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ORIGINAL ARTICLE

Retrospective Cohort Study

Comparison of fecal calprotectin levels and endoscopic scores for predicting relapse in patients with ulcerative colitis in remission

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Abstract

BACKGROUND

Although the usefulness of endoscopic scores, such as the Mayo Endoscopic Subscore (MES), Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and Ulcerative Colitis Colonoscopic Index of Severity (UCCIS), and biomarkers such as fecal calprotectin (FC) for predicting relapse in ulcerative colitis (UC) has been reported, few studies have included endoscopic scores for evaluating the entire colon.

AIM

To compare the usefulness of FC value and MES, UCEIS, and UCCIS for predicting relapse in patients with UC in clinical remission.

METHODS

In total, 75 patients with UC in clinical and endoscopic remission who visited our institution between February 2019 and March 2022 were enrolled. The diagnosis of UC was confirmed based on the clinical presentation, endoscopic findings, and histology, according to the current established criteria for UC. Fecal samples were collected the day before or after the colonoscopy for measurement of FC. Endoscopic evaluations were performed using MES, UCEIS, and UCCIS. The primary outcome measure of this study was the assessment of the association between relapse within 12 mo and MES, UCEIS, UCCIS, and FC. The secondary outcome was the comparison between endoscopic scores and biomarkers in en-rolled

patients with UC with mucosal healing.

RESULTS

FC and UCCIS showed a significant correlation with UCEIS (r = 0.537, P < 0.001 and r = 0.957, P < 0.001, respectively). Receiver-operating characteristic analysis for predicting MES 0 showed that the area under the curve of UCCIS was significantly higher than that of FC (P < 0.01). During the 1-year observation period, 18 (24%) patients experienced a relapse, and both the FC and UCCIS of the relapse group were significantly higher than that of the remission group. The cut-off values for predicting relapse were set at FC = 323 mg/kg and UCCIS = 10.2. The area under the curve of the receiver-operating characteristic analysis for predicting relapse did not show a significant difference between FC and UCCIS. The accuracy of the endoscopic scores and biomarkers in predicting relapse was 86.7% for UCCIS, 85.3% for UCEIS, 76.0% for FC, and 73.3% for MES.

CONCLUSION

The three endoscopic scores and FC may predict UC relapse during clinical remission. Among these scores, UCEIS may be the most useful in terms of ease of evaluation and accuracy.

Key Words: Ulcerative colitis; Mayo Endoscopic Subscore; Ulcerative Colitis Endoscopic Index of Severity; Ulcerative Colitis Colonoscopic Index of Severity; Fecal calprotectin; Relapse

Core Tip: We evaluated the usefulness of fecal calprotectin and endoscopic scores, including the Mayo Endoscopic Subscore, Ulcerative Colitis Endoscopic Index of Severity (UCEIS), and Ulcerative Colitis Colonoscopic Index of Severity, in patients with ulcerative colitis (UC) in remission. All three endoscopic scores and fecal calprotectin are useful for predicting relapse in UC. The UCEIS is easy to evaluate and appears to be highly accurate in predicting relapse.

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INTRODUCTION

With the advances in treatment options for ulcerative colitis (UC), achieving mucosal healing has become a key therapeutic goal[1]. Mucosal healing is evaluated using endoscopic scores, such as the Mayo Endoscopic Subscore (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[2,3]. Although endoscopic examination is the most direct method for the evaluation of mucosal healing, frequent endoscopic examinations are not recommended owing to the associated costs and potential risks, along with the physical burden and psychological stress on the patient. Consequently, biomarkers are used as a method of evaluating mucosal status as an alternative to endoscopic examination[4]. Biomarkers such as fecal calprotectin (FC), immunological fecal occult blood test, and leucine-rich alpha-2 glycoprotein have been reported to be useful in UC[5-12]. Particularly, FC has shown a significant correlation with endoscopic scores and reflects mucosal activity in UC[5,6]. In addition, FC is widely used in clinical practice and often employed as a marker in large-scale clinical trials of new therapeutic agents to determine their therapeutic efficacy[13-15].

The endoscopic score can predict the prognosis of UC, with higher scores indicating higher rates of subsequent hospitalizations and surgeries[16-18]. A previous report on patients with UC with mucosal healing showing an MES of 1 or less showed that the subsequent relapse rate was significantly higher in the MES 1 group than in the MES 0 group[19]. Thus, while the endoscopic score has been shown to contribute to the prediction of subsequent relapse, biomarkers have also been identified as effective predictors[20-25]. Particularly, there are many reports on the prediction of relapse in UC using FC[20-24].

As previously mentioned, biomarkers reflect the endoscopic scores and contribute to the subsequent prediction of prognosis. In this study, we analyzed the relative efficacy of endoscopic scores against that of biomarkers in predicting relapse. Considering the possibility that this analysis may require a more detailed endoscopic score than just MES and UCEIS, we also incorporated the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS), which provides a comprehensive assessment of the overall colorectal score[26,27].

MATERIALS AND METHODS

Patients and disease assessments

In total, 75 patients with UC in clinical remission who visited the Hamamatsu University School of Medicine between February 2019 and March 2022 were enrolled. These patients were diagnosed with UC based on their clinical presentation, endoscopic findings, and histology according to the current established criteria for UC[28]. Patients diagnosed with enteritis, including Crohn's disease and inflammatory bowel disease unclassified, were excluded.

In this study, the clinical activity of UC was evaluated using the clinical activity index (CAI) according to Rachmilewitz [29]. Endoscopic scores for UC were assessed using MES, UCEIS, and UCCIS[2,3,26]. MES was evaluated according to the following criteria: 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[2]. The UCEIS score was evaluated by calculating the sum of three descriptors: vascular pattern (score 0-2), erosions and ulcers (score 0-3), and bleeding (score 0-3)[3]. The UCCIS score was assessed using the following descriptors in the five segments of the ascending colon, transverse colon, descending colon, sigmoid colon, and rectum: vascular pattern (score 0-2), granularity (score 0-2), erosions and ulcers (score 0-4), and bleeding/friability (score 0-2). These descriptor scores were then applied to the following formula: UCCIS = 3.1 × sum (vascular pattern across five segments) + 3.6 × sum (granularity across five segments) + 3.5 × sum (ulceration across five segments) + 2.5 × sum (bleeding/friability across five segments)[26]. Clinical remission was defined as CAI 4 or less, and mucosal healing was defined as MES 0 or MES 1. Patients who met these criteria were included in this study.

Biomarker measurement

Fecal samples were collected in plastic tubes for FC measurement and stored at -20 ℃ until shipment to the laboratory (SRL Inc., Tokyo, Japan). The measurements were performed using a Phadia 250 Immunoassay Analyzer (HITACHI Ltd., Tokyo, Japan) and Elia A Calprotectin 2 reagent (Phadia GmbH, Freiburg, Germany) using fluorescence enzyme immunoassay principles. As colonoscopic preparation could influence the results of FC, fecal samples were collected the day before or after the colonoscopy.

Study design

This retrospective, single-center observational study aimed to evaluate whether MES, UCEIS, UCCIS, and FC serve as predictors of clinical relapse. The primary outcome measure was the assessment of the association between relapse within 12 mo and MES, UCEIS, UCCIS, and FC. The secondary outcome was the comparison between endoscopic scores and biomarkers in the enrolled patients with UC with mucosal healing.

Patients enrolled in this study made outpatient visits at intervals of 3 or more months. These patients were outpatients for more than 12 mo or until relapse. Clinical relapse was defined as an increase in CAI above baseline due to the worsening of diarrhea and abdominal pain or frequent or bloody stools requiring modification or addition of treatment. Changes in treatment were made at the discretion of each attending physician.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., United States) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[30]. Differences were assessed using the Mann-Whitney U test or Student's *t*-test. Correlations were analyzed using Spearman's correlation coefficient. Receiver-operating characteristic (ROC) analysis was performed for endoscopy score and relapse prediction. The cumulative non-failure rate was evaluated using Kaplan-Meier analysis with the log-rank test. $P < 0.05$ was considered statistically significant.

Ethical statement

The study protocol was reviewed and approved by the ethics committee of Hamamatsu University School of Medicine (No. 20-322). This study was conducted in accordance with the Good Clinical Practice principles in adherence to the Declaration of Helsinki.

RESULTS

Patient characteristics

In total, 75 patients with UC were enrolled in this study. The baseline patient characteristics are shown in Table 1. The median patient age and disease duration were 49 years and 8 years, respectively. A total of 43 patients had an MES of 0, and 32 had an MES of 1. UCEIS scores ranged from 0 to 3, and the median UCCIS and FC values were 0 and 174 mg/kg, respectively.

Association between FC and endoscopic score

First, the association between endoscopic score and FC was assessed in enrolled patients with UC with MES 0 and 1. FC and UCCIS were significantly higher in the MES 1 group than in the MES 0 group ($P < 0.001$ and $P < 0.001$, respectively; Figure 1A and B). Both FC and UCCIS showed a significant correlation with UCEIS ($r = 0.537$, $P < 0.001$ and $r = 0.957$, $P < 0.001$, respectively; Figure 1C and D). A significant correlation was also observed between FC and UCCIS ($r = 0.506$, $P <$

Table 1 Baseline patient characteristics

Characteristic	All, *n* = 75
Age in yr, median [IQR]	49 [36, 62]
Male/Female, *n* (%)	45 (60.0)/30 (40.0)
Disease duration in yr, median [IQR]	8 [5, 13]
Disease extent, *n* (%)	
Extensive colitis	45 (60.0)
Left-sided colitis	24 (32.0)
Proctitis	6 (8.0)
CAI by the Rachmilewitz index, median [IQR]	0 [0, 1]
MES, *n* (%)	
MES 0	43 (57.3)
MES 1	32 (42.7)
UCEIS, *n* (%)	
UCEIS 0	39 (52.0)
UCEIS 1	17 (22.7)
UCEIS 2	13 (17.3)
UCEIS 3	6 (8.0)
UCCIS, median [IQR]	0 [0, 6.7]
FC in mg/kg, median [IQR]	174 [43, 810]
Medication used during the study, *n* (%)	
Oral 5-ASA	48 (64.0)
Suppository steroids	2 (2.7)
Systemic steroids	9 (12.0)
Immunomodulators	23 (30.7)
Biologics	30 (40.0)

5-ASA: 5-aminosalicylic acid; CAI: Clinical activity index; FC: Fecal calprotectin; IQR: Interquartile range; MES: Mayo Endoscopic Subscore; UCCIS: Ulcerative Colitis Colonoscopic Index of Severity; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

0.001; Figure 1E). ROC analysis to predict MES 0 showed cut-off values of FC 385 mg/kg and UCCIS 6.6, with an area under the curve (AUC) of 0.858 [95% confidence interval (CI): 0.770-0.946] and 0.987 (95%CI: 0.969-1.000; Table 2). The AUC of UCCIS was significantly higher than that of FC ($P < 0.001$; Figure 2).

Association between FC and endoscopic scores, and clinical relapse

In total, 18 (24.0%) patients experienced clinical relapse during the 1-year follow-up period. The baseline FC and UCCIS values were significantly higher in the relapse group than in the remission group ($P < 0.001$ and $P < 0.001$, respectively; Figure 3A and B). In the ROC analysis for predicting clinical relapse, the cut-off value for FC was 323 mg/kg, and the AUC was 0.813 (95%CI: 0.698-0.927; Figure 3C). The cut-off value for UCCIS was 10.2, and the AUC was 0.823 (95%CI: 0.697-0.949), with no significant difference (Figure 3C).

Kaplan-Meier analysis of remission rate grouped by cut-off value

Kaplan-Meier analysis was used to assess the remission maintenance rate by grouping by each endoscopic score and cut-off value. When the endoscopic score was grouped by MES 0 and 1 and UCEIS ≤ 1 and ≥ 2, a significant difference was observed in the log-rank test ($P < 0.001$ and $P < 0.001$, respectively; Figure 4A and B). The analysis also revealed significant differences between the FC < 323 and FC ≥ 323 groups and UCCIS < 10.2 and UCCIS ≥ 10.2 groups using the log-rank test ($P < 0.001$ and $P < 0.001$, respectively; Figure 4C and D). Regarding the accuracy of relapse prediction, UCCIS had the highest accuracy at 86.7%, followed by UCEIS at 85.3% (Table 3). The accuracies of FC and MES were 76.0% and 73.3%, respectively.

Table 2 Receiver-operating characteristic analysis of fecal calprotectin and Ulcerative Colitis Colonic Index of Severity for predicting Mayo Endoscopic Subscore 0

Factor	FC	UCCIS
Cut-off value	385	6.6
AUC (95%CI)	0.858 (0.770-0.946)	0.987 (0.969-1.000)
PPV	0.793	0.992
NPV	0.804	0.994
Sensitivity	0.719	0.992
Specificity	0.804	0.985
Accuracy	0.800	0.947

AUC: Area under the curve; CI: Confidence interval; FC: Fecal calprotectin; NPV: Negative predictive value; PPV: Positive predictive value; UCCIS: Ulcerative Colitis Colonoscopic Index of Severity.

Table 3 Comparison of accuracy of relapse prediction between fecal calprotectin levels, Ulcerative Colitis Colonoscopic Index of Severity, Mayo Endoscopic Subscore, and Ulcerative Colitis Endoscopic Index of Severity

Factor	Sensitivity	Specificity	PPV	NPV	Accuracy
FC ≥ 323	0.500	0.933	0.833	0.737	0.760
UCCIS ≥ 10.2	0.750	0.898	0.667	0.930	0.867
MES 1	0.833	0.702	0.469	0.930	0.733
UCEIS ≥ 2	0.722	0.895	0.684	0.911	0.853

FC: Fecal calprotectin; MES: Mayo Endoscopic Subscore; NPV: Negative predictive value; PPV: Positive predictive value; UCCIS: Ulcerative Colitis Colonoscopic Index of Severity; UCEIS: Ulcerative Colitis Endoscopic Index of Severity.

DISCUSSION

This study showed that FC, MES, UCEIS, and UCCIS are useful for predicting relapse in patients with UC in clinical remission. Endoscopic and biomarker assessment must be used in current clinical practice for UC, in which achievement of mucosal healing is the goal of treatment because endoscopic scores and biomarkers have been reported to contribute to subsequent prognosis in patients with UC[16-25]. MES, a simple endoscopic score, is often used in large-scale clinical trials and real-world clinical practice. Although the simplicity of MES makes it easy to use, it cannot be used for detailed scoring[2]. On the other hand, UCEIS, which evaluates vascular, bleeding, and erosion/ulcer patterns, is capable of providing a more detailed evaluation compared to MES[3]. However, the assessment of MES and UCEIS is performed on the most active lesions, located in the sigmoid colon or rectum, thus only assessing localized areas. There are several reports on endoscopic scores that evaluate the activity of the entire colon. UCCIS, like UCEIS, is calculated by scoring each item and substituting those scores into the formula[26]. Although UCCIS evaluates the entire colon, its complexity of scoring poses considerable challenges.

Biomarkers quantify activity and enable detailed evaluation of inflammation[21]. In Japan, endoscopic examination and biomarker measurements cannot be performed in the same month. As previously mentioned, each endoscopic score and biomarker has its own advantages and disadvantages. To the best of our knowledge, no studies have yet compared the abilities of MES, UCEIS, UCCIS, and FC, a representative biomarker, to predict relapse.

In this study, we investigated the prediction of relapse and evaluated the relationship between FC, UCEIS, and UCCIS in patients with a mucosal healing score of MES 1 or less. A few reports on biomarkers have evaluated the association between biomarkers and endoscopic scores in the entire severity range of MES, from 0 to 3. Guardiola *et al*[31] reported that FC is useful for evaluating UC activity, including histological evaluation, in patients with UC who are in clinical and endoscopic remission. Previously, we reported a significant correlation between FC and UCCIS in UC with an MES ≤ 1 (r = 0.653, P < 0.001)[32]. In that study, FC showed a significant correlation with UCEIS and UCCIS, indicating that FC is a sensitive biomarker that reflects endoscopic activity even among patients who have achieved mucosal healing.

Regarding the prediction of relapse, which is the main purpose of this study, it was found that FC, MES, UCEIS, and UCCIS are all useful for predicting relapse within 1 year. Several reports on the prediction of recurrence using endoscopic scores have shown that MES 1 was associated with a significantly higher risk of relapse compared to MES 0 and MES 1 [19]. We have also previously shown the usefulness of MES for relapse prediction in the analysis that examined the relapse prediction ability of fecal occult blood test[33]. Conversely, Yamamoto *et al*[34] reported that a similar analysis did not show a significant difference in predicting 1-year relapse, suggesting that the relapse prediction ability of MES is

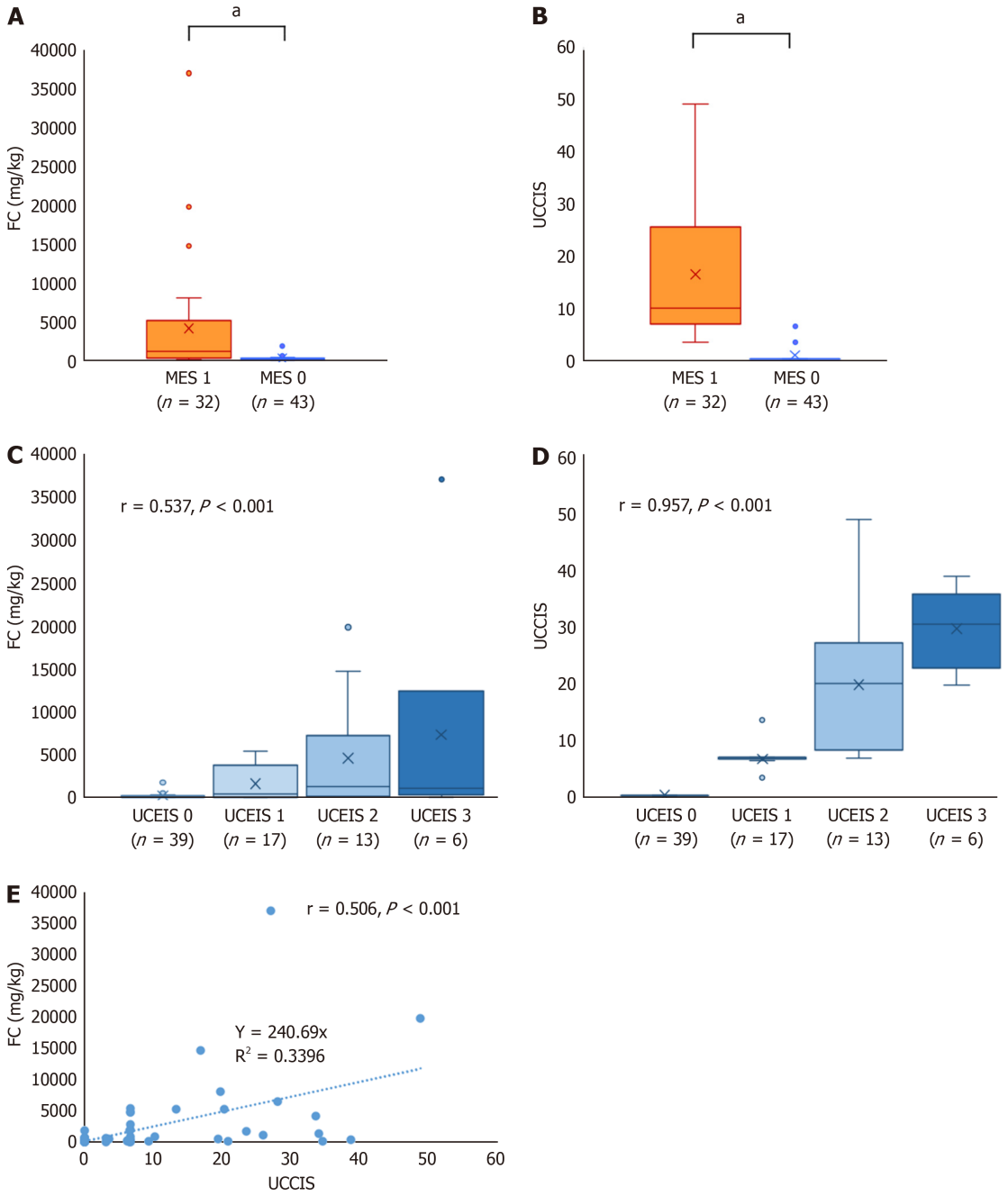

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Figure 1 Association between fecal calprotectin and endoscopic scores. A: Differences in fecal calprotectin (FC) levels between Mayo Endoscopic Subscore (MES) groups; B: Differences in the Ulcerative Colitis Colonic Index of Severity (UCCIS); C: Correlation with the Ulcerative Colitis Endoscopic Index of Severity; D: Relationship between FC and UCCIS; E: Correlation between FC and UCCIS. [a]*P* < 0.001.

controversial. Arai *et al*[35] examined relapse prediction using UCEIS and reported that UCEIS is useful in mid- to long-term relapse prediction. We previously reported recurrence prediction using UCCIS, and the analysis was performed over a long-term observation period of 2 years and 5 years[36].

The cut-off of UCEIS in this study was set at 2, and the analysis was performed accordingly. This was because other UCEIS scores were also grouped and analyzed; however, the analysis grouped by scores of 2 or more and 1 or less showed the most accurate results. Arai *et al*[35] also reported that grouping based on a UCEIS cut-off of 2 or higher and 1 or lower was useful, and the cut-off value of UCEIS 2 was considered to be valid. Moreover, we did not perform multivariate analysis because UCEIS and UCCIS have a strong correlation close to 1, and including both these variables would have rendered the statistical analysis inconsequential. Instead, we examined the sensitivity, specificity, positive predictive values, negative predictive values, and accuracy. Regarding accuracy, both UCEIS and UCCIS exhibited an accuracy of 80% or more and were considered to be useful scores for predicting relapse. However, the UCCIS is an extremely complicated scoring system in which four items are evaluated across five colonic segments, and the scores are substituted into a formula. Therefore, it is not realistic to use this score in clinical practice. Hence, the UCEIS emerges as a preferable endoscopic scoring system in predicting relapse, owing to its accuracy and ease of use in clinical practice.

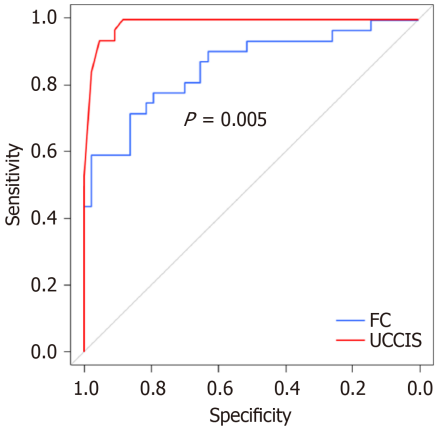

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Figure 2 Receiver-operating characteristic analysis of fecal calprotectin and Ulcerative Colitis Colonic Index of Severity for predicting Mayo Endoscopic Subscore 0. FC: Fecal calprotectin; UCCIS: Ulcerative Colitis Colonic Index of Severity.

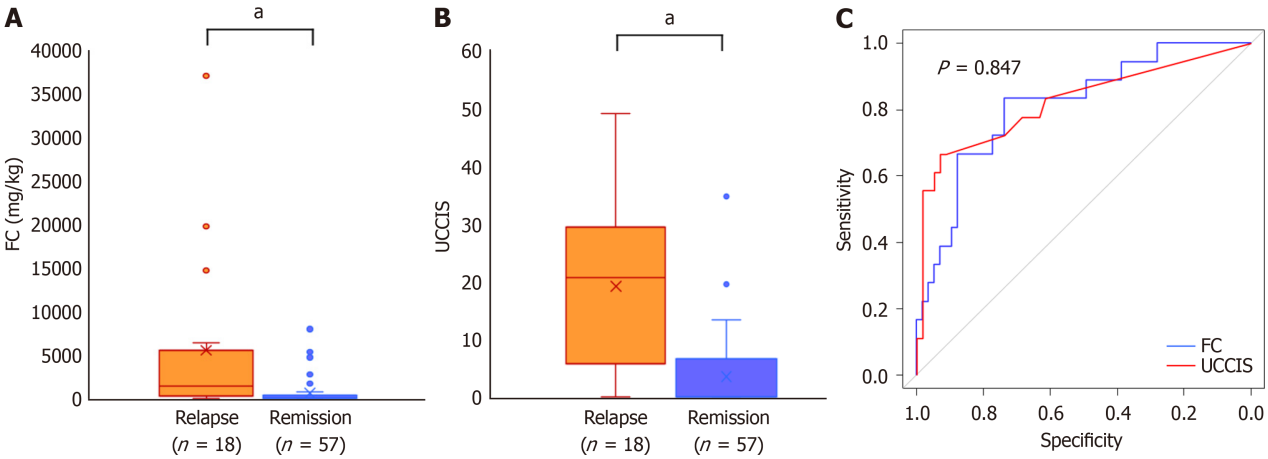

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Figure 3 Differences between fecal calprotectin and Ulcerative Colitis Colonic Index of Severity in terms of predicting relapse and the receiver-operating characteristic analysis for predicting relapse. A: Difference in fecal calprotectin (FC) levels between the relapse and remission groups; B: Difference in Ulcerative Colitis Colonic Index of Severity (UCCIS) between the relapse and remission groups; C: Receiver-operating characteristic analysis of FC and UCCIS for predicting relapse within 1 year. [a]$P < 0.001$. FC: Fecal calprotectin; UCCIS: Ulcerative colitis colonic index of severity.

Intensifying treatment based on the UCEIS score in real-world clinical practice could help prevent relapse; hence, further prospective studies in this regard are desired.

The strength of this study is that endoscopic examination and biomarker measurements were performed simultaneously. However, currently, biomarkers and endoscopic measurements cannot be performed together in clinical practice. Nevertheless, several limitations to this study must be acknowledged. First, it was a single-center retrospective analysis conducted in a small number of patients. Second, our results were not compared with other biomarkers, such as leucine-rich alpha-2 glycoprotein; histological findings were also not considered. Third, biomarker and endoscopic evaluations were not performed at the time of relapse.

CONCLUSION

In conclusion, MES, UCEIS, UCCIS, and FC were useful for predicting relapse in patients with UC in clinical remission. Among the three endoscopic scores evaluated, UCEIS may be the most useful in terms of ease of evaluation and predictive accuracy.

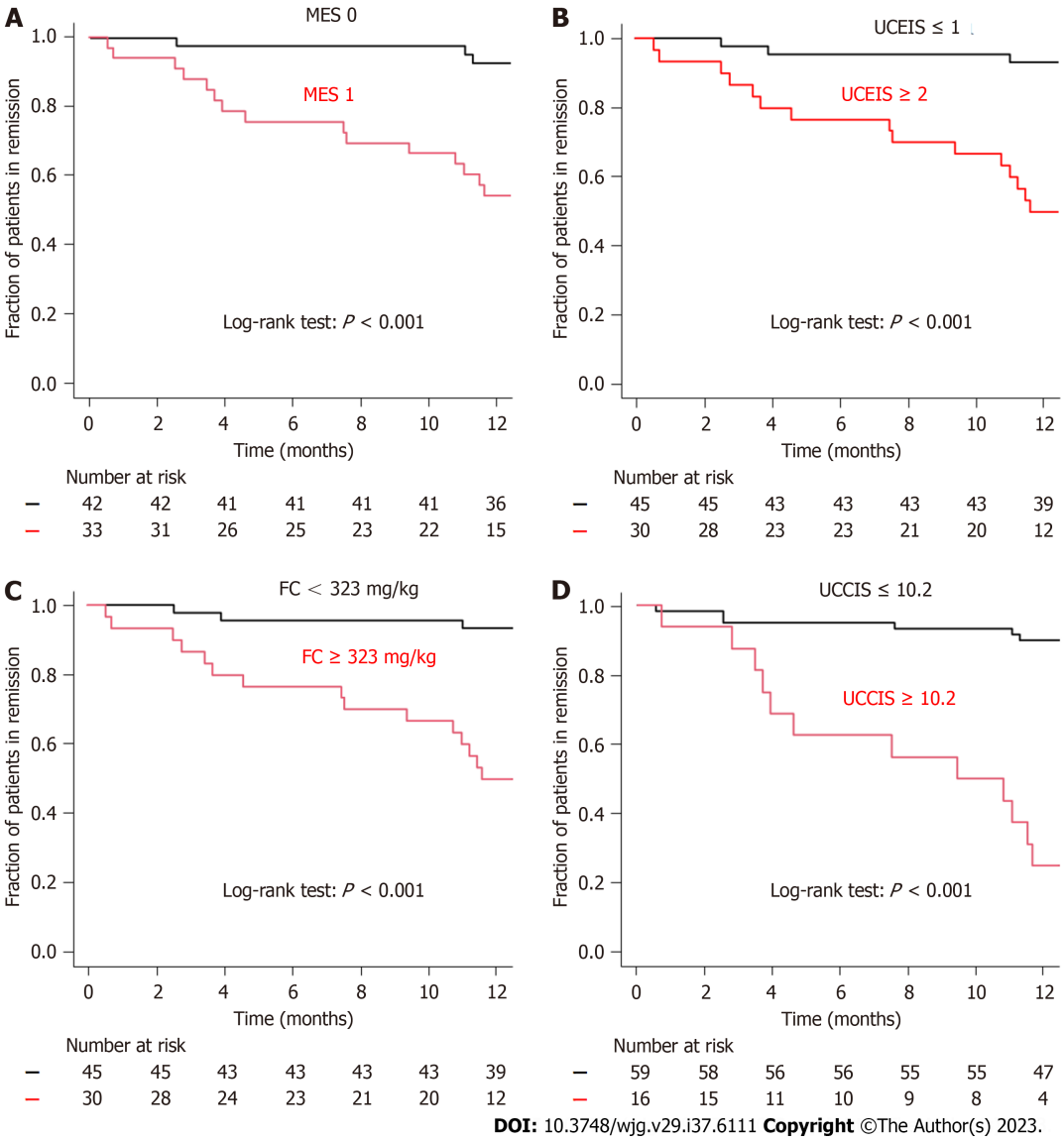

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Figure 4 Kaplan-Meier analysis of relapse-free rates. A: Mayo Endoscopic Subscore; B: Ulcerative Colitis Endoscopic Index of Severity; C: Fecal calprotectin levels; D: Ulcerative Colitis Colonic Index of Severity. FC: Fecal calprotectin; MES: Mayo endoscopic subscore; UCCIS: Ulcerative colitis colonic index of severity; UCEIS: Ulcerative colitis endoscopic index of severity.

ARTICLE HIGHLIGHTS

Research background

The goal of ulcerative colitis (UC) treatment is to achieve mucosal healing, for which endoscopic evaluation is recommended. To avoid endoscopy, fecal calprotectin (FC), which may be an alternative biomarker for UC, was reported to be useful in evaluating patients. Although endoscopic scores and FC, in addition to traditional biomarkers and the Mayo Endoscopic Subscore (MES), are useful for predicting relapse in patients with UC in remission, no studies have compared the predictive abilities of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS), which assesses the entire colon.

Research motivation

To evaluate whether FC and MES, UCEIS, and UCCIS are useful for predicting relapse in patients with UC in clinical remission.

Research objectives

Overall, 75 patients with UC in clinical remission, with a clinical activity index (CAI) according to Rachmilewitz score was ≤ 4, underwent colonoscopic examination and FC measurements.

Research methods

We assessed whether the enrolled patients experienced UC relapse within 12 mo after endoscopic examination and FC

measurement. Clinical relapse was defined as an increase in CAI above baseline due to worsening of diarrhea and abdominal pain or frequent or bloody stools, requiring modification or addition of treatment. We also evaluated the association between endoscopic scores and FC.

Research results

Cut-off values and areas under the curve (AUC) for FC and UCCIS in the receiver-operating characteristic analysis to predict clinical relapse were 323 mg/kg, 0.813 [95% confidence interval (CI)]: 0.698-0.927], and 10.2, for FC, AUC, and UCCIS, respectively.

The AUC was 0.823 (95%CI: 0.697-0.949). Univariate analysis was performed using these cut-off values (FC < 323 mg/kg *vs* ≥ 323 mg/kg; UCCIS < 10.2 *vs* ≥ 10.2; MES 0 *vs* 1; and UCEIS ≤ 1 *vs* ≥ 2). The accuracy of relapse prediction was the highest with UCCIS, followed by UCIES, FC, and MES.

Research conclusions

MES, UCEIS, UCCIS, and FC were useful for predicting relapse in patients with UC in clinical remission.

Research perspectives

UCCIS comprehensively evaluates the endoscopic activity of UC, helping to predict its relapse. However, its complexity poses a challenge. Among the three endoscopic scores, UCEIS may be the most useful in terms of ease of evaluation and accuracy.

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FOOTNOTES

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