negative FIT for mucosal healing (Mayo 0) were 0.92 and 0.71, respectively. When mucosal healing was defined as Mayo 0 or 1, those were 0.60 and 0.87, respectively. In addition, a positive FIT ($\geq$ 100 ng/ml) predicted mucosal inflammation (Mayo 2 or 3) with sensitivity 0.87 and specificity 0.60, respectively.

CONCLUSIONS: The FIT can effectively and noninvasively evaluate mucosal healing in UC. This easy, rapid method can help evaluate and control disease activity of UC.

STUDY HIGHLIGHTS

1. WHAT IS CURRENT KNOWLEDGE

・Mucosal healing in ulcerative colitis (UC) is associated with sustained clinical remission and considered to be a treatment goal.

・Confirmation of mucosal healing requires colonoscopy.

・Quantitative fecal immunochemical tests (FITs) can quantify occult blood in many fecal samples and have been used to screen for colorectal neoplasia.

・The use of FITs for evaluation of colon mucosa of UC patients has scarcely been reported.

2. WHAT IS NEW HERE

・FIT results effectively reflected the mucosal status in UC.

・A negative FIT result could predict mucosal healing with sufficient sensitivity and specificity.

・By making use of FIT, treatment strategy for UC patients could be determined in many situations without performing colonoscopy.

Introduction

Ulcerative colitis (UC) is an idiopathic chronic inflammatory disorder that affects the innermost lining or mucosa of the colon and rectum, manifesting as continuous areas of inflammation and ulceration with no segments of normal tissue.(1) UC patients have symptoms such as diarrhea and bloody stool, unless appropriate treatment is provided. Aminosalicylates are the usual first-line treatment for UC, and 60-70% of patients with mild to moderate UC respond to them. Corticosteroid treatment is considered in patients with more severe symptoms when aminosalicylates are not effective. However, intravenous steroids are not effective in 20-30% of patients, and these patients ultimately are likely to require colectomy.(2)

Current opinions increasingly cite the need to achieve not only clinical response but also endoscopic mucosal healing in the treatment of UC. Mucosal healing is associated with sustained clinical remission, and reduced rates of hospitalization and surgical resection.(3) In addition, a recent study indicated that early mucosal healing after administration of infliximab for UC was correlated with improved clinical outcomes including avoidance of colectomy.(4) Another report showed that lack of mucosal healing after initial corticosteroid therapy was associated with late negative outcomes.(5)

Although endoscopic evaluation is necessary for confirmation of mucosal healing, undergoing colonoscopy is invasive and burdensome to patients. In addition, the colonoscopic procedure can worsen the disease condition even in UC patients in remission.(6) Therefore, noninvasive methods of evaluating and predicting mucosal status are eagerly desired. Although it was previously reported that fecal calprotectin and lactoferrin could be useful markers of intestinal inflammation,(7) the measurements

of these materials are not simple and not available in all institutions.

Quantitative fecal immunochemical tests (FITs) can measure hemoglobin concentrations in feces using an antibody for human hemoglobin. Such methods have been used to screen for colorectal neoplasia not only in Japan but Western countries instead of guaiac-based fecal occult blood tests.(8-10) In addition, FITs have the advantage of rapidly and simultaneously quantifying blood in many fecal samples with automated equipment.(8) The amount of fecal blood most likely reflects mucosal status in UC. In particular, occult blood can be present in feces of UC patients in clinical remission but without mucosal healing. Such fecal occult blood can be detected by FIT, and therefore, a negative FIT result may reflect and predict mucosal healing noninvasively.

In this study, we measured fecal hemoglobin concentrations by FIT in UC patients who had undergone colonoscopy. The ability of FIT to indicate the mucosal status, particularly mucosal healing, was examined by comparing fecal hemoglobin concentrations with colonoscopic findings.

Materials and Methods

Patients

Ambulatory UC patients who periodically visited Okayama University Hospital were routinely requested to prepare and bring fecal samples at each visit beginning in 2006, in order to evaluate the amount of fecal occult blood with an FIT. All UC patients who underwent scheduled colonoscopy between January 2006 and August 2011 were considered eligible for this study. All of the patients had an established diagnosis of UC according to endoscopic and histologic assessments and had received medical therapy. In this study, we compared colonoscopic findings with FIT results obtained on the day of colonoscopy or within one month before colonoscopy. Patients who did not have FIT results within one month before colonoscopy and patients with changes in abdominal symptoms or treatment after the FIT but before colonoscopy were excluded from this study.

Clinical disease activity was evaluated using the Mayo scores, consisting of the following 4 subscores: stool frequency (0, normal number for this patient; 1, 1-2 stools more than normal; 2, 3-4 stools more than normal; and 3, ≥ 5 stools more than normal), rectal bleeding (0, no blood seen; 1, streaks of blood with stool less than half the time; 2, obvious blood with stool most of the time; and 3, blood alone passes), endoscopic findings (0, normal or inactive disease; 1, mild disease with erythema, decreased vascular pattern, mild friability; 2, moderate disease with marked erythema, absent vascular pattern, friability, erosions; and 3, severe disease with spontaneous bleeding, ulceration), and physician's global assessment (0, normal; 1, mild disease; 2, moderate disease; and 3,severe disease). (11) Clinical remission was defined as a Mayo stool frequency subscore of 0 or 1 and a Mayo rectal bleeding subscore of 0.(4) All other

patients were considered to have clinically active disease. The study protocol was approved by the institutional review board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. Informed consent was obtained from each patient.

Fecal sampling and instrument for FIT analysis

Details of the method used for the FIT were described previously.(8, 9, 12) Briefly, patients prepared fecal samples on the morning of or the day before the clinic visit using an OC-Hemodia sampling probe (Eiken Chemical, Tokyo, Japan) provided by the manufacturer of the kit. An 8 cm × 2 cm test tube-shaped container holds the sampling probe. The patient inserts the probe into several different areas of stool and then firmly places it back into the tube to seal it. The probe tip with the fecal sample is suspended in a standard volume of hemoglobin-stabilizing buffer. Submitted stool samples were immediately processed and examined using OC-SENSOR neo (Eiken Chemical), which can accurately measure fecal hemoglobin concentration from 50 ng/ml – 1000 ng/ml. Fecal specimens with a hemoglobin concentration over 1000 ng/ml were measured by dilution. On the other hand, fecal specimens with a hemoglobin concentration less than 50 ng/ml were categorized as one (0 – 50 ng/ml) because FIT results are inaccurate when the hemoglobin concentration is less than 50 ng/ml. In general, stools with a hemoglobin concentration more than several thousands ng/ml were recognized as bloody stools.(12)

Colonoscopy

On the day of the colonoscopy, patients received a polyethylene glycol-based or magnesium citrate-based electrolyte solution for bowel preparation according to the instructions for use. After the colonic lavage was finished, patients underwent the

colonoscopy. Patients were excluded if the colonoscopic examination was incomplete because of problems with the bowel preparation or if the colonoscope could not be inserted into the cecum.

Mucosal status of UC was assessed using the Mayo endoscopic subscore classification. Evaluation was performed at each portion of the colorectum (cecum, ascending, transverse, descending, and sigmoid colon, and rectum), and the maximum score in the colorectum of each patient was used for analysis. Mucosal healing was defined as an endoscopy score of '0', or '0 or 1' throughout the colorectum.

Statistical analysis

Statistical analysis was conducted using the JMP program (version 9, SAS Institute, Cary, NC, USA). Spearman rank correlation was performed to determine the association between fecal hemoglobin concentrations and the Mayo endoscopic scores or the total Mayo score, and the trend between them was evaluated using the Cochran-Armitage trend test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio with 95% confidence intervals (CIs) for detecting mucosal status based on FIT results were determined. To estimate appropriate cutoff values for the FIT, receiver operating characteristic (ROC) curve analysis was performed. The predictive value of FIT versus mucosal healing on the risk of relapse was examined using Cox proportional hazards regression. All *p* values were two-sided and considered significant when less than 0.05.

Results

Clinical characteristics of patients

A total of 310 colonoscopies that were accompanied by corresponding FIT results were performed in 152 UC patients (77 men, 75 women; median age at UC onset 30 years) (Table 1). Of 310 colonoscopy cases, 134 (43%) were performed in patients in clinical remission, while the other 176 (57%) were performed in patients with clinically active disease. Colonoscopy findings revealed that the maximum endoscopic subscore for the colorectum was Mayo 0 in 48 (15%) cases, Mayo 1 in 123 (40%) cases, Mayo 2 in 106 (34%) cases, and Mayo 3 in 33 (11%) cases. Among 262 patients with endoscopic activity (Mayo 1-3), 162 (62%) had the maximum degree of mucosal inflammation in the rectum, 49 (19%) had in the sigmoid colon, and 51 (19%) had in the descending colon or more proximal part. On the other hand, FIT results indicated that more than one third of cases had fecal hemoglobin concentrations of 100 ng/ml or less (120/310, 39%), while approximately half of the remaining cases had fecal hemoglobin concentrations of more than 1000 ng/ml (106/310, 34%).

Correlation between FIT results and colonoscopic findings

The correlation between FIT results and colonoscopic findings is shown in Figure1. Spearman rank correlation coefficient and the corresponding p value for the correlation were 0.5409 and $p < 0.0001$, respectively. Since the cutoff value of hemoglobin concentration 100 ng/ml is usually used in colorectal cancer (CRC) screening,(13) the proportions of cases with hemoglobin concentration < 100 ng/ml were examined in relation to the Mayo score. The proportion of cases with hemoglobin concentration < 100 ng/ml was greatest in cases with Mayo 0 (44/48, 92%), and gradually decreased as the Mayo scores increased (Mayo 1: 58/123, 47%; Mayo 2:

14/106, 13%; and Mayo 3: 4/33, 12%). The trend of the decrease in relation to the Mayo endoscopic score was statistically significant ($p < 0.0001$, Cochran-Armitage trend test). This trend was similarly observed when analysis was restricted on patients with active disease (176 cases, Figure 1, red dots, $p = 0.035$) and when restricted on a single colonoscopy per patient (152 cases, Supplemental figure 1, $p < 0.001$). In addition to the correlation of FIT results with colonoscopic findings, the significant correlation between FIT results and disease activity (the total Mayo score) was observed (Supplemental figure 2, Spearman rank correlation coefficient = 0.70, $p < 0.001$).

Sensitivity, specificity and predictive values of fecal hemoglobin concentration for mucosal status

Table 2 shows the sensitivity, specificity, PPV, NPV, positive likelihood ratio, negative likelihood ratio and accuracy of the fecal hemoglobin concentration in relation to mucosal healing. When a negative FIT result was defined as < 100 ng/ml as in case of CRC screening, the sensitivity, specificity, PPV, NPV and accuracy of a negative FIT result for mucosal healing (Mayo 0) were 0.92, 0.71, 0.37, 0.97 and 0.74, respectively. Because the ROC curve indicated that 60 ng/ml was an optimal threshold (data not shown), those values in the case of a 60 ng/ml cutoff were 0.94, 0.74, 0.40, 0.98 and 0.70, respectively. The analysis restricted on a single colonoscopy per patient showed slightly lower sensitivity (0.83, negative FIT < 100 ng/ml) and slightly higher specificity (0.83, negative FIT < 100 ng/ml) (Supplemental Table 1). The interval between FIT and colonoscopy did not affect significantly on the sensitivity and specificity (within 1 week, 1-3 weeks, and 3 weeks or more: sensitivity; 0.88, 0.91, and 0.93, specificity; 0.74, 0.69, and 0.69, respectively). Analysis according to extent of disease revealed that the test performance on proctitis was somewhat low, compared to

other disease types (pancolitis, left-side colitis, and proctits: sensitivity; 0.93, 1.00, and 0.67, specificity; 0.71, 0.76, and 0.68, respectively).

Since the definition of mucosal healing has not definitely been established, we next determined the sensitivity, specificity etc. of a negative FIT for the Mayo endoscopic index 0 or 1 (Table 3). In this analysis, sensitivity was lower (0.60, negative FIT < 100 ng/ml) and specificity was higher (0.87, negative FIT < 100 ng/ml) than in case for the Mayo 0 only. In addition, as was expected, PPV was markedly higher (0.85, negative FIT < 100 ng/ml).

In addition to the prediction of mucosal healing, the correlation between FIT results and endoscopically active diseases was examined (Table 4). The sensitivity and specificity of a positive FIT result (hemoglobin concentration $\geq$ 100 ng/ml) for the Mayo endoscopic score 2 or 3 were 0.87 and 0.60, respectively. In this context, predictive power of a positive FIT result on the risk of relapse in clinically quiescent patients was determined using the Cox proportional hazards model. The hazard ratio of a positive FIT result ($\geq$ 100 ng/ml) for relapse was 1.72 (95%CI 0.93-3.00, p = 0.061), while the ratio of endoscopically active diseases (Mayo 1-3) for relapse was 2.13 (95%CI 1.16-4.24, p = 0.012). This suggests that a positive FIT result would be close to, but not go beyond endoscopic activity as the risk of relapse.

The predictive power of FIT results for mucosal status varied according to the definition of mucosal healing due to the skewed variation of endoscopic activities of our cohort. However, negative FIT results predicted mucosal healing with sufficient sensitivity and specificity, and therefore, UC patients in clinical remission with a negative FIT result could be regarded as being sufficiently treated. In contrast, a positive FIT result would imply the need of stricter follow-up. Thus, by making use of

FIT, treatment strategy for UC patients could be determined in many situations without performing colonoscopy.

Discussion

In this study, we compared FIT results and colonoscopy findings in UC patients, and found that FIT results accurately reflected the mucosal status in UC. In addition, a negative FIT result effectively predicted mucosal healing in UC. Therefore, FIT can be useful in evaluating mucosal healing after remission induction therapy. Moreover, because repeated evaluations of mucosal healing are required over the duration of UC, the noninvasive, low-cost, and rapid FIT is a suitable method that can be applied at each patient's hospital or clinic visit. Its use would be helpful in reducing the burden of undergoing colonoscopy to confirm mucosal healing.

After the accumulation of evidence for the value of mucosal healing in Crohn's disease (CD),(14, 15) mucosal healing also has also been regarded as an important clinical goal in UC. Studies of infliximab have played important roles in establishing evidence of mucosal healing in the field of UC as well as in CD. The follow-up study of the Active UC Trials–showed that mucosal healing after 8 weeks of infliximab was correlated with improved clinical outcomes including avoidance of colectomy.(4) Moreover, several additional studies indicated that mucosal healing in UC can alter the course of UC with reductions in hospitalization rates and surgical resections,(16) and by lowering the risk of dysplasia and adenocarcinoma of the colon.(16-18) A recent report showed that lack of mucosal healing after the first corticosteroid therapy was associated with late negative outcomes.(5)

Thus, achieving mucosal healing in UC has become an important clinical goal. However, evaluation of mucosal healing by endoscopy is burdensome for patients. In addition to the colonoscopy procedure itself, bowel preparations, possible worsening of disease after colonscopy, and high cost are all matters of concern to patients. Moreover,

because repeated confirmation of mucosal healing is required over the long term, patients must undergo repeated colonoscopies. To overcome the most problematic clinical point in evaluating mucosal healing, surrogate noninvasive markers of mucosal healing have been explored.

Although results using blood markers, including C-reactive protein, have been disappointing in predicting mucosal healing as well as in evaluating clinical activity of UC,(19) fecal calprotectin, a major protein found in the cytosol of inflammatory cells, has been examined extensively to determine its correlation with disease status of IBD and was found to be the only marker to predict activity of UC as shown by endoscopy. Schoepher et al. reported that fecal calprotectin values were more closely correlated with the Rachmilewitz endoscopic activity index than clinical symptoms or blood markers, and showed that the fecal calprotectin with cuttoff values of $\geq$ 50 μg/g had the best performance in sensitivity (93%), specificity (71%), PPV (91%), NPV (81%), and accuracy (89%) for detection of endoscopically active disease (defined as Rachmilewitz Endoscopic Activity Index $\geq$ 4).(20)

Thus, fecal calprotectin was shown to be an effective pioneer as a fecal marker of mucosal healing in UC.(20) However, FIT has several advantages in comparison with fecal calprotectin. First, FIT is simpler and less costly. To measure fecal calprotectin, 5 – 10 g of stool is required, while the FIT requires only insertion of a probe into the stool, making it more user friendly and possibly resulting in better compliance. The dietary restriction that is required in guaiac-based fecal occult blood tests but not with the FIT makes the latter test more accessible to UC patients.

The cost of each FIT is minimal and mainly limited to the cost of the collecting tube, although the automated equipment (OC-Sensor neo at our institution) is rather

expensive, usually costing tens of thousands of dollars. However, this equipment is also used for CRC screening. Therefore, at least in Japan, tertiary medical centers, including our institute, usually have such equipment. The FIT for UC patients is probably available even in smaller institutes, including general practices, because many low-cost manual kits for FIT are available, although such kits cannot quantify fecal hemoglobin. However, qualitative methods could be substituted for the testing equipment described in this report, because sensitivity of each manual kit corresponds to a unique cutoff value of a quantitative method. Cutoff values we used in this study (60 – 100 ng/ml) are those usually used in CRC screening,(9, 21) and therefore, the sensitivity of the majority of manual kits would be similar to ours.

The rapidity of the FIT is another advantage. Automated FIT equipment can usually measure more than 100 samples in a few minutes, while measurement of fecal calprotectin requires the enzyme-linked immunosorbent assay technique,(22) which usually takes several hours. Therefore, FIT can be easily performed for many outpatients before a doctor's visit, and helpful for evaluating disease activity of patients in a short time.

When mucosal healing was defined as Mayo 0, the sensitivity, specificity, and NPV of the FIT was equal to fecal calprotectin as shown previously but the PPV was relatively lower for mucosal healing. The PPV could be comparable when mucosal healing was defined as Mayo 0 or 1. In our study, we adopted the Mayo endoscopic index in evaluating of mucosal status, while Schoepher et al.(20) adopted Rachimilewitz endoscopic index < 4 as mucosal healing. The difference in definitions of mucosal healing may have brought about the difference in sensitivity, specificity etc. In future studies, comparison of the ability to detect mucosal healing between fecal calprotectin

and FIT should be performed using the same cohort and the same definition of mucosal healing.

There are limitations to this study. First, we adopted the 1-day method of FIT, in which stool is collected for only 1 day. In CRC screening, stool collection for 2 or 3 days is usually recommended as superior to a single collection in terms of sensitivity for colorectal neoplasia.(23-25) In this study that targeted mucosal healing in UC patients, the FIT examination of 2 or 3 fecal samples may have raised sensitivity to slight mucosal inflammation. Consequently, the examination of multiple samples might reduce the proportion of negative FIT results in patients with a Mayo 1 endoscopic index, and therefore, specificity and PPV for Mayo 0 only of negative FIT results may be improved. Second, the FIT cannot be used in women during menstruation as the value of fecal hemoglobin concentration may be inaccurate. Lastly, we did not examine mucosal healing in CD patients, although that had been done with fecal calprotectin.(26) Because detection of bleeding in the small intestine by the FIT has not been definitely determined, patients with CD involving only the colon may be a target for FIT in future studies.

In conclusion, our study revealed that FIT results effectively reflected the mucosal status in UC and that a negative FIT was strongly correlated with mucosal healing. This noninvasive, easy, low-cost and rapid method can help in the evaluation and control of disease activity in UC. In addition, our findings indicated an important new application for FIT in addition to CRC screening.

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Figure Legends

Figure 1. Correlation between fecal hemoglobin concentrations and colonoscopic findings.

The fecal hemoglobin level was positively correlated with endoscopic activity (Spearman rank correlation coefficient = 0.5409, $p < 0.0001$). The proportion of cases with a hemoglobin concentration < 100 ng/ml was greater in cases with Mayo 0 (92%), and the proportions were gradually decreased with increases in the Mayo endoscopic subscore (Mayo 1: 47%, Mayo 2: 13%, and Mayo 3: 12%). The trend of a decrease in the proportion of negative results according to increases in the Mayo subscore was statistically significant ($p < 0.0001$, Cochran-Armitage trend test). This trend was similarly observed when analysis was restricted on patients with active disease (176 cases , red dots, $p = 0.035$).

Table 1. Characteristics of study patients, colonoscopy findings and results of fecal immunochemical tests

Patients	
Total	152
Median (range) age at onset	30 (4-80)
Gender	
Male	77 (51%)
Female	75 (49%)
Number of colonoscopy	
1	74 (49%)
2	23 (15%)
≥3	55 (36%)
Extent of disease	
Pancolitis	98 (65%)
Left-side colitis	31 (20%)
Proctitis	23 (15%)
Colonoscopy	
Total	310
Median (range) duration of disease, months	135 (0.57-487)
Median (range) age of undergoing colonoscopy	31 (4-71)
Median (range) intreval between FIT and colonoscopy, days	16 (1-29)
Clinical activity	
Remission stage	134 (43%)
Active stage	176 (57%)
Purpose of colonoscopy	
Evaluation of disease	138 (45%)
Surveillance	172 (55%)
Concomitant medications	
Aminosalicylate	291 (94%)
Corticosteroids	75 (24%)
Mercaptopurine/Azathioprine	129 (42%)
Tacrolimus	10 (3%)
Colonoscopy findings (maximum index in the colorectum)	
Mayo 0	48 (15%)
Mayo 1	123 (40%)
Mayo 2	106 (34%)
Mayo 3	33 (11%)
Fecal hemoglobin concentrations (ng/ml)	
0 - 50	110 (36%)
51 - 100	10 (3%)
101 - 1000	84 (27%)
1001 - 10000	87 (28%)
10001 -	19 (6%)

Table 2. Sensitivity, specificity, and predictive values of fecal immunochemical tests for mucosal healing (Mayo endoscopic score 0)

	Fecal Hb concentration ＜100 ng/ml	Fecal Hb concentration ＜60 ng/ml
Sensitivity (95% CI)	0.92 (0.84-0.99)	0.94 (0.87-1.00)
Specificity (95% CI)	0.71 (0.65-0.76)	0.74 (0.69-0.79)
PPV (95% CI)	0.37 (0.28-0.45)	0.40 (0.31-0.49)
NPV (95% CI)	0.97 (0.96-1.00)	0.98 (0.97-1.00)
Accuracy (95% CI)	0.74 (0.69-0.79)	0.70 (0.72-0.82)
Positive likelihood ratio	3.16 (2.63-3.44)	3.48 (2.88-3.80)
Negative likelihood ratio	0.12 (0.05-0.27)	0.11 (0.05-0.26)

Hb, hemoglobin; PPV, positive predictive value; NPV, negative predictive value;
CI, confidence interval

Table 3. Sensitivity, specificity, and predictive values of fecal immunochemical tests for mucosal healing (Mayo endoscopic score 0 or 1)

	Fecal Hb concentration ＜100 ng/ml	Fecal Hb concentration ＜60 ng/ml
Sensitivity (95% CI)	0.60 (0.55-0.63)	0.58 (0.54-0.61)
Specificity (95% CI)	0.87 (0.82-0.91)	0.90 (0.85-0.94)
PPV (95% CI)	0.85 (0.79-0.90)	0.88 (0.82-0.92)
NPV (95% CI)	0.64 (0.60-0.67)	0.64 (0.60-0.66)
Accuracy (95% CI)	0.72 (0.67-0.77)	0.72 (0.67-0.77)
Positive likelihood ratio	4.61 (3.04-7.17)	5.75 (3.57-9.56)
Negative likelihood ratio	0.46 (0.41-0.55)	0.47 (0.42-0.54)

Hb, hemoglobin; OR, odds ratio; CI, confidence interval

Table 4. Sensitivity, specificity, and predictive values of fecal immunochemical tests for endoscopically active diseases (Mayo endoscopic score 2 or 3)

	Fecal Hb concentration ≥ 100 ng/ml	Fecal Hb concentration ≥ 120 ng/ml
Sensitivity (95% CI)	0.87 (0.82-0.91)	0.86 (0.80-0.90)
Specificity (95% CI)	0.60 (0.55-0.63)	0.62 (0.58-0.66)
PPV (95% CI)	0.64 (0.60-0.67)	0.65 (0.61-0.68)
NPV (95% CI)	0.85 (0.79-0.90)	0.84 (0.78-0.89)
Accuracy (95% CI)	0.72 (0.67-0.77)	0.73 (0.68-0.78)
Positive likelihood ratio	2.16 (1.83-2.47)	2.25 (1.89-2.61)
Negative likelihood ratio	0.22 (0.14-0.33)	0.23 (0.15-0.34)

Hb, hemoglobin; OR, odds ratio; CI, confidence interval

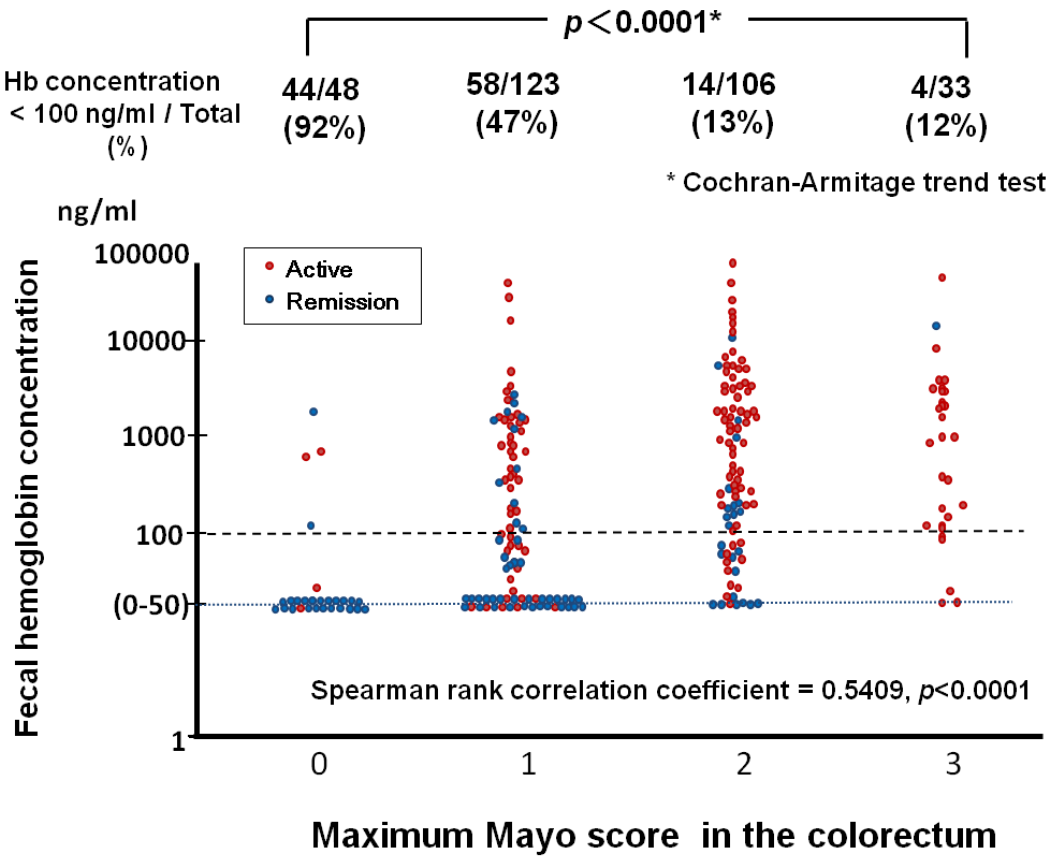
p＜0.0001*
Hb concentration
< 100 ng/ml / Total
(%)
44/48
(92%)
58/123
(47%)
14/106
(13%)
4/33
(12%)
* Cochran-Armitage trend test
ng/ml
100000
10000
1000
100
(0-50)
1
Active
Remission
Fecal hemoglobin concentration
Spearman rank correlation coefficient = 0.5409, p<0.0001
0
1
2
3
Maximum Mayo score in the colorectum

Figure 1