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Manuscript Title

Milan Ultrasound Criteria predict relapse of ulcerative colitis in remission

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Short Title: Ultrasound predicts relapse of ulcerative colitis in remission

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Abstract

Introduction

Bowel ultrasound is a non-invasive alternative to endoscopy for assessing the disease activity of ulcerative colitis; however, it is unclear whether bowel ultrasound can predict subsequent relapse from remission.

Materials and Methods

A retrospective cohort study enrolled patients with ulcerative colitis who underwent bowel ultrasound between July 2018 and July 2021 during clinical remission (patient-reported outcome-2 ≤ 1 and no rectal bleeding) for at least 3 months and were followed up for 1 year. Ultrasonographic findings (bowel wall thickness, bowel wall flow, bowel wall stratification, and enlarged lymph nodes), Milan Ultrasound Criteria, Mayo endoscopic subscore, C-reactive protein, and fecal calprotectin levels and their association with subsequent clinical relapse were assessed. Relapse was defined as rectal bleeding score ≥ 1, stool frequency score ≥ 2, or treatment intensification for symptoms.

Results

31% of the patients (18/58) relapsed within 1 year. No single ultrasonographic finding predicted relapse, whereas Milan Ultrasound Criteria > 6.2 (p = 0.019), Mayo endoscopic subscore ≥ 1 (p = 0.013), and fecal calprotectin ≥ 250 μg/g (p = 0.040) were associated with a shorter time to relapse in the log-rank test. Milan Ultrasound Criteria > 6.2 (hazard ratio 3.22; 95% confidence interval 1.14-9.08, p = 0.027) and Mayo endoscopic subscore ≥ 1 (hazard ratio 8.70; 95% confidence interval 1.11-68.1, p = 0.039) showed a higher risk of relapse according to a Cox proportional hazards model.

Discussion/Conclusion

Bowel ultrasound can predict subsequent clinical relapse from remission in patients with ulcerative colitis using the Milan Ultrasound Criteria.

1. Introduction

Advances in ulcerative colitis (UC) treatment have enabled short-term symptomatic improvement and maintenance of long-term remission. In the management of UC, the monitoring strategy during clinical remission differs from that for active disease. Endoscopy is a useful modality for assessing mucosal inflammation, and endoscopic mucosal healing is considered a treatment target because asymptomatic patients may still have endoscopically active mucosal inflammation[1]. Endoscopic healing correlates well with the maintenance of long-term remission[2,3]. However, endoscopy can be invasive for patients, and frequent monitoring is not feasible.

Therefore, biomarkers are expected to be less invasive. Several studies have reported that C-reactive protein (CRP) was not useful in predicting relapse in patients with UC in remission[4]. Fecal calprotectin (FC) has been reported to be associated with the risk of relapse[4]. However, biomarkers cannot determine the extent or degree of inflammation, which is also important for relapse prediction[5].

Bowel ultrasound (BUS) is a non-invasive transmural imaging technique that also reflects endoscopic findings[6–14]. Bowel wall thickness (BWT) and bowel wall flow (BWF) are indicators of endoscopic severity, and the extent of inflammation can also be evaluated[6–14]. BWT has been reported to be the best indicator of endoscopic activity[13]. However, it is unclear whether BUS can predict relapse from remission.

Therefore, we investigated whether BUS can predict subsequent relapse from remission in patients with UC and ultrasonographic factors associated with relapse.

2. Methods

2-1. Study design

This single-center, retrospective cohort study was conducted from July 2018 to July 2021 based on a chart review. The inclusion criteria were A) patients with a confirmed diagnosis of UC, B) patients who had been in stable clinical remission for at least 3 months and underwent BUS, and C) patients who were followed up for ≥ 1 year after the BUS. Exclusion criteria were: as follows A) patients with proctitis, B) untreated patients at the time of BUS, C) patients who had started cytapheresis, systemic prednisolone (PSL), tacrolimus, biological agents, or small molecules within 3 months of the BUS, and D) patients whose reason for BUS was unrelated to UC (diverticulitis, infectious enteritis, etc.). The primary outcome was defined as the maintenance of clinical remission 1 year after BUS. Clinical remission was defined as patient-reported outcome-2 (PRO2)[15] ≤ 1, no rectal bleeding, and without relapse. Relapse was defined as a rectal bleeding sub-score ≥ 1, stool frequency sub-score ≥ 2, or treatment intensification associated with symptoms. Treatment intensification was defined as addition, dose-escalation, or switch of treatment but excluded dose adjustment of thiopurines.

2-2. Bowel Ultrasound

BUS was performed as previously reported[12,14]. Briefly, Aplio 500 (Canon Medical Systems Corporation, Tokyo, Japan) was used with convex (4 MHz), microconvex (6 MHz), and linear probes (7-10 MHz). Transabdominal ultrasound (TAUS) of the colon was performed. BWT (normal range; colon < 3 mm), BWF (color Doppler signal (color Doppler gain: 3-5 MHz, typical flow: 4.6-6.0 m/s)), bowel wall stratification (BWS), lymph node enlargement, and Milan Ultrasound Criteria (MUC = 1.4 × BWT + 2 × presence of BWF (0 = absence, 1 = presence of color Doppler signal)[8,16,17] were evaluated in each segment. The BWT was adopted as the maximum value from two longitudinal and two cross-sectional measurements. All measurements were performed and recorded at the time of the ultrasound examination; therefore, they were not influenced by the subsequent outcomes. All ultrasound procedures were performed by experienced gastroenterologists or sonographers with adequate training.

2-3. Analysis Items

PRO2 was prospectively recorded in medical charts in routine clinical practice. Remission rates at 3, 6, and 12 months were analyzed based on the above definition. Endoscopic findings were extracted if conducted within 3 months before or after the ultrasound. The Mayo endoscopic subscore (MES) is routinely graded and recorded in reports for the most severely inflamed part. The TAUS findings were extracted from the most severely inflamed segment of the colon.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MUC in predicting relapse at 3, 6, and 12 months after the ultrasound was determined. FC was extracted within 3 months before or after ultrasonography; FC was measured immediately or within 1 week after storage at 4℃. FC was measured using the gold colloid agglutination method (NS Prime automated analyzer (Alfresa Pharma Corporation, Osaka, Japan)).

2-4. Statistical Analysis

Spearman rank correlation coefficient was used to analyze the correlation between bowel ultrasonography and MES (evaluation of the most severe part). Relapse-free survival was calculated using Kaplan-Meier curves. The log-rank test and the Cox proportional hazards model evaluated the association between each study item and relapse. Pearson's chi-square test was used for relapse by time series after BUS. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the JMP software program version 16.1.0 (SAS Institute). Since this was a retrospective study, the sample size was not predetermined. However, assuming that the proportion of patients in remission with MUC > 6.2 is 20% [17], a sample size of 45 cases is considered sufficient. If data were missing, it was excluded from the analysis for each variable.

2-5. Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All patients gave their informed consent in the form of opt-out and therefore written consent was not obtained. Opt-out informed consent protocol was used for use of participant data for research purposes. This consent procedure was reviewed and approved by [the Research Ethics Committee of Kitasato University Kitasato Institute Hospital], approval number [20001], date of decision [April 9, 2020]. The Research Ethics Committee of Kitasato University Kitasato Institute Hospital approved the study protocol and all relevant documents (Kitasato University Kitasato Institute Hospital approval number: 20001).

3. Results

3-1. Patient Characteristics

A total of 58 patients were included in this study (shown in Table. 1). The mean age was 46 years old, 37 (63.8%) patients were male, 39 (67.2%) had pancolitis, and the median disease duration was 116 months. Current therapy consisted of 5-ASA in 52 patients (89.7%), topical therapy in 10 patients (17.2%), immunomodulators in 24 patients (41.4%), prednisolone in 1 patient (1.7%), anti-TNF-α agents in 15 patients (25.9%), and vedolizumab in 2 patients (3.4%). Most patients were corticosteroid-free except for only one patient on 1 mg of PSL. Forty-two patients underwent full colonoscopies. No patients de-escalated the treatment during the study period.

3-2. Correlation of BUS and endoscopy

TAUS findings showed a median BWT of 2.4 mm (interquartile range (IQR) 1.9-3.4 mm) and positive BWF in 10 patients (17.2%), while only a small number of patients had a loss of BWS (n = 2, 3.4%) and enlarged lymph nodes (n = 1, 1.7%). The median MUC was 3.50 (IQR 2.66-5.18) (shown in Table. 2). The agreement between ultrasound findings (BWT, BWF, MUC) and endoscopic (MES) in the most severely affected segment was as follows: 0.88, 0.98, and 0.88, respectively. MUC showed the highest coefficiency with MES (0.61) when evaluated for the colon using TAUS (shown in Fig. 1).

Interestingly, the MUC score was ≤ 6.2 in all patients with an MES of 0 (shown in Table. 3). The predictive ability of MUC > 6.2 to distinguish between MES ≥ 1 and 0 was as follows: sensitivity 0.24, specificity 1.00, PPV 1.00, NPV 0.47, and area under the curve (AUC) 0.67 (shown in Fig. 2).

3-3. Prediction of Relapse

Of the 58 patients, 18 (31.0%) relapsed within 1 year (shown in Fig. 3, 4A). MES ≥ 1 was significantly correlated with a shorter time to relapse (p = 0.013) (shown in Fig. 4B). FC ≥ 250 μg/g was significantly associated with a shorter time to relapse (p = 0.040), whereas CRP level was not (shown in Fig. 4C, 4D). Interestingly, although neither BWT (p = 0.82) nor BWF (p = 0.20) was predictive by themselves (shown in Fig. 5A, 5B), BUS was able to predict relapse by calculating MUC. MUC > 6.2 was strongly predictive (p = 0.019) (shown in Fig. 5C).

Univariate analysis using the Cox proportional hazards model showed a significant correlation with relapse for MUC > 6.2 (hazard ratio (HR) 3.22, 95% confidence interval (CI) 1.14-9.08, p = 0.027) and MES ≥ 1 (HR 8.70, 95% CI 1.11-68.1, p = 0.039). FC ≥ 250 μg/g had an increased risk of relapse but was not significantly correlated with relapse (HR 3.38, 95% CI 0.98-11.7, p = 0.053) (shown in Table. 4).

One case (1.7%) was hospitalized, and no cases were operated on within 1 year.

The sensitivity, specificity, PPV, and NPV of MUC > 6.2 for relapses at different time points (3, 6, and 12 months) showed high specificity of 0.90-0.91 and NPV of 0.74-0.90 (shown in Table. 5). Predictive values of FC ≥ 250 μg/g for relapse within 1 year were 0.64 for sensitivity, 0.75 for specificity, 0.58 for PPV, and 0.79 for NPV (shown in Online Supplementary Material).

Pearson's chi-squared test showed a significant correlation between MES ≥ 1 and relapse at each time point, while MUC > 6.2 was significantly correlated with relapse at 3 (odds ratio (OR) 7.04: 1.41-35.1, $p = 0.0091$) and 6 months (OR 6.41:1.40-29.2, $p = 0.0095$). In particular, 4 of 9 patients with MUC > 6.2 relapsed at 3 months, indicating that MUC > 6.2 was able to identify high-risk patients with short-term relapse. BWT and BWF were not significantly correlated with relapse according to the time series (shown in Table. 6).

4. Discussion

This study is the first to evaluate the predictive role of MUC in the future relapse of patients with UC in stable remission. We have shown that MUC can predict relapse with high accuracy, whereas BWT and BWF alone cannot.

It has been proposed that BUS could be used as an alternative to endoscopy. BWT and BWF have been reported to correlate with clinical activity[7,9], detect endoscopic inflammation[7–10,12–14,16], and be useful in determining the response to treatment[6,7,9,14,18]. In contrast, MUC may be more useful in estimating MES: it has been reported that a MUC score > 6.2 can distinguish between endoscopically active (MES 2,3) and inactive disease (MES 0,1)[16]. In a previous report, MUC > 6.2 had the highest specificity for predicting endoscopic activity than BWT and BWF alone[8]. Consistent with these previous reports, our present study also confirmed that MUC had the highest correlation with MES compared to BWT and BWF alone.

Endoscopic healing is considered an important target for treatment because it predicts relapse in patients in remission[2]. Therefore, we investigated whether BUS, which reflects endoscopy, can predict relapse. There are several previous reports on the prognostic value of BUS; Parente et al. reported BWT > 6 mm and positive BWF 3 months after initiation of systemic steroid predicted endoscopically severe disease after 15 months in patients with moderately to severely active UC[6]. Allocca et al. stated that patients with UC with MUC > 6.2 are at higher risk of the need for steroids, treatment modification, hospitalization, and colectomy[17]. Les et al. reported that BWT and BWF can predict the need for treatment intensification in patients with inflammatory bowel disease (IBD)[19]. However, this is the first report to examine the prediction of relapse by ultrasound limited to patients with UC in clinical remission.

In this study, relapse was not predicted by BWT or BWF alone. Rieder et al. reported that 100% of resected colonic specimens from patients with UC showed some degree of fibrosis, which develops along with inflammation[20]. It has been reported that BWT correlates with both inflammation and fibrosis and cannot distinguish between them[21]. In our study, the reason why MUC score > 6.2 was significantly correlated with relapse, even when limited to patients with UC in remission, maybe because the MUC adds bowel wall flow to the wall thickening and thus discriminates actual bowel inflammation.

Consistent with previous reports, endoscopy was able to predict relapse in this study. Patients with an MES of 1 have been reported to have a higher risk of relapse than those with an MES of 0[1,22], consistent with our results. MUC score > 6.2 not only had 100% specificity and PPV to discriminate MES ≥ 1 but also was more specific than MES ≥ 1 for detecting early (especially within 3 months) relapse. However, regardless of the BUS, few relapses were observed in patients with an MES of 0. BUS can assess submucosal inflammation, which cannot be assessed by endoscopy and may have extracted a population at a higher risk of relapse than endoscopy.

In patients with UC, if the epithelium is completely healed (which implies MES of 0), there may be no need to consider transmural inflammation, but on the other hand, it may be important that the presence of submucosal inflammation is a high risk for relapse in patients with MES > 0.

In addition to ultrasound, CRP and FC levels were also examined to predict relapse. CRP is an inexpensive and conventional biomarker. It has been reported to be unable to predict relapse in patients with UC in remission[4], and in our study, CRP ≥ 0.3 mg/dl was also unable to predict relapse. It may be due to its short half-life and be affected by a variety of systemic inflammatory diseases, including infectious diseases. FC is also a simple biomarker reflecting intestinal inflammation and has been reported to be useful in predicting relapse in UC in clinical remission[4]. In this study, FC ≥ 250 μg/g was significantly correlated with relapse within 1 year, but not with relapse within 3 or 6 months. The sensitivity of FC was higher than that of MUC (MUC, 0.28; FC, 0.64), but the specificity was lower (MUC, 0.90; FC, 0.75). In a previous meta-analysis, FC had a sensitivity of 0.75 and a specificity of 0.77[23]. Although there were missing data for FC in this study, MUC had a higher specificity for clinical relapse than FC compared with previous reports. In this study, the total colon was observed on ultrasound, and BWT, BWF, and MUC were examined in the most severely affected areas. However, the range of activity is also important for predicting relapse[5]. This may be because FC does not identify the affected area. Taken together, BUS is superior to other biomarkers for a definitive diagnosis. This study provides an important insight into a minimally invasive monitoring algorithm in patients with UC in remission, and it might be reasonable to screen first with FC because FC has higher sensitivity and NPV than MUC (shown in Online Supplementary Material). Therefore, it may be more reasonable to conduct BUS only when FC is elevated, and early intervention may be considered for patients with MUC > 6.2, considering the high risk of short-term relapse even without endoscopy.

Our study has several limitations. First, this study was conducted at a single center. Therefore, the number of cases was small and multivariate analysis was not performed. More cases and multivariate analyses are needed to further analyze the predictive ability. Second, this is a retrospective study by reviewing medical records. Therefore, endoscopy and fecal calprotectin measurements were not conducted in all patients. It is also possible that not all relapses were accurately identified. Third, the sample size was too small to conduct the multivariate analysis.

In conclusion, BUS can predict subsequent relapse from remission in patients with UC using MUC. In particular, MUC ≤ 6.2 suggests a low risk of relapse and may be a treatment target alternative to endoscopy.

Statements

Acknowledgment (optional)

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Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All patients gave their informed consent in the form of opt-out and therefore written consent was not obtained. Opt-out informed consent protocol was used for use of participant data for research purposes. This consent procedure was reviewed and approved by [the Research Ethics Committee of Kitasato University Kitasato Institute Hospital], approval number [20001], date of decision [April 9, 2020]. The Research Ethics Committee of Kitasato University Kitasato Institute Hospital approved the study protocol and all relevant documents (Kitasato University Kitasato Institute Hospital approval number: 20001).

Conflict of Interest Statement

MM served as an endowed chair of Abbvie GK, EA Pharma, Zeria Pharmaceutical, JIMRO, Kyorin Pharmaceutical, and Mochida Pharmaceutical.

SS served as a speaker for Janssen Pharmaceutical, AbbVie, Takeda Pharmaceutical, Kyorin Pharmaceutical, Pfizer, Astellas, Mitsubishi Tanabe Pharma, EA Pharma, Nippon Kayaku, and Zeria Pharmaceutical and as an endowed chair for AbbVie GK, JIMRO, Zeria Pharmaceutical, Kyorin Pharmaceutical, Mochida Pharmaceutical, and EA Pharma and received travel grants from IOIBD.

YY received research grants from Abbvie GK.

YM served as a speaker of AbbVie GK; received research funding from Japan Foundation for Applied Enzymology; and as an endowed chair of AbbVie GK, JIMRO, Zeria Pharmaceutical, Kyorin Pharmaceutical, Mochida Pharmaceutical, Otsuka Holdings, and EA Pharma.

MN served as a speaker or consultant in Covidien, Mochida Pharmaceutical, Takeda Pharmaceutical, Zeria Pharmaceutical, Kyorin Pharmaceutical, and Nippon Kayaku and received research funding from Mitsubishi Tanabe Pharma and the Japanese Foundation for Research and Promotion of Endoscopy.

TH received lecture fees from Aspen Japan, Abbvie GK, Ferring, Gilead Sciences, Janssen, JIMRO, Mitsubishi-Tanabe Pharma, Mochida Pharmaceutical, Pfizer, Takeda Pharmaceutical, advisory/consultancy fees from Apo Puls Station, Abbvie GK, Bristol-Myaers Squibb, Celltrion, EA Pharma, Eli Lilly, Gilead Sciences, Janssen, Kyorin, Mitsubishi-TanabePharma, Nichi-

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Author Contributions

SS and TK contributed to the analysis design. Data were collected by MM and MT. MM and TK contributed to the drafting of the manuscript. MM and SS contributed to the statistical analysis. MM, SS, MT, YY, RK, YM, AH, MN, TH and TK critically reviewed and revised the manuscript for intellectual content. MM, SS, MT, YY, RK, YM, AH, MN, TH and TK approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

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Figure Legends

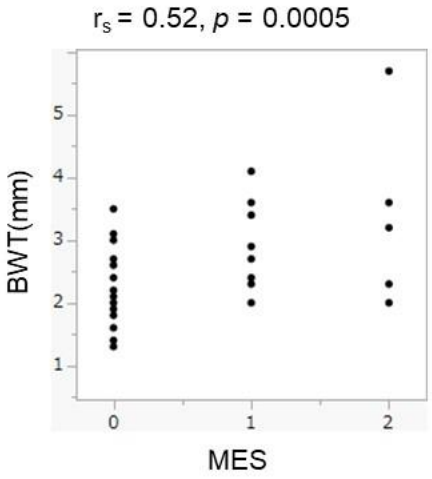
Fig. 1. Correlation (r_s, Spearman rank test) between bowel ultrasonographic findings (bowel wall thickness (BWT), bowel wall flow (BWF), and Milan Ultrasound Criteria (MUC)) and Mayo endoscopic subscore (MES) of the colon excluding the rectum.

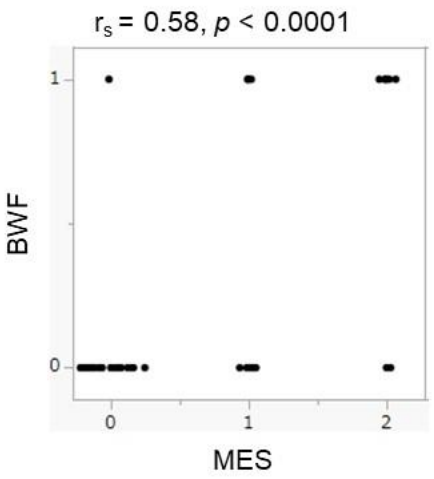
Fig. 2. A receiver operating characteristic: the ability to distinguish between Mayo endoscopic subscore (MES) 0 and ≥ 1 by Milan Ultrasound criteria (MUC)

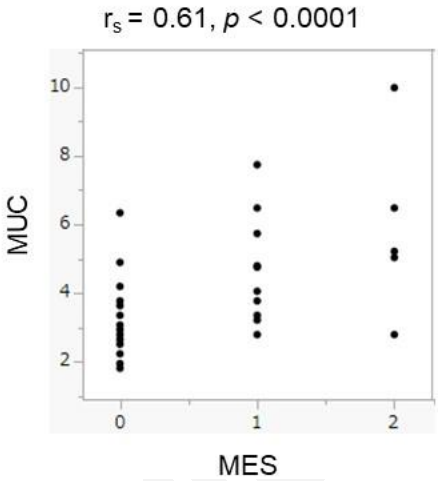
Fig. 3. The number of patients with a relapse at each time point

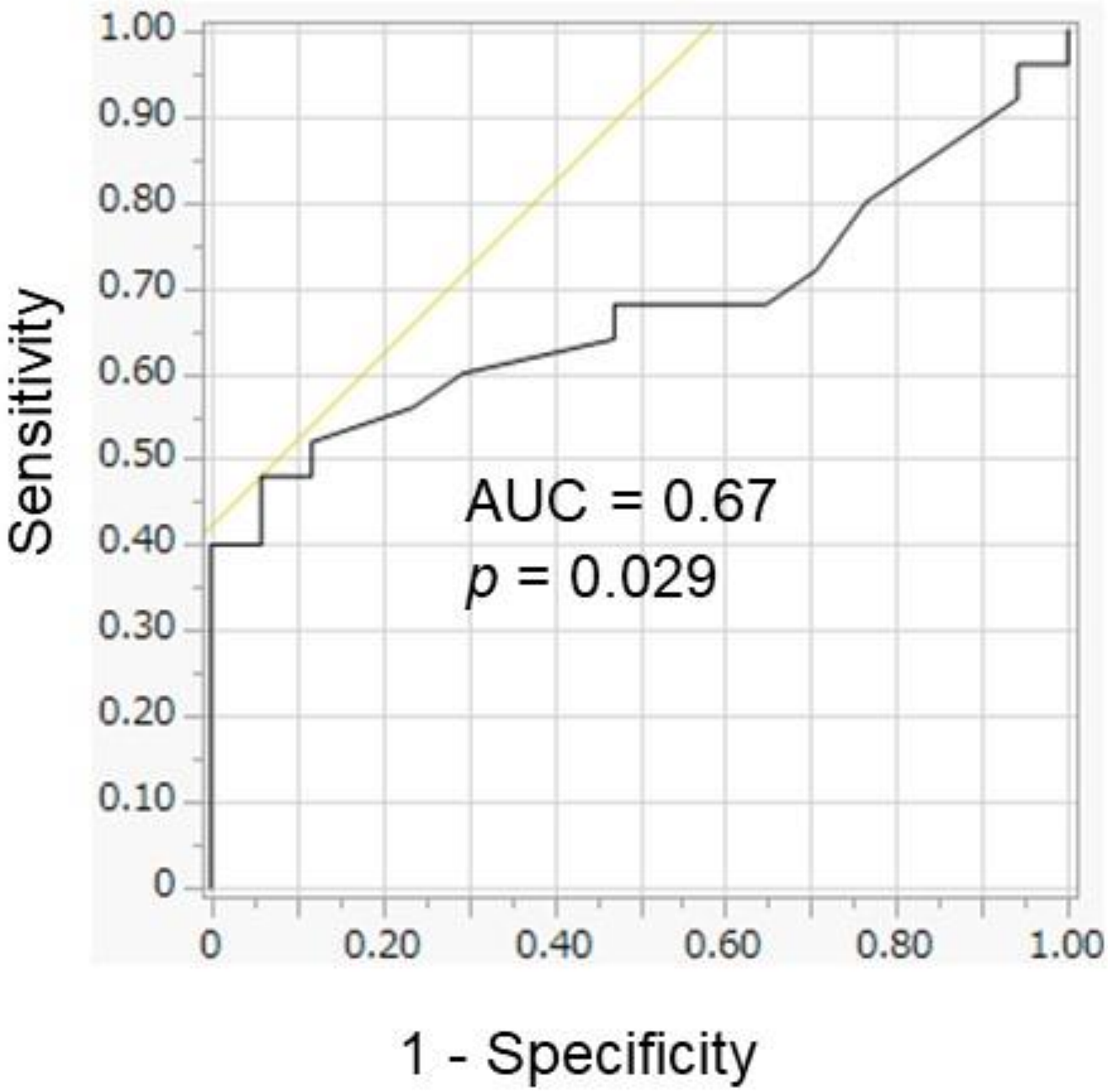
Fig. 4. Kaplan-Meier curves of relapse-free survival. (A) All patients, (B) Mayo endoscopic subscore (MES) of the colorectum, (C) fecal calprotectin (FC), (D) C-reactive protein (CRP).

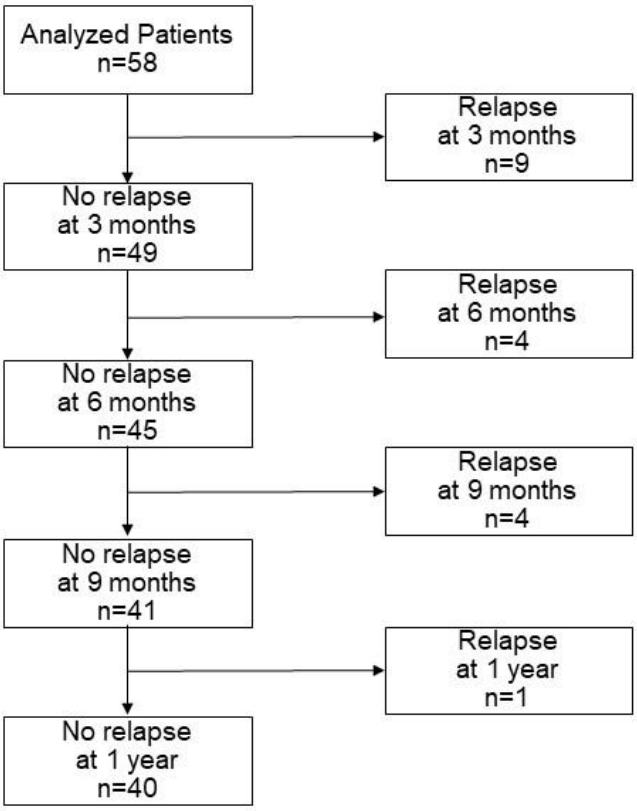
Fig. 5. Kaplan-Meier curves of relapse-free survival in patients with (A) bowel wall thickness (BWT), (B) bowel wall flow (BWF), (C) Milan Ultrasound Criteria (MUC).

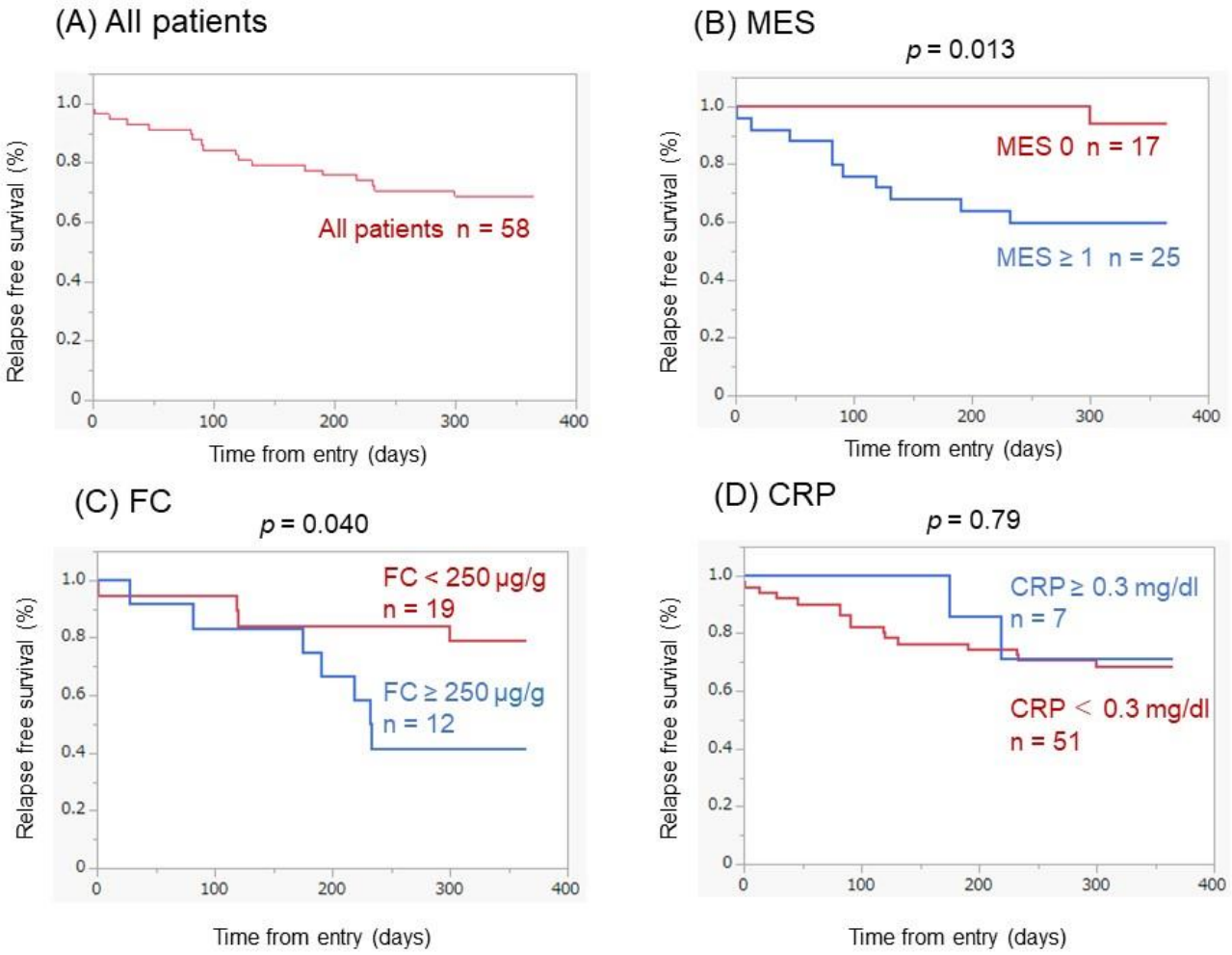


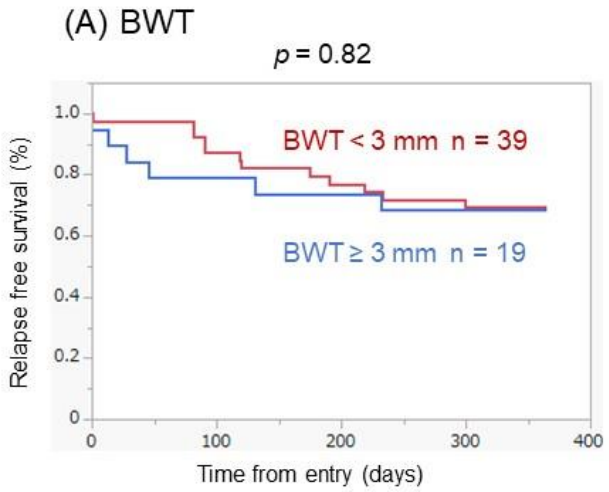


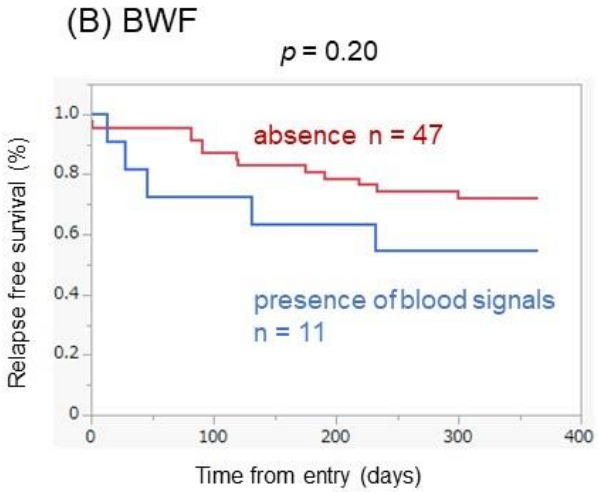



Sensitivity
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0
AUC = 0.67
p = 0.029
0
0.20
0.40
0.60
0.80
1.00
1 - Specificity


Analyzed Patients
n=58
Relapse
at 3 months
n=9
No relapse
at 3 months
n=49
Relapse
at 6 months
n=4
No relapse
at 6 months
n=45
Relapse
at 9 months
n=4
No relapse
at 9 months
n=41
Relapse
at 1 year
n=1
No relapse
at 1 year
n=40


(A) All patients
Relapse free survival (%)
All patients n = 58
Time from entry (days)
(B) MES
p = 0.013
MES 0 n = 17
MES ≥ 1 n = 25
Relapse free survival (%)
Time from entry (days)
(C) FC
p = 0.040
FC < 250 µg/g
n = 19
FC ≥ 250 µg/g
n = 12
Relapse free survival (%)
Time from entry (days)
(D) CRP
p = 0.79
CRP ≥ 0.3 mg/dl
n = 7
CRP < 0.3 mg/dl
n = 51
Relapse free survival (%)
Time from entry (days)


(A) BWT
p = 0.82
BWT < 3 mm n = 39
BWT ≥ 3 mm n = 19
Relapse free survival (%)
Time from entry (days)


(B) BWF
p = 0.20
absence n = 47
presence of blood signals
n = 11
Relapse free survival (%)
Time from entry (days)

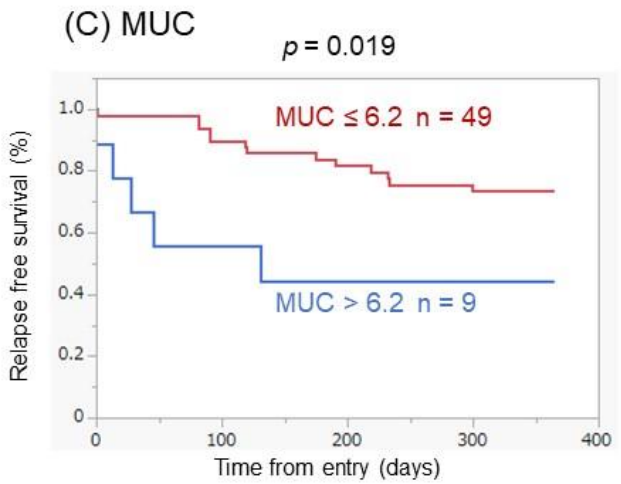

(C) MUC
p = 0.019
MUC ≤ 6.2 n = 49
MUC > 6.2 n = 9
Relapse free survival (%)
Time from entry (days)

Table 1. Patient's characteristics

Variable	n = 58
Age, years	46 ± 17
Male	37 (63.8)
Body mass index, kg/㎡	22 ± 3.4
Smoking	4 (6.9)
Pancolitis： Left-sided	39 (67.2)：19
Disease duration, month	116 [65-197]
WBC, 10^3/μL	5.04 [4.08-5.93]
CRP, mg/dL	0.03 [0.01-0.11]
FC, μg/g[a]	127 [43-615]
Alb, g/dL	4.4 [4.2-4.6]
Hb, g/dL	13.7 [12.8-14.9]
MES 0/1/2/3[b]	17/13/11/1
Current treatment	
5-ASA	52 (89.7)
Topical therapy	10 (17.2)
IM	24 (41.4)
PSL	1 (1.7)
Anti-TNF-α agents	15 (25.9)
VDZ	2 (3.4)
TOF	0 (0)
TAC	0 (0)
History of previous treatment	
PSL	37 (63.8)
Anti-TNF-α agents	11 (19.0)
VDZ	0 (0)
TOF	1 (1.7)
TAC	7 (12.1)

Data are presented as n (%), median [IQR], or mean ± SD.

WBC, white blood cell; Alb, albumin; Hb, hemoglobin; CRP, C-reactive protein; FC, fecal calprotectin; MES, Mayo endoscopic subscore; ASA, aminosalicylic acid; IM, immunomodulator; PSL, prednisolone; TNF-α, tumor necrosis factor-α; VDZ, vedolizumab; TOF, tofacitinib; TAC, tacrolimus.

[a]n = 31

[b]n = 42

Table 2. Bowel ultrasonographic findings

Variable	**n = 58 (colon)**
BWT, mm	2.4 [1.9-3.4]
BWF	10 (17.2)
BWS	2 (3.4)
enlarged lymph nodes	1 (1.7)
MUC	3.50 [2.66-5.18]

Data are presented as n (%), median [IQR].

BWT, bowel wall thickness; BWF, bowel wall flow; BWS, bowel wall stratification; MUC, Milan Ultrasound Criteria.

Table 3. Correlation between MUC and MES

		MES		Total
		≥ 1	0	
MUC	> 6.2	6	0	6
	≤ 6.2	19	17	36
Total		25	17	42

Data are presented as n.

MES, Mayo endoscopic subscore; MUC, Milan Ultrasound Criteria.

Table 4. Univariate analysis (Cox proportional hazards model) for the risk factor of subsequent clinical relapse

Variable	**HR (95% CI)**	***p* value**
Pancolitis	0.91 (0.34-2.42)	0.85
Disease duration ≥ 114 (median, months)	1.85 (0.70-4.94)	0.22
Treatment		
IM	0.26 (0.07-0.89)	0.032*
Biological	0.71 (0.23-2.15)	0.54
History of systemic steroid	0.87 (0.34-2.26)	0.78
CRP ≥ 0.3 mg/dL	0.82 (0.19-3.56)	0.79
FC ≥ 250 μg/g	3.38 (0.98-11.7)	0.053
MUC > 6.2	3.22 (1.14-9.08)	0.027*
MES ≥ 1	8.70 (1.11-68.1)	0.039*

IM, immunomodulator; CRP, C-reactive protein; FC, fecal calprotectin; MUC, Milan Ultrasound Criteria; MES, Mayo endoscopic subscore.

*$p < 0.05$

Table 5. Predictive values of MUC for relapse within 1 year

		3 months	6 months	1 year
MUC > 6.2	**Sensitivity**	0.44	0.39	0.28
	Specificity	0.90	0.91	0.90
	PPV	0.44	0.56	0.56
	NPV	0.90	0.84	0.74

MUC, Milan Ultrasound Criteria; PPV, positive predictive value; NPV, negative predictive value.

Table 6. Relapse of time series in endoscopy (MES) and bowel ultrasound (BWT, BWF, MUC)

			3 months		6 months		1 year	
		n	**relapse**	***p* value**	**relapse**	***p* value**	**relapse**	***p* value**
MES	≥ 1	25	6/25 (24%)	0.029*	8/25 (32%)	0.0095*	10/25 (40%)	0.014*
	0	17	0/17 (0%)		0/17 (0%)		1/17 (6%)	
FC (μg/g)	≥ 250	12	2/12 (17%)	0.30	3/12 (25%)	0.53	7/12 (58%)	0.035*
	< 250	19	1/19 (5%)		3/19 (16%)		4/19 (21%)	
BWT (mm)	≥ 3	19	4/19 (21%)	0.42	5/19 (26%)	0.62	6/19 (32%)	0.95
	< 3	39	5/39 (13%)		8/39 (21%)		12/39 (31%)	
BWF	＋	11	3/11 (27%)	0.23	4/11 (36%)	0.22	5/11 (46%)	0.25
	－	47	6/47 (13%)		9/47 (19%)		13/47 (28%)	
MUC	> 6.2	9	4/9 (44%)	0.0091*	5/9 (56%)	0.0095*	5/9 (56%)	0.084
	≦ 6.2	49	5/49 (10%)		8/49 (16%)		13/49 (27%)	

MES, Mayo endoscopic subscore; FC, fecal calprotectin; BWT, bowel wall thickness; BWF, bowel wall flow; MUC, Milan Ultrasound Criteria.

*$p < 0.05$