Predicting Ulcerative Colitis Relapse in Clinical Remission With Fecal Immunochemical Occult Blood Test or Prostaglandin E-Major Urinary Metabolite

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INTRODUCTION: **The fecal immunochemical occult blood test (FIT) and prostaglandin E-major urinary metabolite (PGE-MUM) have been reported to predict the relapse of ulcerative colitis (UC) during remission. In this study, we directly compared FIT and PGE-MUM in predicting relapse and examined the effect of disease duration on these biomarkers.**

METHODS: **Measurements of 2 biomarkers and endoscopic examination were performed in 73 patients with UC in remission. The patients were followed up for 12 months, and clinical relapse was evaluated. In addition, we divided the patients into long-term disease duration and short-term disease duration groups for analysis.**

RESULTS: **Twenty-one patients (28.8%) relapsed within 12 months. FIT and PGE-MUM levels were significantly higher in the relapsed group than in the remission group. Cutoff values of FIT and PGE-MUM for predicting relapse using receiver operating characteristic analysis were 65.0 ng/mL (area under the curve [AUC]: 0.723) and 25.2 μg/g·Cr (AUC: 0.701), respectively. Patients with FIT ≥ 65.0 ng/mL and PGE-MUM ≥ 25.2 μg/g·Cr had a higher risk of clinical relapse. In the short-term disease duration group, the AUCs of FIT were larger than those of PGE-MUM using receiver operating characteristic analysis, in most instances. By contrast, the AUCs of PGE-MUM were larger than those of FIT in most cases in the long-term disease groups.**

DISCUSSION: **FIT and PEG-MUM were highly accurate in predicting clinical relapse in UC patients with short and long disease durations in remission, respectively.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A816, http://links.lww.com/CTG/A817, http://links.lww.com/CTG/A818

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INTRODUCTION

Ulcerative colitis (UC) is a refractory disease characterized by symptoms including diarrhea, bloody stools, and abdominal pain, with repeated relapses and remissions (1). In recent years, the goals for treating UC have been to prevent relapse and maintain remission to improve long-term prognosis. This requires an intense treatment regimen for patients with UC in remission, at the first sign of relapse, before clinical relapse occurs (2). The endoscopic score was initially proposed as a predictor of relapse, and in a study evaluating the Mayo endoscopic subscore (MES) of UC patients with mucosal healing, it was reported that UC relapse was significantly more likely to occur in the MES 1 group than in the MES 0 group (3,4). It was also reported that the UC endoscopic index of severity, which is often used in clinical trials as an endoscopic score, such as MES, can predict relapse (5,6). However, from the viewpoint of patients' burden and cost, frequent colonoscopy is not considered an efficient approach.

The use of biomarkers for predicting UC relapse has been reported as an alternative method for endoscopic scores, especially using fecal biomarkers, such as fecal occult blood tests (FIT) and fecal calprotectin (FC), which have been shown to predict subsequent relapses in patients with UC in clinical remission (7–11). Some studies have investigated the relapse prediction of FIT and FC, which when measured simultaneously revealed that

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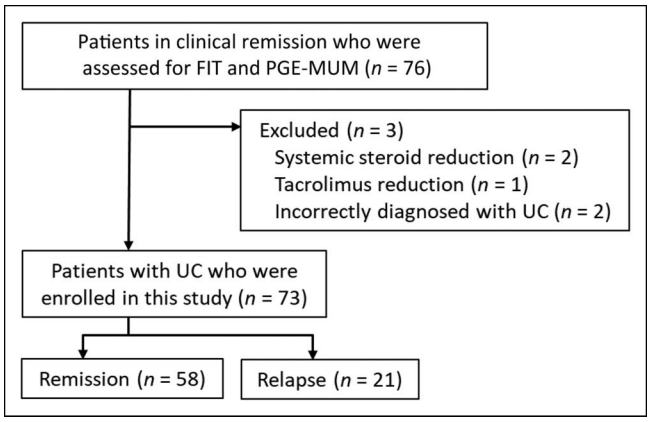

Figure 1. Study flowchart. Patients in clinical remission were tested for the fecal immunochemical occult blood test (FIT) and prostaglandin E-major urinary metabolite (PGE-MUM). Five patients were excluded and 73 patients with ulcerative colitis (UC) were enrolled in this study. Twenty-one patients relapsed and the remaining 58 patients were in clinical remission for 12 months.

more accurate relapse prediction is possible by using a combination of these 2 fecal biomarkers (8,9,11).

Arai et al. reported that the urinary biomarker prostaglandin E-major urinary metabolite (PGE-MUM) reflected the endoscopic activity of patients with UC (12). In our previous analysis of the correlation of FIT and PGE-MUM with endoscopic scores and the achievement of mucosal healing for disease duration, we found that predictability based on FIT and PGE-MUM was more accurate in groups with short and long disease durations, respectively (13). We also have previously reported that PGE-MUM could predict relapse in patients with UC in clinical remission (14). However, PGE-MUM was the only biomarker that was measured while investigating clinical relapse.

In this study, we compared and analyzed the relapse prediction by PGE-MUM and FIT. We also investigated the effect of disease duration on the prediction of clinical relapse using FIT, which has not been previously reported.

MATERIAL AND METHODS

Patients

Patients with UC in clinical remission and mucosal healing at Hamamatsu University School of Medicine between August 2016 and October 2020 were enrolled in this study. Patients were diagnosed with UC according to the guidelines based on the clinical course, the evaluation of typical symptoms, and endoscopic and histological findings.

Enrolled patients were assessed for clinical activity and endoscopy scores at the time of enrollment. Clinical activity was assessed using the Rachmilewitz index, and the criterion for clinical remission of the clinical activity index was defined as 4 or less (15). Endoscopic scores were assessed using MES (16). The criteria for MES were as follows: 0, normal or inactive disease; 1, mild disease with erythema, decreased vascular pattern, and mild friability; 2, moderate disease with marked erythema, absence of vascular patterns, friability, and erosions; and 3, severe disease with spontaneous bleeding and ulceration. In this study, only MES 0 or 1 was analyzed for mucosal healing and patients with MES 2 or 3 were excluded. Patients who were incorrectly diagnosed with UC, such as indeterminate colitis and unclassified inflammatory bowel disease, were excluded. In addition, because smoking, chronic fibrosing interstitial pneumonia, and malignant diseases are known to elevate PGE-MUM levels (17–22), UC patients with these conditions were also excluded. It is established that the discontinuation of current treatments may result in relapse; therefore, patients tapering off drugs including systemic steroids, tacrolimus, immunomodulators, 5-aminosalicylic acid, or advanced therapy were excluded. Outpatient visits were conducted at intervals of no more than 3 months over a year or until relapse. Clinical relapse was defined as an increase in the clinical activity index above baseline due to the worsening of diarrhea, frequent or bloody stools, and patients requiring a change or modification of therapy. The levels of FIT and PGE-MUM at enrollment were not known to the attending physicians. The change or modification of the treatment of UC was left to the discretion of each attending physician.

Study design

This study was conducted prospectively in a single facility. The purpose of this study was to evaluate FIT and PGE-MUM as clinical relapse markers and the associated effect of the disease duration. The primary outcome measure of this study was an assessment of the association between FIT and PGE-MUM and the occurrence of relapse within 12 months. The secondary end points were assessments of the association between FIT and PGE-MUM and clinical relapse subgroup analysis of patients with long-term and short-term disease duration.

Measurements of biomarkers

Fecal samples for FIT were obtained on or before the day of colonoscopic preparation. The enrolled patients prepared fecal samples using a stool collection kit (Eiken Chemical, Tokyo, Japan). The submitted samples were immediately processed and examined using an OC Sensor io (Eiken Chemical).

Spot urinary samples for the measurement of PGE-MUM were collected during the morning endoscopic examination. The collected urine samples were frozen at −20 °C and delivered to the SRL Hachioji Laboratory (Tokyo, Japan). The values were measured with a γ-counter (Hitachi) using a bicyclic PGE-MUM radioimmunoassay kit (Fujirebio, Tokyo, Japan). To account for the effect of urine concentration, PGE-MUM levels were corrected for urinary creatinine levels.

Statistical analysis

Statistical analyses of the data were performed using the SPSS version 27 (IBM Armonk, New York). EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for R because it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics (23). Differences between median values were compared using the Mann-Whitney *U* test or Fisher exact test. Receiver operating characteristic analysis was conducted to determine the optimal cutoff for each value and the rate for predicting failure over 12 months. The cumulative remission rate was analyzed using Kaplan-Meier analysis and Cox proportional hazard regression.

Ethical consideration

This prospective study protocol was reviewed and approved by the Ethics Committee of Hamamatsu University School of Medicine

Table 1. Baseline characteristics of patients

Characteristics	n = 73
Age (yr), median (IQR)	46.0 (18.0–83.0)
Male/female, n (%)	48 (65.8)/25 (34.2)
Disease duration (yr), median (IQR)	7.0 (0.3–37.0)
Disease extent, n (%)	
Extensive colitis	42 (57.5)
Left-sided colitis	22 (30.1)
Proctitis	9 (12.3)
CAI (Rachmilewitz index), median (IQR)	0.0 (0.0–4.0)
MES, n (%)	
MES 0	48 (65.8)
MES 1	25 (34.2)
FIT (ng/mL), median (IQR)	30.0 (30.0–15,100.0)
PGE-MUM (μg/g·Cr), median (IQR)	20.30 (0.8–97.3)
Medication at study, n (%)	
Oral 5-ASA	49 (67.1)
Suppository steroids	3 (4.1)
Systemic steroids	6 (8.2)
Immunomodulators	25 (34.2)
Advanced therapy	15 (20.5)

5-ASA, 5-aminosalicylic acid; CAI, clinical activity index; FIT, fecal immunochemical occult blood test; IQR, interquartile range; MES, Mayo endoscopic subscore; PGE-MUM, prostaglandin E-major urinary metabolite.

(number 18–228). This study was conducted in accordance with the principles of Good Clinical Practice in adherence to the Declaration of Helsinki. All enrolled patients provided written informed consent to participate in this study.

RESULTS

Patient characteristics

Seventy-three patients with UC in clinical remission were enrolled in this study (Figure 1) (Table 1). The median patient age and disease duration were 46 years and 7.0 years, respectively. Regarding the endoscopic score, 48 patients had a MES of 0 and a MES of 1 was observed in the remaining 25 patients. The median values of the biomarkers FIT and PGE-MUM were 30.0 ng/mL and 20.3 μg/g·Cr, respectively.

Comparison of biomarkers between the groups of relapse and remission

During the 12-month follow-up period, 21 of the 73 patients (28.8%) experienced clinical relapse. The initial FIT and PGE-MUM values in the relapse group were significantly higher than those in the remission group ($P = 0.001$ and $P = 0.007$, respectively) (Figure 2a, b). The optimal cutoff value of FIT for predicting clinical relapse during the 12 months was 61.0 ng/mL, and the area under the curve (AUC) was 0.723 (95% confidence interval [CI]: 0.599–0.846) (Figure 3) (Table 2). For PGE-MUM, the cutoff value of was 25.2 μg/g·Cr and the AUC was 0.701 (95% CI: 0.558–0.844), showing no significant difference between the AUCs of the 2 biomarkers ($P = 0.836$).

Comparison of MES, FIT, and PGE-MUM for predicting subsequent relapse

Kaplan-Meier analysis was performed by grouping according to the MES and biomarker cutoff values. The relapse-free rate during the 12 months of MES 0 (77.1%) was significantly higher than that of MES 1 (56.0%) (log-rank test: $P = 0.020$) (Figure 4a). In the FIT < 60 ng/mL group, 40 of the 48 patients (83.3%) maintained remission over the 12 months, whereas in the FIT ≥ 60 ng/mL group, 11 of the 25 patients (44.0%) maintained remission (log-rank test, $P < 0.001$) (Figure 4b). The maintenance rate of remission was significantly higher in the PGE-MUM ≥ 25.2 μg/

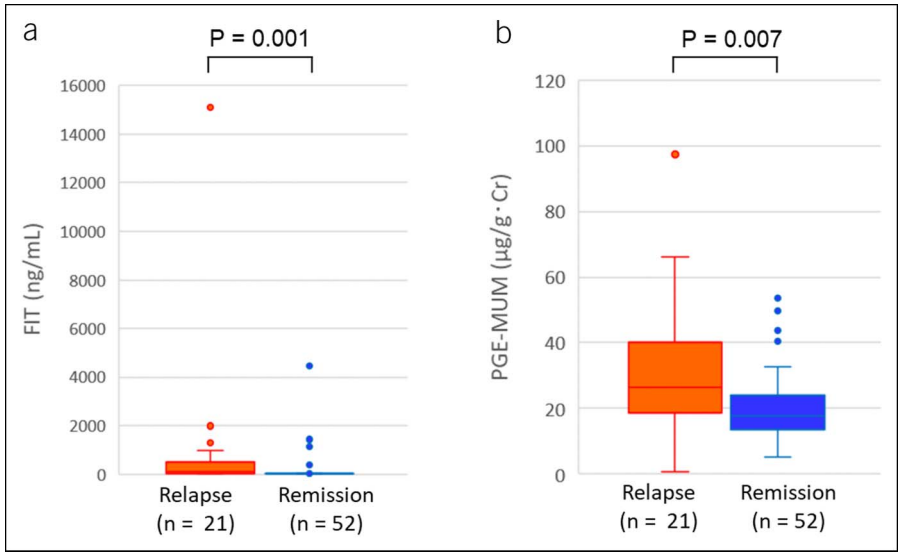

Figure 2. Differences in the initial values of the 2 biomarkers between patients with ulcerative colitis at relapse and remission. (**a**) The fecal immunochemical occult blood test (FIT) value in the relapse group is significantly higher than that in the remission group ($P = 0.001$). (**b**) The prostaglandin E-major urinary metabolite (PGE-MUM) value in the relapse group is significantly higher than that in the remission group ($P = 0.007$).

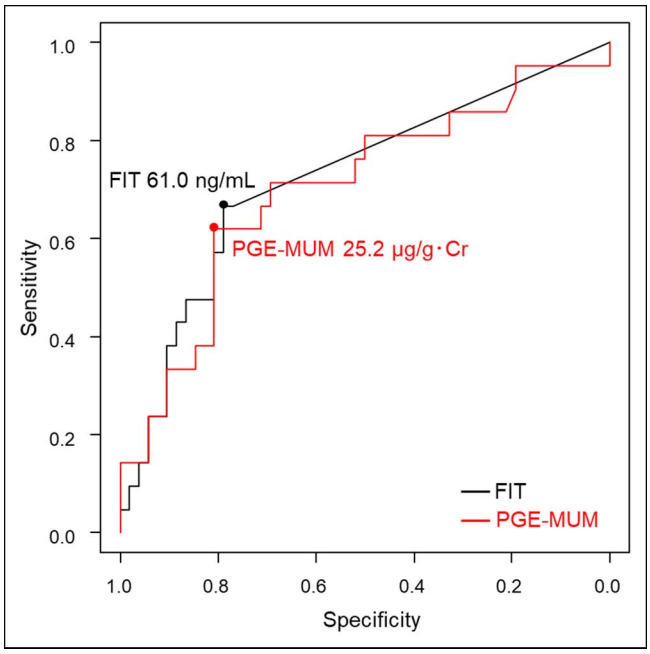

Figure 3. The receiver operating characteristic analysis of the fecal immunochemical occult blood test (FIT) and prostaglandin E-major urinary metabolite (PGE-MUM) for predicting relapse during 12 months. FIT 16 ng/mL and PGE-MUM 25.2 μg/g·Cr were the optimal cutoff values for predicting relapse. The area under the curve (AUC) of FIT and PGE-MUM were 0.723 (95% confidence interval [CI]: 0.599–0.846) and 0.701 (95% CI: 0.558–0.844), respectively. There was no significant difference between the AUC values for the biomarkers.

g·Cr group (43.5%) than in the PGE-MUM < 25.2 μg/g·Cr group (82.0%) (log-rank test: $P < 0.001$) (Figure 4c).

Additional Kaplan-Meier analysis was performed by dividing the patients into 4 groups on the basis of the positive and negative results for FIT and PGE-MUM: FIT (−) PGE-MUM (−), FIT < 60 ng/mL and PGE-MUM < 25.2 μg/g·Cr; FIT (−) PGE-MUM (+), FIT < 60 ng/mL and PGE-MUM ≥ 25.2 μg/g·Cr; FIT (+) PGE-MUM (−), FIT ≥ 60 ng/mL and PGE-MUM < 25.2 μg/g·Cr; and FIT (+) PGE-MUM (+), FIT ≥ 60 ng/mL and PGE-MUM ≥ 25.2 μg/g·Cr (Figure 4d). The group presenting with FIT (−) PGE-MUM (−) had a 94.1% maintenance rate of remission while those who were positive for both had a 22.2% maintenance rate. Furthermore, the group presenting with FIT (−) PGE-MUM (−) showed a significant difference in the remission rate compared with that in the other 3 groups by Kaplan-Meier analysis. In addition, multivariate analysis revealed an increased risk of relapse for the groups positive for at least 1 biomarker (Table 3).

Effect of disease duration on the clinical relapse prediction by FIT and PGE-MUM

We examined the effect of disease duration on the prediction of relapse by FIT and PGE-MUM. For the long-term disease duration analysis, the FIT and PGE-MUM values of relapse and the remission groups were compared with each subgroup with a disease duration of more than 1–11 years (see Table, Supplementary Digital Content 1, http://links.lww.com/CTG/A816). Both FIT and PGE-MUM showed no significant differences in the subgroups of more than 1–8 years and 1–9 years, respectively. For

Table 2. The receiver operating characteristic analysis of FIT and PGE-MUM for predicting relapse in 12 months

	FIT	PGE-MUM
Cutoff value	61.0 ng/mL	25.2 μg/g·Cr
AUC [95% CI]	0.723 [0.599–0.846]	0.701 [0.558–0.844]
Sensitivity (%) [95% CI]	0.667 [0.667–0.430]	0.619 [0.384–0.819]
Specificity (%) [95% CI]	0.788 [0.788–0.653]	0.808 [0.675–0.904]
Accuracy (%) [95% CI]	0.753 [0.639–0.847]	0.753 [0.639–0.847]
Positive likelihood [95% CI]	3.152 [1.720–5.775]	3.219 [1.680–6.168]
Negative likelihood [95% CI]	0.423 [0.227–0.787]	0.472 [0.269–0.827]

AUC, area under the curve; CI, confidence interval; FIT, fecal immunochemical occult blood test; PGE-MUM, prostaglandin E-major urinary metabolit.

the short-term analysis (disease duration of less than 5–30 years), FIT showed significant differences except for the subgroup of less than 5 years, whereas PGE-MUM showed significant differences only in the subgroup of less than 11–30 years (see Table, Supplementary Digital Content 2, http://links.lww.com/CTG/A817). The receiver operating characteristic curve evaluation for the long-term disease duration group revealed that the AUC of PGE-MUM was higher than that of FIT in all subgroups, except in the subgroup with a disease duration of 11 years or more (Table 4). Similar assessments of short-term disease duration showed that the AUC of FIT was higher than that of PGE-MUM in all subgroups except the group with duration less than 25 years (Table 5).

DISCUSSION

As previously mentioned, FIT and PGE-MUM biomarkers are used clinically to predict the clinical relapse of patients with UC (7–11). Currently, there are no reports on the prediction of UC relapse that have directly compared FIT and PGE-MUM. In this study, we compared the relapse prediction of these 2 biomarkers. Furthermore, we examined the influence of disease duration on the prediction of relapse by these biomarkers.

We observed that the cutoff value of FIT for predicting relapse within 1 year was 60 ng/mL. In other studies, Nakarai et al. reported a cutoff value of 110 ng/mL while Yamamoto et al. reported a cutoff value of 135 ng/mL for predicting clinical relapse during a 1-year observation period (8,9). Although there are differences in the observation period, entry criteria, and end point in each report, the FIT cutoff value in this study was considered to be valid. In our previous report, the cutoff value of PGE-MUM for predicting clinical relapse was 26.3 μg/g·Cr, which was close to the value (25.2 μg/g·Cr) determined in this study (14).

To evaluate the validity of the subjects enrolled in this study, Kaplan-Meier analysis was performed in the MES 0 group vs the MES 1 group, in which a significant difference was observed in the log-rank test. This was also observed in previous studies (3,4). Next, Kaplan-Meier analysis was performed on the groups with cutoff values of FIT 60 ng/mL and PGE-MUM 25.2 μg/g·Cr. In this analysis, significant differences in the remission maintenance rate were observed for both biomarkers. Furthermore, a similar analysis was performed on the 4 groups of patients using a combination of these 2 biomarkers (Figure 3d). Similar to the results of our study, the Kaplan-Meier analysis reported by

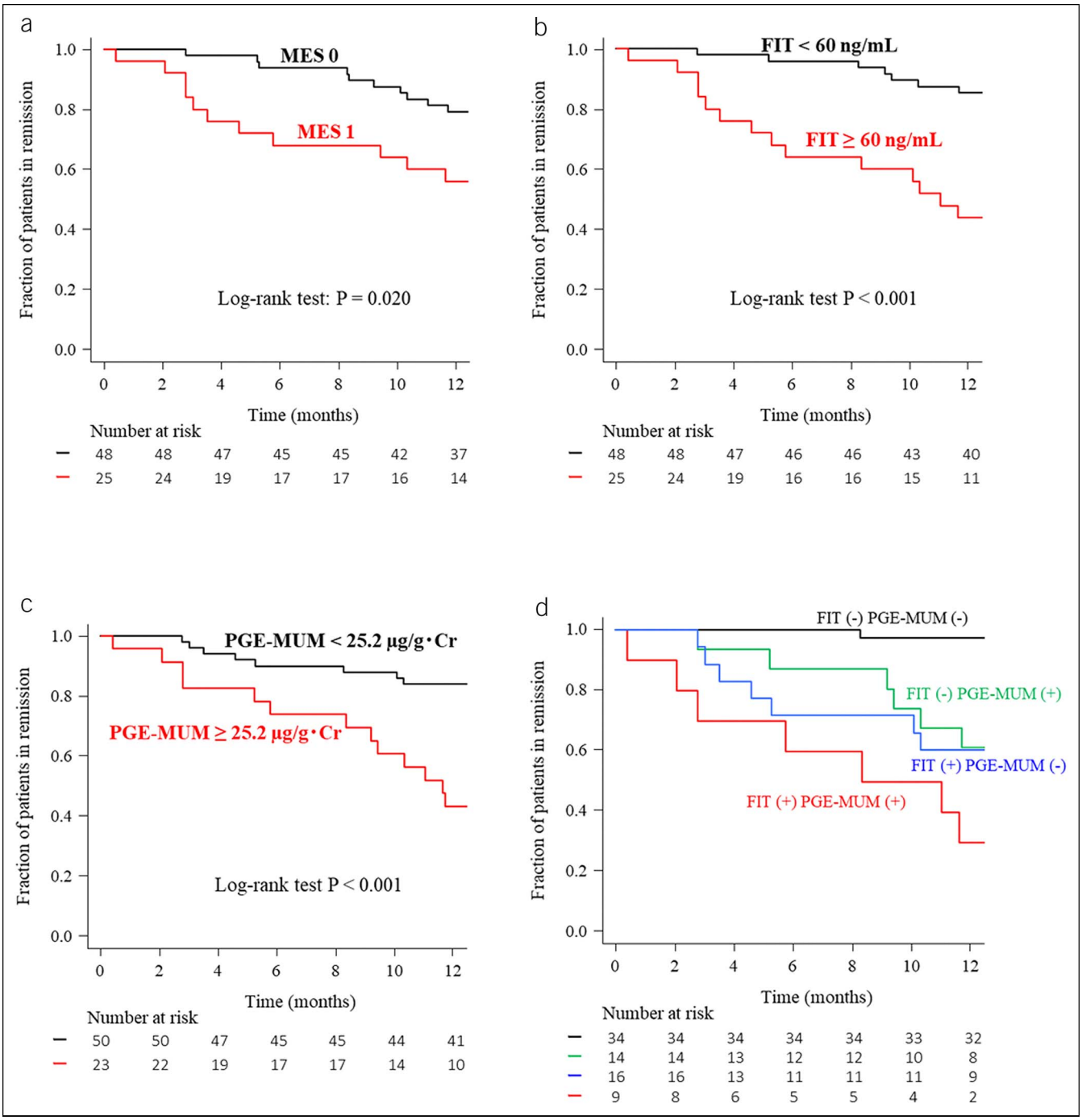

Figure 4. Kaplan-Meier time-to-relapse curves of patients with ulcerative colitis in relation to the Mayo endoscopic subscore (MES) (**a**), fecal immunochemical occult blood test (FIT) (**b**), and prostaglandin E-major urinary metabolite (PGE-MUM) (**c**). Kaplan-Meier time-to-relapse curves in relation to FIT and PGE-MUM as the following: FIT (−) PGE-MUM (−), FIT < 60 ng/mL and PGE-MUM < 25.2 μg/g·Cr; FIT (−) PGE-MUM (+), FIT < 60 ng/mL and PGE-MUM ≥ 25.2 μg/g·Cr; FIT (+) PGE-MUM (−), FIT ≥ 60 ng/mL and PGE-MUM < 25.2 μg/g·Cr; and FIT (+) PGE-MUM (+), FIT ≥ 60 ng/mL and PGE-MUM ≥ 25.2 μg/g·Cr (**d**).

Nakarai et al. (8) revealed that there was a significant difference in the remission maintenance rate. In a study by Naganuma et al., (11) the Kaplan-Meier analysis indicated that FC-positive and FIT-positive groups showed a significant difference between the FC-negative and FIT-positive groups and the FC-positive and FIT-negative groups in the log-rank test, respectively. In our study, the FIT (−) PGE-MUM (+) group and the FIT-(+) PGE-MUM (−) group showed significant differences when compared with the FIT (−) PGE-MUM (−) group. The FIT (−) PGE-MUM (+) group and the FIT (+) PGE-MUM (−) group showed no significant differences on comparison with the FIT (+) PGE-MUM (+) group. This may be because of the small sample size. By contrast, in the Kaplan-Meier analysis on the 3 groups of both positive and negative markers, a significant difference was

Table 3. Multivariate analysis of FIT and PGE-MUM for predicting relapse over 12 months

	Multivariate analysis		
	HR	95% CI	*P*-value
FIT (−) PGE-MUM (−)	1		
FIT (+) PGE-MUM (−)	19.82	2.434–161.3	0.005
FIT (−) PGE-MUM (+)	17.42	2.095–144.8	0.008
FIT (+) PGE-MUM (+)	46.63	5.710–380.0	<0.001

CI, confidence interval; FIT, fecal immunochemical occult blood test; HR, hazard ratio; PGE-MUM, prostaglandin E-major urinary metabolite.

observed among all the groups (see Figure, Supplementary Digital Content 3, http://links.lww.com/CTG/A818).

Interestingly, a comparison of the 4 groups in this study revealed that 31.3% of the patients (5/16) in the FIT (+) PGE-MUM (−) group relapsed at 6 months, whereas only 14.3% of the patients (2/14) in the FIT (−) PGE-MUM (+) group relapsed. In the FIT (−) PGE-MUM (+) group, 4 patients (28.6%) relapsed in the remaining 6 months. Based on the results, FIT and PGE-MUM predicted early and late relapse, respectively. Although the mechanism of the early-stage relapse predictive capacity of FIT is unknown, it was also observed in a previous study with FIT-positive, FIT-negative, and FC-positive groups (8).

We previously reported the influence of disease duration on PGE-MUM and FIT in a study of endoscopic scores, (13,24) where we demonstrated the strong correlation between FIT and endoscopic scores. We also indicated that PGE-MUM may be superior to FIT as a biomarker in patients with long-term disease duration. Based on the results of these studies, we evaluated the relationship between disease duration and relapse prediction, by grouping long-term and short-term disease duration and including FIT for a comparative analysis.

Table 4. Receiver operating characteristic analysis of FIT and PGE-MUM for predicting relapse in the long-term disease duration group

	AUC [95% CI]		
Disease duration	FIT	PGE-MUM	*P*-value
≥1 yr (n = 68)	0.714 [0.583–0.846]	0.760 [0.636–0.884]	0.634
≥2 yr (n = 64)	0.738 [0.605–0.871]	0.748 [0.617–0.879]	0.917
≥3 yr (n = 52)	0.710 [0.546–0.874]	0.780 [0.634–0.926]	0.519
≥4 yr (n = 51)	0.729 [0.568–0.890]	0.793 [0.649–0.936]	0.553
≥5 yr (n = 45)	0.717 [0.545–0.889]	0.824 [0.674–0.975]	0.340
≥6 yr (n = 39)	0.714 [0.522–0.905]	0.816 [0.647–0.984]	0.405
≥7 yr (n = 37)	0.707 [0.513–0.902]	0.817 [0.649–0.984]	0.375
≥8 yr (n = 35)	0.675 [0.467–0.884]	0.797 [0.618–0.976]	0.373
≥9 yr (n = 31)	0.601 [0.359–0.844]	0.747 [0.523–0.971]	0.402
≥10 yr (n = 27)	0.650 [0.411–0.889]	0.743 [0.523–0.962]	0.594
≥11 yr (n = 22)	0.677 [0.403–0.951]	0.677 [0.430–0.924]	1.000

AUC, area under the curve; CI, confidence interval; FIT, fecal immunochemical occult blood test; PGE-MUM, prostaglandin E-major urinary metabolite.

Table 5. Receiver operating characteristic analysis of FIT and PGE-MUM for predicting relapse in the short-term disease duration group

	AUC [95% CI]		
Disease duration	FIT	PGE-MUM	*P*-value
<30 yr (n = 71)	0.725 [0.602–0.849]	0.700 [0.558–0.842]	0.810
<25 yr (n = 66)	0.737 [0.609–0.864]	0.756 [0.618–0.894]	0.859
<20 yr (n = 60)	0.743 [0.612–0.875]	0.737 [0.589–0.885]	0.953
<15 yr (n = 55)	0.759 [0.625–0.892]	0.726 [0.568–0.884]	0.780
<11 yr (n = 51)	0.733 [0.591–0.876]	0.704 [0.529–0.878]	0.819
<10 yr (n = 46)	0.741 [0.593–0.889]	0.663 [0.477–0.849]	0.560
<9 yr (n = 42)	0.784 [0.641–0.928]	0.651 [0.462–0.839]	0.307
<8 yr (n = 38)	0.755 [0.595–0.915]	0.609 [0.399–0.819]	0.330
<7 yr (n = 36)	0.731 [0.561–0.901]	0.589 [0.368–0.810]	0.378
<6 yr (n = 34)	0.719 [0.544–0.895]	0.581 [0.359–0.803]	0.393
<5 yr (n = 28)	0.702 [0.503–0.900]	0.526 [0.275–0.778]	0.337

AUC, area under the curve; CI, confidence interval; FIT, fecal immunochemical occult blood test; PGE-MUM, prostaglandin E-major urinary metabolite.

It was observed that the AUC of FIT tended to be higher in the short-term disease duration group than in the PGE-MUM group, and the AUC of the long-term illness group tended to be higher in the PGE-MUM group. We believe that the reason for this tendency is that patients with long-term disease duration experienced repeated recurrences and remissions, resulting in the scarring of the intestinal mucosa. Because FIT is a biomarker that reflects the amount of bleeding, it may be difficult for FIT to reflect the mucosal surface in long-term affected patients with UC because of the small amount of bleeding occurring despite endoscopic mucosal activity. By contrast, because PGE-MUM is associated with intestinal inflammation, it is likely that it can reflect the endoscopic findings associated with inflammation in UC patients with long disease periods. As such, we believe that disease duration affects the association between biomarkers and endoscopic scores and subsequently the prediction of relapse. From these results, we concluded that FIT and PGE-MUM estimation is preferred for UC patients with short and long disease durations, respectively, for predicting clinical relapse.

This study has several limitations. First, this single-center study had a small sample size. Most studies on predicting biomarker relapse have included more than 100 cases (8,9,11). Therefore, a larger sample size is required for further validation of the findings from this study. Second, the biomarkers were not compared with FC. Along with FIT, FC has been reported in many biomarker studies and is also widely used in clinical practice. Few studies have reported the relationship between FC and disease duration in UC. As such, future studies including the prediction of relapse are required with this biomarker. Third, in this study, the treatment of UC was changed or modified owing to clinical relapse, and endoscopy was not performed in all cases at the time of relapse. In some cases, endoscopy was not performed when the activity was slightly increased. There were also some mild cases that were improved by only increasing the dose of 5-aminosalicylic acid. Finally, FIT and PGE-MUM were not measured at the time of relapse.

In this study, it was demonstrated that FIT and PGE-MUM biomarkers can predict the clinical relapse of patients with UC while in remission. In addition, the combination of these biomarkers resulted in more accurate predictions. Furthermore, it was demonstrated that FIT may be useful for predicting relapse in the short-term disease duration and PGE-MUM in the long-term disease duration.

CONFLICTS OF INTEREST

Guarantor of the article: Ken Sugimoto, MD, PhD.

Specific author contributions: N.I. and K.S. designed the study. K.S., T. Matsuura, Y.A., T. Miyazu, S. Tamura, and S Tani collected the data. M.Y., M.I., and Y.H. analyzed the data. N.I. and K.S. wrote the manuscript. S.O. and T.F. provided critical insights into manuscript preparation. All authors have approved the final version of the manuscript.

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Potential competing interests: None to report.

Data availability statement: All the data needed to evaluate the conclusions of the manuscript are presented herein. Additional data related to this study may be requested from the authors.

Study Highlights

WHAT IS KNOWN

- ✓ The fecal immunochemical occult blood test and prostaglandin E-major urinary metabolite predict ulcerative colitis relapse during remission.
- ✓ However, the predictive ability of these biomarkers has not been directly compared.

WHAT IS NEW HERE

- ✓ The fecal immunochemical occult blood test can predict clinical relapse in short-term ulcerative colitis patients in remission.
- ✓ Prostaglandin E-major urinary metabolite can predict clinical relapse in long-term ulcerative colitis patients in remission.

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