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Retrospective Cohort Study

Comparison of fecal calprotectin and endoscopic score for predicting relapse of ulcerative colitis in remission

FC, MES, UCEIS and UCCIS predict relapse of UC

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Abstract

BACKGROUND

Although, the usefulness of endoscopic scores and biomarkers for predicting relapse in ulcerative colitis has been reported, there are few studies including endoscopic score evaluating entire colon.

AIM

To compare the usefulness of fecal calprotectin (FC) and endoscopic score including Mayo endoscopic subscore (MES), ulcerative colitis endoscopic index of severity (UCEIS), and ulcerative colitis colonoscopic index of severity (UCCIS) for predicting relapse in patients with ulcerative colitis (UC) in clinical remission.

METHODS

Seventy-five patients with UC in clinical and endoscopic remission who have visited our institution between February 2019 and March 2022 were enrolled. Biomarker

measurement and endoscopic evaluation using MES, UCEIS, and UCCIS were performed, and subsequent clinical course was followed.

RESULTS

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

CONCLUSION

Three endoscopic scores and FC may predict relapse in UC in clinical remission. Among the endoscopic 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

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Core Tip: We evaluated the usefulness of fecal calprotectin (FC) and endoscopic scores including MES, UCIES and UCCIS of patients with ulcerative colitis (UC) in remission.

Three endoscopic scores and FC are useful for predicting relapse in UC. UCEIS is an easy-to-evaluate score and appears to be highly accurate in predicting relapse.

INTRODUCTION

Achieving mucosal healing has become a therapeutic goal as the variety of treatment options for ulcerative colitis (UC) increases[1]. Mucosal healing is evaluated by endoscopic scores, such as Mayo endoscopic subscore (MES) and ulcerative colitis endoscopic index of severity (UCEIS), have been used[2,3]. Although endoscopic examination is the most direct method for the evaluation of mucosal healing, frequent endoscopic examinations are not recommended due to the risks associated, such as the physical burden and psychological stress on the patient, and cost. 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 (FIT), and leucine-rich alpha-2 glycoprotein (LRG), have been reported to be useful in UC[5–12]. Particularly, FC showed a significant correlation with endoscopic scores and was shown to reflect mucosal activity in UC[5,6]. In addition, FC is widely used in clinical practice and often measured in large-scale clinical trials of new therapeutic agents to determine therapeutic efficacy[13–15].

The endoscopic score can predict prognosis in UC; moreover, a higher endoscopic score indicates higher subsequent hospitalization and surgery rates[16–18]. A previous report of patients with UC with mucosal healing of MES 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, endoscopic score has been shown to contribute to the prediction of subsequent relapse, and biomarkers have been shown to predict relapse as well[20–25]. Particularly, there are many reports on the prediction of relapse in UCin FC[20–24].

As mentioned above, the biomarker reflects the endoscopic score and contributes to subsequent prognosis prediction. Since the superiority of the endoscopic score and biomarkers must be evaluated for relapse prediction, we analyzed it in this study. Considering the possibility that this analysis may require a more detailed endoscopic

score than MES and UCEIS, we also evaluated ulcerative colitis colonoscopic index of severity (UCCIS), which evaluated the overall colorectal score[26,27].

MATERIALS AND METHODS

Patients and disease assessments

Seventy-five patients with UC in clinical remission who attended Hamamatsu University School of Medicine between February 2019 and March 2022 were enrolled. These patients were diagnosed with UC based on clinical presentation, endoscopic findings, and histology according to the current established criteria for UC[28]. Enteritis, such as CD and inflammatory bowel disease unclassified, was excluded.

In this study, clinical activity index (CAI) according to Rachmilewitz *et al*[29] was used for evaluating the clinical activity of UC. 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 fives 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 that meet these criteria were enrolled in this study.

Biomarker measurement

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

Study design

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

Patients enrolled in this study had outpatient visits not more frequently than three 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., USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[30]. Evaluation of the differences was performed using the Mann–Whitney U test or Student's *t*-test. Correlations were analyzed using Spearman's correlation. Receiver operating characteristic (ROC) analysis was performed for endoscopy score and relapse prediction. Cumulative non-failure rate was evaluated

using Kaplan–Meier analysis with log-ran. $P < 0.05$ was considered statistically significant.

Ethical statement

This study protocol was reviewed and approved by the ethics committee of Hamamatsu University School of Medicine (number 20-322). This study was conducted in accordance with the Good Clinical Practice principles in adherence to the Declaration of Helsinki.

RESULTS

Patient characteristics

Seventy-five patients with UC were enrolled in this study, and baseline patient characteristics are shown in Table 1. The median patient age and disease duration were 49 and 8 years, respectively. A total of 43 patients are MES 0, and 32 patients are MES 1. UCEIS ranged from 0 to 3, and the median UCCIS and FC 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, b). FC and UCCIS showed significant correlation with UCEIS, respectively ($r = 0.537$, $P < 0.001$ and $r = 0.957$, $P < 0.001$, respectively) (Figure 1c, d). FC and UCCIS showed a significant correlation ($r = 0.506$, $P < 0.001$) (Figure 1e). ROC analysis to predict MES 0 showed cut-off values of FC 385 mg/kg, UCCIS 6.6, and 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

Eighteen patients (24.0%) had clinical relapse during the one-year follow-up period. Baseline FC and UCCIS were significantly higher in the relapse group than in the remission group (P < 0.001 and P < 0.001, respectively) (Figure 3a, b). In the ROC analysis for predicting clinical relapse, the FC cut-off was 323 mg/kg, and the AUC was 0.813 (95%CI: 0.698–0.927) (Figure 3c). The cut-off value of UCCIS was 10.2, and the AUC was 0.823 (95%CI: 0.697–0.949), showing no significant difference between the AUCs of FC and UCCIS (Figure 3c).

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

Kaplan–Meier analysis was performed on 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 shown in the log-rank test (P < 0.001 and P < 0.001, respectively) (Figure 4a, 4b). Kaplan–Meier analysis between the FC < 323 and FC ≥ 323 groups and UCCIS < 10.2 and UCCIS ≥ 10.2 groups also showed a significant difference in log-rank test (P < 0.001 and P < 0.001, respectively) (Figure 4c, 4d). 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%.

DISCUSSION

This study showed that MES and UCEIS, UCCIS, and FC are useful for predicting relapse in patients with UC in clinical remission. Endoscopic and biomarker assessment must be used in current UC clinical practice, 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]. A simple endoscopic score, MES, is often used in large-scale clinical trials and real-world clinical practice. Although MES can be easily scored, its simplicity makes it difficult to finely score[2]. In addition, UCEIS scores vascular, bleeding, and erosion/ulcer patterns and is capable of a more detailed evaluation than MES[3]. However, the assessment of MES and UCEIS is

performed at the most active lesion or sigmoid colon or rectum and can only assess localized areas. There are several reports of 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]. UCCIS evaluates the whole colon, but the complexity of scoring is a major problem.

On the other hand, biomarkers quantify activity and enable detailed evaluation of inflammation[21]. In Japan, it is a rule that endoscopic examination and biomarker measurement cannot be performed in the same month. As described above, each endoscopic score and biomarker has advantages and disadvantages. To date, no studies have compared and evaluated relapse prediction for MES, UCEIS, UCCIS, and fecal calprotectin, which is a representative biomarker.

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

Regarding the prediction of relapse, which is the main purpose of this study, FC, MES, UCEIS, and UCCIS are useful for predicting relapse within one year. Several reports on the prediction of recurrence using endoscopic scores showed that MES 1 has a significantly higher risk of relapse when comparing MES 0 and MES 1.[19]. We have also shown the usefulness of MES as a relapse prediction in the analysis that examined the relapse prediction of FIT in the past[33]. Conversely, Yamamoto *et al*[34] reported that a similar analysis did not show a significant difference in predicting one-year relapse, suggesting that relapse prediction in MES is 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 in this report, the analysis was performed over a long-term observation period of two and five years.[36]

The cut-off of UCEIS was defined as 2, and analysis was performed in this study. This was because other UCEIS scores were also grouped and analyzed; however, the analysis grouped by 2 or more and 1 or less was the most accurate. Arai *et al*[35] also reported that grouping with UCEIS 2 or higher and 1 or lower was useful, and the cutoff value of UCEIS 2 was considered to be valid. Moreover, we did not perform multivariate analysis because UCEIS and UCCIS have strong correlation close to 1, and these two variables did not result in significant statistical analysis as related values. Instead, we examined sensitivity, specificity, positive predictive values, negative predictive values, and accuracy. Regarding accuracy, UCEIS and UCCIS exhibited an accuracy of 80% or more and were considered to be useful scores for relapse. However, UCCIS is an extremely complicated scoring system in which four items are evaluated in five colonic segments, and the scores are substituted into a formula. It is not realistic to use in clinical practice. For this reason, we thought that UCEIS would be useful in predicting relapse, in terms of endoscopic scores, considering accuracy and ease of use in clinical practice. Intensifying treatment based on the UCEIS score in real-world clinical practice may contribute to the prevention of relapse; hence, further prospective studies are desired.

The strength of this study is that endoscopic examination and biomarker measurements were performed simultaneously. Biomarkers and endoscopic measurements cannot be performed together in clinical practice. Conversely, there are several limitations in this study. First, this study was a retrospective analysis in a small number of patients at a single center. Second, there was no comparison with other biomarkers, such as LRG or histological findings. Third, biomarkers and endoscopic evaluation at the time of relapse were not performed.

CONCLUSION

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

ARTICLE HIGHLIGHTS

Research background

The goal of ulcerative colitis (UC) treatment is to achieve mucosal healing. Endoscopic evaluation is recommended in UC. 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 UC in remission, no studies have compared the usefulness of relapse prediction based on 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 of UC in clinical remission.

Research objectives

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

Research methods

We assessed whether enrolled patients developed 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 receiver operating characteristic analysis to predict clinical relapse were 323 mg/kg, 0.813 (95%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 with 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 highest with UCCIS followed by UCIES, FC, and MES.

Research conclusions

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

Research perspectives

UCCIS comprehensively evaluates the endoscopic activity of UC, which may contribute to the prediction of relapse. However, the challenge is that the evaluation is complicated. Among the three endoscopic scores, the UCEIS may be the most useful in terms of ease of evaluation and accuracy.

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