Establishment of a Novel Scoring System for Colon Capsule Endoscopy to Assess the Severity of Ulcerative Colitis—Capsule Scoring of Ulcerative Colitis

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Background: The usefulness of second-generation colon capsule endoscopy (CCE-2) for ulcerative colitis (UC) has not been fully demonstrated. This study aimed to develop an endoscopic severity score of UC for CCE-2.

Methods: Patients diagnosed with UC were enrolled prospectively and underwent colonoscopy and CCE-2 on the same day. The collected CCE-2 videos were adopted for the development of the score. These videos were scored by 4 blinded inflammatory bowel disease experts. The items validated with the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) were used as the candidate items, some of which were automatically assessed using the workstation. Each item was divided into proximal and distal parts at the splenic flexure and then individually assessed. The image readers simultaneously evaluated the inflammation severity using the visual analog scale (VAS). The descriptors that contribute to this scale were evaluated, and a model to predict the VAS was constructed. The UCEIS was scored by other endoscopists using colonoscopy videos. The correlation coefficients with fecal calprotectin, blood tests, and Lichtiger index were calculated.

Results: The final scoring system was fixed as "vascular pattern sum (proximal + distal) + bleeding sum + erosions and ulcers sum (minimum–maximum, 0–14)" and was named Capsule Scoring of Ulcerative Colitis (CSUC). The correlation coefficient of CSUC with biomarkers and clinical score was similar to that of the UCEIS.

Conclusions: We developed a new simple score using the 3 descriptors of CCE-2.

Key Words: colon capsule endoscopy, ulcerative colitis, inflammatory bowel disease

INTRODUCTION

The clinical evaluation of ulcerative colitis (UC) is often investigated by performing a colonoscopy based on the diffuse extension of mucosal damage, severity of erosion, and/or ulcer. Because patients with UC are reported to have a favorable prognosis when mucosal healing has been confirmed,[1, 2] confirmation of mucosal healing using colonoscopy is crucial for UC patients. Thus, colonoscopy is an essential examination; however, when severe inflammation occurs in the colon, observing the entire colon or performing colonoscopy itself from the perspective of safety is impossible in some cases, such as pain and risk of perforation.

Capsule endoscopy (CE) allows for noninvasive observation of the intestinal mucosa, and second-generation colon capsule endoscopy (CCE-2) is widely used for colon cancer screening.[3] The usefulness of CCE-2 with regard to the surveillance of colonic polyps has been demonstrated.[4] However, a limited number of studies have reported its usefulness with regard to UC alone.[5, 6]

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Hosoe et al.[7] conducted clinical studies using CCE-2 in patients with UC and reported its safety and efficacy. A colon preparation method was performed using a reduced total dose of laxative for patients with UC.[8] In these studies, a difference in visibility was noted between CCE-2 and colonoscopy findings. The findings were considered to be affected by the differences in the observation conditions between colonoscopy and CCE-2, such as the presence or absence of air insufflation. Therefore, assessing the results of tests performed using the CCE-2 based on the existing colonoscopy score is considered inappropriate, and developing a new endoscopic severity assessment score for CCE-2 is necessary.

For colonoscopy, various scoring systems to evaluate UC inflammation have been reported.[9–14] However, many of the scoring systems are used without validation.[15] The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is 1 of the scoring systems that have been developed in a statistically systematic manner[16] and validated in a later study.[17] Due to its high reproducibility, the UCEIS is widely used to assess UC inflammation, and its usefulness has been reported.[17–19] The aim of this study was to develop, using a statistically systematic method, a new endoscopic severity assessment score of UC for CCE-2 utilizing a part of the development method for the UCEIS.

METHODS

Study Design

This prospective multicenter study was conducted at the Keio University Hospital, Kitasato University Kitasato Institute Hospital, Tokyo Medical and Dental University Medical Hospital, Toho University Medical Center Sakura Hospital, and Ofuna Chuo Hospital. After approval was obtained from the ethics committee of each study site, the present study was registered, as required, with the registry endorsed by the International Committee of Medical Journal Editors (UMIN ID000005107). Written informed consent was obtained from all patients. This study consisted of 2 phases. Eligible patients had a histologically confirmed diagnosis of UC. Excluded patients had contraindications for small bowel capsule[20] and/or were allergic to the bowel preparation materials. In phase 1, patients with UC were prospectively enrolled to develop a new endoscopic severity assessment score of UC for CCE-2. In phase 2, using the score, additional patients were further enrolled prospectively, and the score was validated to determine whether it could evaluate the clinical condition of patients with UC. This paper reports the results of phase 1. Phase 1 consisted of 2 parts. In phase 1-1, 40 patients diagnosed with UC were enrolled prospectively and underwent colonoscopy and CCE-2 on the same day to collect colonoscopy videos and CCE-2 videos. The collected CCE-2 videos were used in the development of the score, except for those that failed to capture the entire colon (when total colon observation was not possible with CCE-2) or those with a poor colon preparation. Of the 4-point grading scale (poor, fair, good, and excellent) reported by Leighton et al.,[21] the cleansing level of poor,[8] which is inappropriate for the assessment of UC inflammation, was adopted as the definition of poor colon preparation. The CCE-2 videos were scored by 4 blinded inflammatory bowel disease experts (T.O., M.H., K.M., and N.Y.). Because assessment of more items than colonoscopy using the CCE-2 was considered difficult, the items validated with the UCEIS were used as the candidate items (descriptors) for the score. Moreover, the items to be automatically assessed using the workstation were also adopted as the criteria for the score (Table 1). Each descriptor was divided into proximal and distal parts at the splenic flexure and then individually assessed (Fig. 1). With "completely normal" assumed as 0 and "worst ever seen" as 100, the image readers simultaneously evaluated the inflammation severity of the entire colon from the CCE-2 videos using the visual analog scale (VAS). Meanwhile, with regard to the colonoscopy videos, 2 expert endoscopists (N.H. and T.Ko.) independently assessed the UCEIS of both the proximal and distal parts. After completion of scoring all the videos, when the colonoscopy assessment of the 2 experts differed, consensus was reached after mutual discussion, and the result was used as the gold standard. Fecal calprotectin and blood levels of hemoglobin, white blood cell (WBC), and C-reactive protein (CRP) of the enrolled patients were measured. The background and clinical scores (Lichtiger index) of the patients were also collected. Fecal calprotectin assay was performed by Thermo Fisher Scientific (Tokyo, Japan), and calprotectin was measured after blinding to the clinical and endoscopic profiles. The results of fecal calprotectin within 3 days before the CCE-2, the results of blood tests within 7 days before the CCE-2, and the results of background and clinical scores of the patients immediately before the CCE-2 were adopted.

In phase 1-2, the items to be scored (descriptors) that contribute to the VAS were searched from the collected data, and a model (estimation of the weight for each item) to predict the VAS was constructed. Meanwhile, the contribution of the score by region of the colon (proximal, distal, or the sum of both) was also examined, and an endoscopic severity assessment score of UC for CCE-2 was developed. Subsequently, the intra- and interobserver agreement (kappa coefficient) and the proportion of agreement were calculated to examine the reproducibility of the score. In addition, the correlation coefficient (*rho*) with fecal calprotectin, blood tests (hemoglobin, WBC, and CRP), and clinical score (Lichtiger index) were estimated to examine the extent to which the CCE-2 score reflects the clinical condition.

CCE-2 Method and CCE-2 Scoring Method

All the enrolled patients underwent CCE-2 and colonoscopy on the same day. The test schedule is shown in Supplementary Table 1. The previously reported regimen[8] with an addition of 1 booster dose of magnesium citrate (23 g [600 mL]) was used as the colon preparation method. Even if the capsule had not been excreted, colonoscopy was performed 7 hours

TABLE 1: Descriptors and Definitions

Descriptor (Score Most Severe Lesions)	Likert Scale Anchor Points	Definition
Vascular pattern	Normal (0)	Normal vascular pattern
	Patchy obliteration (1)	Obliterated area ≤30%
	Obliterated (2)	Obliterated area >30%
Bleeding	None (0)	No visible blood detected by SBI
	Mild (1)	No. bleeding picture detected by SBI ≤10
	Severe (2)	No. bleeding picture detected by SBI >10
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤5-mm) defects in the mucosa
	Superficial ulcer (2)	Larger (>5-mm) defects in the mucosa
	Deep ulcer (3)	Larger (>5-mm) and deeper excavated defects in the mucosa, with a slightly raised edge

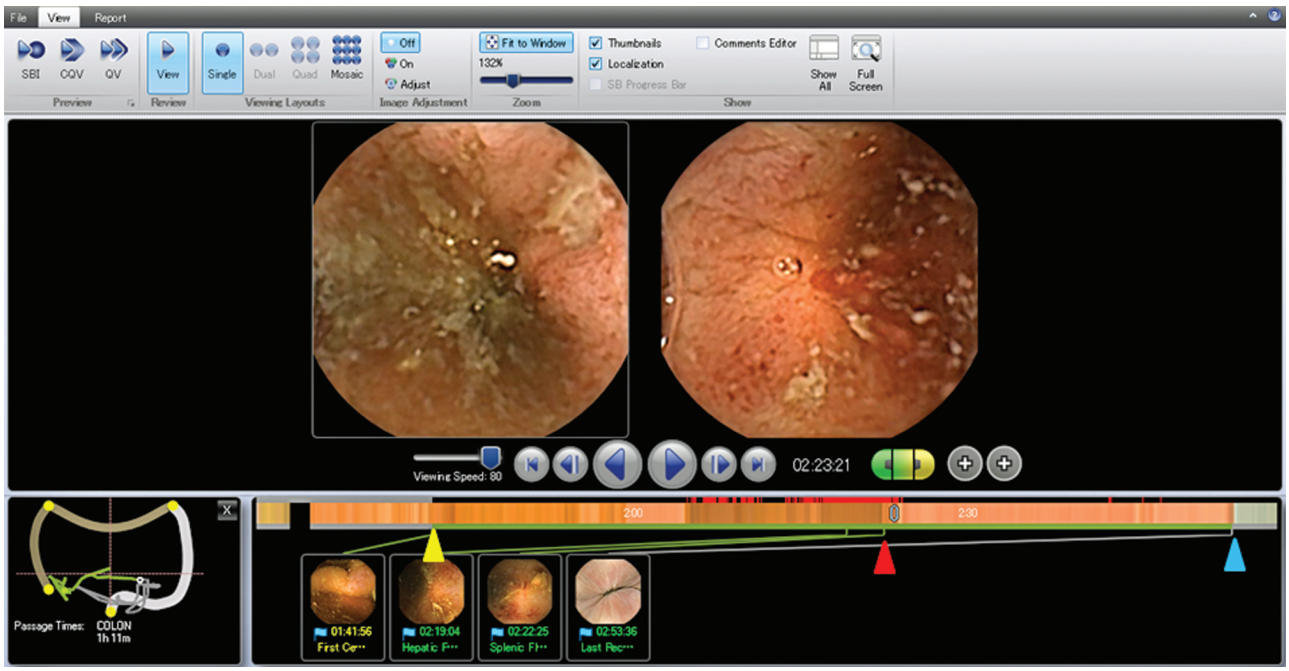

FIGURE 1. Colon capsule endoscopic software image of the starting point of the reading. The cecal image and the last rectal image on each CCE-2 video were marked in advance. The yellow triangle indicates the first cecal point; red triangle, splenic flexure; and blue triangle, last rectal point. Each CCE-2 reader read the CCE image from the yellow triangle to the blue triangle and scored the proximal part (from the yellow triangle to the red triangle) and distal part (from the red triangle to the blue triangle).

after swallowing it (4 pm), and the capsule was retrieved during colonoscopy. The CCE-2 (PillCam COLON 2; Medtronic, Yokneam, Israel) was used, and Rapid 8.1 software was utilized for reading images. A screen display at the time of the CCE-2 score assessment is shown in Figure 1. The videos marked with the first cecal image and the last rectal image in advance were read and scored only for the colon. For clarification, Figure 1 is marked with yellow (cecal point), red (splenic flexure), and blue triangles (last rectal point) on the color bar for the time axis. The image that had been automatically determined and proposed by the software was used as the splenic flexure image. The colon was divided into proximal (from the yellow triangle to the red triangle) and distal parts (from the red triangle to the blue triangle), and the scores at the points of maximum intensity of the respective inflammations were adopted. Because the CCE-2 image reading software has a red color detection function (suspected blood indicator [SBI]), images with bleeding were first automatically detected using the SBI. The number of detected images with bleeding was counted, and the bleeding was scored by region. Next, the vascular pattern was scored based on

whether the obliterated zone of the vascular pattern on the time axis bar was at least 30% or not. With regard to the descriptor in terms of erosions and ulcers, the mucosal defect was measured using the measurement function (polyp size estimation [PSE]) in the CCE-2 image reading software, and whether it was at least 5 mm was assessed. A deep ulcer was classified as a clear deep ulcer. A manual for these assessment methods was distributed to the CCE-2 readers in advance, and the readers read the images after approximately 30 minutes of explanation. Each reader randomly read each image twice in a blinded manner to evaluate the reliability of image reading.

Statistical Analysis

Demographic factors and baseline characteristics of enrolled UC patients were summarized. To search for descriptors that highly correlated with VAS assessed from the CCE-2 videos, we performed a simple linear regression analysis with VAS scores as the dependent variable for each descriptor with regard to the location (proximal and distal) and their sum. A multiple regression analysis was then conducted to construct a model to explain the VAS using multiple descriptors. The multiple regression analysis was conducted for all 27 combinations of the 3 descriptors and 3 locations (proximal, distal, and sum). In the regression analysis, the model was fit by each reader and averaged over readers by including reader as a factor in the model. The model fit was evaluated with the coefficient of determination (R^2).

Correlations between 2 variables were estimated using Spearman's rank correlation coefficient or Pearson's correlation coefficient. Two-tailed P values <0.05 were considered significant. SPSS, version 22, software (IBM Armonk, NY, USA) was used for all statistical analyses.

RESULTS

Thirty-eight patients were enrolled. Of these patients, 16 were excluded due to refusal to participate (1 patient), poor colon preparation (3 patients), and incomplete observation of the entire colon using the CCE-2 (12 patients). Finally, 22 enrolled patients (age 50.8 ± 12.2, 18 males and 4 females) were included in the analysis. No adverse events related to the study were observed. The backgrounds of the analyzed patients are shown in Table 2. The median clinical score (Lichtiger score) was 3 (range of Lichtiger score, number of patients: 0–3, 19; 4–7, 0; 8–10, 3). With regard to the disease type, total colitis was 50.0%; left-sided colitis, 31.8%; and proctitis, 18.2%. The mean image reading time of the 4 CCE-2 readers was 12.1 ± 6.6 minutes.

Score Development

Univariate regression analysis

A simple linear regression analysis was conducted with VAS scores as the dependent variable for each descriptor with regard to the location (proximal and distal) and their sum. Each reader randomly read each image twice; thus, replication data were obtained on each descriptor. In the simple regression analysis, the sum of vascular pattern, the proximal or sum of bleeding, and the sum of erosions and ulcers were highly correlated with the VAS (R^2: sum of vascular pattern 0.496–0.762 [minimum–maximum], proximal of bleeding 0.371–0.875, sum of bleeding 0.249–0.8, sum of erosions and ulcers 0.301–0.778).

Multiple regression analysis and final model

To construct a model to explain the VAS using multiple descriptors, we conducted a multiple regression analysis. This

TABLE 2: Backgrounds of the Examined Videos

No. Patients		22
Sex, male/female		18/4
Mean age ± SD (range), y		50.8 ± 12.2 (27–75)
Mean disease duration ± SD (range), y		8.0 ± 7.3 (4–30)
Disease activity		
Median Lichtiger index (minimum–maximum)		3 (0–10)
Type of disease, No. (%)		
	Total colitis	11 (50.0)
	Left-sided	7 (31.8)
	Proctitis	4 (18.2)
Medications, No. (%)		
	5-ASA	15 (68.2)
	5-ASA + AZA	4 (18.2)
	5-ASA + AZA + Anti TNFα	2 (9.1)
	Tacrolimus + AZA + steroid	1 (4.5)

Abbreviations: 5-ASA, 5-aminosalicylic acid; AZA, azathioprine

analysis was conducted for all 27 combinations of the 3 descriptors and 3 locations (proximal, distal, and sum). The R^2 for the simple regression analysis model of each descriptor when the readers were taken as a factor was 0.236–0.668, and the R^2 for the multiple regression analysis model when the readers were taken as a factor was 0.586–0.817. Similar to the simple linear regression analysis, vascular pattern sum, bleeding proximal or sum, and erosions and ulcers sum were useful covariates for VAS prediction. The estimated regression coefficients for the 2 models showed a good model fit to the data. To simplify, we converted the regression coefficients to integers. The Pearson correlation coefficient between the predicted and observed values of VAS calculated using the 2 models was 0.89 (model 1: vascular pattern sum, bleeding proximal, erosions and ulcers sum; fit: R^2 = 0.817, 0.793; prediction formula: predicted value of VAS = 7 × vascular pattern sum + 11 × bleeding proximal + 10 × erosions and ulcers sum; model 2: vascular pattern sum, bleeding sum, erosions and ulcers sum; fit: R^2 = 0.812, 0.777; prediction formula: predicted value of VAS = −1 + 7 × vascular pattern sum + 5 × bleeding sum + 10 × erosions and ulcers sum). To simplify the score calculation considering the clinical use, model 3 was assumed as vascular pattern sum, bleeding sum, and erosions and ulcers sum (with the weighting assumed as 1 for all the descriptors), which resulted in the following fit: R^2 = 0.774, 0.745 and prediction formula: predicted value of VAS = 7.7 × (vascular pattern sum + bleeding sum + erosions and ulcers sum). The plots of the predicted and observed values of VAS calculated using model 3 are shown in Figure 2. Although Figure 2 shows the results of replication 1 data only, the Pearson correlation coefficient between the predicted and observed values of VAS was 0.88, which was comparable to models 1 and 2. To simplify the score calculation in clinical use, we adopted model 3 as the final model. The final scoring system was fixed as "vascular pattern sum + bleeding sum + erosions and ulcers sum (minimum–maximum, 0–14)". This scoring system was named Capsule Scoring of Ulcerative Colitis (CSUC).

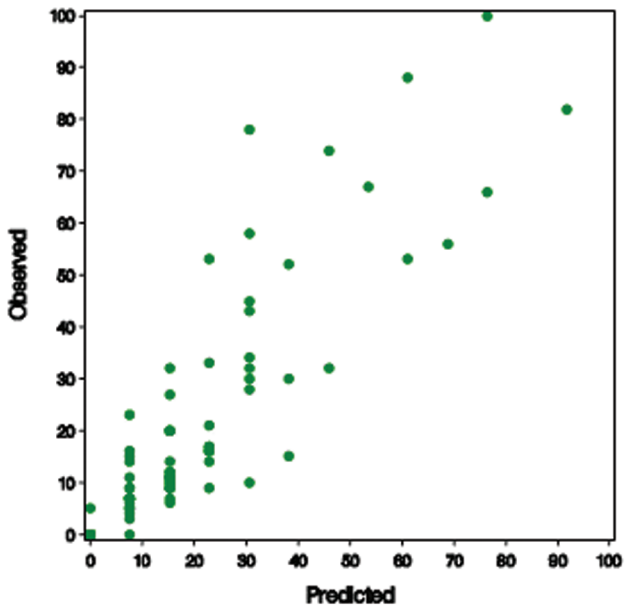

FIGURE 2. Plots of observed vs predicted VAS values with final model. Final model (predicted value of VAS) = 7.7 × (vascular pattern sum + bleeding sum + erosions and ulcers sum). The Pearson correlation coefficient between the predicted and observed values of VAS was 0.88.

Score Validation

The intra- and interobserver agreement (kappa value) and the proportion of agreement are shown in Table 3. The intraobserver agreement was 0.8 or higher, except for bleeding (distal) and ulcer and erosions (proximal). This result shows a high intra-observer reproducibility, as indicated by the total score of 0.86. The interobserver kappa value was around 0.5, which was low due to less dispersion of scores with regard to bleeding. However, the proportion of agreement was very high, with 0.96 for proximal and 0.90 for distal. With regard to erosions and ulcers, dispersion was noted between the observers, with 0.26 for proximal and 0.41 for distal. The mean weighted kappa value of the total score was 0.52. The Spearman's correlation coefficient between CSUC and clinical parameters (fecal calprotectin, blood tests [hemoglobin, WBC, and CRP], and clinical score [Lichtiger index]) is shown in Table 4. The correlation coefficient was almost similar to the UCEIS assessed from the colonoscopy videos, and the coefficients of correlation (ρ) with Lichtiger index were 0.48 and 0.60 for UCEIS and CSUC, respectively (95% confidence interval [CI], 0.42–0.790).

DISCUSSION

Endoscopic evaluation is important in the management of patients with ulcerative colitis. Conventionally, the endoscopic scores that have been used were not validated. However, the UCEIS reported by Travis et al. was developed using a statistically systematic method and subsequently validated.[16] In the present study, the CCE-2 score was developed using a method almost similar to that for the UCEIS. With regard to the inflammation severity of the colon in patients with UC, based on the results of this study, we were able to construct a simple model that could explain approximately 80% of fluctuations in VAS data using the 3 descriptors of the CCE-2 (particularly sum of proximal and distal). The model that uses sum of proximal and distal with regard to vascular pattern and erosions and ulcers, and proximal or sum with regard to bleeding was shown to have a high predictive power. Considering the simplification of score calculation, the sum of these 3 descriptors was adopted as the CSUC. The conventional severity evaluation score of UC inflammation evaluated only the rectum and sigmoid colon or evaluated only the point of maximum intensity. The CSUC is different from the conventional scores in that it evaluates both proximal and distal. As mentioned above, the VAS for inflammation is related not only to the point of maximum intensity, but also to proximal and distal. The inflammation severity is expected to be expressed more accurately using both. On the other hand, a

TABLE 3: Intra- and Interobserver Agreement of Each Descriptor

	Variable (Scored Area)						
	Vascular (proximal)	Vascular (distal)	Bleeding (Proximal)	Bleeding (Distal)	Ulcer and Erosions (Proximal)	Ulcer and Erosions (Distal)	CSUC (Total)
Intra-observer							
Mean weighted kappa value	0.86	0.82	0.86	0.66	0.55	0.82	0.86
95% CI	0.71–1.00	0.60–1.00	0.58–1.00	0.00–1.00	0.00–1.00	0.71–1.00	0.69–1.00
Interobserver							
Mean weighted kappa value	0.53	0.42	0.77	0.27	0.26	0.41	0.52
95% CI	0.17–0.88	0.20–0.64	0.59–0.95	0.00–0.61	0.00–0.66	0.24–0.56	0.45–0.59
Mean proportion of agreement	0.62	0.58	0.96	0.90	0.52	0.60	0.31
95% CI	0.28–0.95	0.40–0.77	0.94–0.98	0.87–0.93	0.16–0.88	0.50–0.70	0.20–0.41

TABLE 4: Spearman Rank Correlation with the CSUC and UCEIS

	Correlation (*rho*)	95% CI
CSUC		
Fecal calprotectin	0.46	0.19–0.72
Lichtiger index	0.60	0.42–0.79
Hemoglobin	0.28	–0.34 to –0.21
WBC	0.40	0.31–0.48
CRP	0.20	0.00–0.45
UCEIS	0.55	0.38–0.72
UCEIS		
Fecal calprotectin	0.50	
Lichtiger index	0.48	
Hemoglobin	–0.12	
WBC	0.33	
CRP	0.13	

sum score such as CSUC might be underscored in patients with severe left-sided disease. In our cohort, disease in 8 left-sided UC patients was detected by colonoscopy (CS). To examine the utility of CSUC in left-sided UC, correlations between CSUC and fecal calprotectin, and those of UCEIS scored by CS and fecal calprotectin, were calculated using Spearman's rank correlation coefficient as surrogate marker. The mean correlation (ρ) between CSUC and fecal calprotectin was 0.46, and that between UCEIS and fecal calprotectin was 0.50. As far as the results of these analyses, CSUC and UCEIS have almost the same performance in reflecting the results of fecal calprotectin even in the left-sided UC. However, these are post hoc analyses with a small cohort, and additional evaluations with a large sample will be needed to resolve these concerns. Capsule endoscopy is a simple, patient-friendly test that involves swallowing only. Images captured while the capsule moves by intestinal peristalsis are downloaded to the workstation and are read by the examiner using the software installed on the workstation. This software is equipped with functions such as automatic determination of the hepatic flexure or splenic flexure, red color detection (SBI), and polyp measurement (PSE). With the hope of improving convenience and reproducibility, these functions, which are unique to CE, were incorporated into this score assessment. The incorporation of this automatic determination enabled image reading in a short time of 12.1 minutes on average. The SBI sometimes detects images without bleeding or redness, whereas it will miss small bleeding. In the CSUC, visible (definite) bleeding images were counted and scored. Thus, images with suspected bleeding were first automatically detected using the SBI. Next, the number of detected images with visible bleeding was counted by sight. Performance of the SBI in detecting the bleeding image of UC was calculated by post hoc analyses. The sensitivity and specificity of SBI for visible bleeding on a region basis were 1.0 (4/4) and 0.75 (30/40), respectively. From these post hoc analyses, SBI could pick up visible bleeding images correctly; however, false positives were sometime occurred. In the intra-observer analysis, the kappa value was 0.8 or higher, except for bleeding (distal) and ulcer and erosions (proximal), showing a high reproducibility. Less dispersion of scores and inadequate power of samples may lead lower and indistinct intra-observer agreement of bleeding (distal) and ulcer and erosions (proximal). On the other hand, in the interobserver analysis, the kappa value was approximately 0.5, and interobserver variation was noted for erosions and ulcers, with 0.26 for proximal and 0.41 for distal. This finding is speculated to be partially attributed to insufficient training because the explanation before the score assessment was performed for approximately 30 minutes. In fact, at the time of the score model construction, differences in the results of image reading were noted among the 4 readers, and about 20% of the results could not be explained with the models in this study. Travis et al. reported an interobserver agreement of 0.3 to 0.4 at the time of UCEIS construction,[16] but it improved to approximately 0.5 in

the subsequent additional study.[17] Considering that this study was performed in a small sample of 22 patients, conducting a large-scale additional study after providing the readers with sufficient training, similar to Travis et al., who conducted an additional study, is necessary to generalize the results. Moreover, the fact that many of the patients enrolled in this study had relatively mild symptoms can be cited as a limitation. Nonetheless, as indicated by the plots of the observed VAS value in Figure 2, constructing a score model was possible because some of the patients had high VAS and endoscopically severe patients were also included. Considering this point, however, performing a large-scale additional study is necessary.

To examine the clinical significance, we examined the correlation of the CSUC with the biomarker (fecal calprotectin), blood tests (hemoglobin, WBC, and CRP), and clinical score (Lichtiger index). Results showed a correlation almost comparable to the UCEIS assessed from the results of colonoscopy. This study is the first to examine the correlation between the CCE-2 findings and fecal calprotectin level.

In our results, the correlation coefficient between the CSUC and fecal calprotectin level was 0.46 (95% CI, 0.19–0.72), which showed a moderate correlation. Theede et al.[22] reported that endoscopic mucosal healing could be confirmed from the fecal calprotectin level and that a correlation with the UCEIS was noted. The fact that the correlation of the fecal calprotectin with the CSUC was almost comparable to the correlation with the UCEIS suggests that endoscopic mucosal healing can also be confirmed with CCE-2. In future studies, based on the comparison of fecal calprotectin level and colonoscopy findings, examining the clinical usefulness by calculating the cutoff value for mucosal healing prediction with the CSUC will be necessary. Evaluation of the clinical usefulness of the CSUC by determining the correlation between the CSUC and clinical relapse is also warranted.

The applicability of CCE-2 for UC in clinical practice is still controversial. One of the factors disturbing the spread of CCE-2 is its high cost. Actually, in Japan, the cost of CCE2 and sigmoidoscopy is 107,200 yen and 9000 yen, respectively, whereas, in recent study, Shi et al.[6] reported that CCE-2 had high accuracy in detecting mucosal lesions and determining disease severity in UC. These results suggest that the performance of CCE-2 in assessing mucosal inflammation of UC is sufficient. Moreover, CCE-2 is a simple, patient-friendly test that involves swallowing only. For the clinician, the reading of the capsule image is considered a time-consuming burden. However, in the current study, image reading occurred in a short time of 12.1 minutes on average. These results suggest that CCE-2 is a comfortable test for the doctor. Recently, computer-aided diagnosis and diagnosis with artificial intelligence (AI) have dramatically changed endoscopic diagnosis. CCE-2 is a good candidate for computer-aided diagnosis. In the near future, AI will enable us to score with CSUC automatically, with the result that CCE-2 will be spread widely.

In conclusion, we developed a new simple Colon capsule endoscopy score, which assesses the inflammation severity of the colon in patients with UC, and which could explain approximately 80% of fluctuations in VAS using the 3 descriptors of CCE-2.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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REFERENCES

1. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology*. 2011;141:1194–1201.
2. Miyoshi J, Matsuoka K, Inoue N, et al. Mucosal healing with oral tacrolimus is associated with favorable medium- and long-term prognosis in steroid-refractory/dependent ulcerative colitis patients. *J Crohns Colitis*. 2013;7:e609–e614.
3. Rex DK, Adler SN, Aisenberg J, et al. Accuracy of capsule colonoscopy in detecting colorectal polyps in a screening population. *Gastroenterology*. 2015;148:948–957.e2.
4. Spada C, Hassan C, Munoz-Navas M, et al. Second-generation colon capsule endoscopy compared with colonoscopy. *Gastrointest Endosc*. 2011;74:581–589.e1.
5. Sung J, Ho KY, Chiu HM, et al. The use of Pillcam Colon in assessing mucosal inflammation in ulcerative colitis: a multicenter study. *Endoscopy*. 2012;44:754–758.
6. Shi HY, Chan FKL, Higashimori A, et al. A prospective study on second-generation colon capsule endoscopy to detect mucosal lesions and disease activity in ulcerative colitis (with video). *Gastrointest Endosc*. 2017;86:1139–1146.e6.
7. Hosoe N, Matsuoka K, Naganuma M, et al. Applicability of second-generation colon capsule endoscope to ulcerative colitis: a clinical feasibility study. *J Gastroenterol Hepatol*. 2013;28:1174–1179.
8. Usui S, Hosoe N, Matsuoka K, et al. Modified bowel preparation regimen for use in second-generation colon capsule endoscopy in patients with ulcerative colitis. *Dig Endosc*. 2014;26:665–672.
9. Baron JH, Connell AM, Kanaghinis TG, et al. Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. *Br Med J*. 1962;2:441–443.
10. Matts SG. The value of rectal biopsy in the diagnosis of ulcerative colitis. *Q J Med*. 1961;30:393–407.
11. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317:1625–1629.
12. Hawthorne AB, Logan RF, Hawkey CJ, et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *BMJ*. 1992;305:20–22.
13. Naganuma M, Ichikawa H, Inoue N, et al. Novel endoscopic activity index is useful for choosing treatment in severe active ulcerative colitis patients. *J Gastroenterol*. 2010;45:936–943.
14. Samuel S, Bruining DH, Loftus EV Jr, et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. *Clin Gastroenterol Hepatol*. 2013;11:49–54.e1.
15. Samaan MA, Mosli MH, Sandborn WJ, et al. A systematic review of the measurement of endoscopic healing in ulcerative colitis clinical trials: recommendations and implications for future research. *Inflamm Bowel Dis*. 2014;20:1465–1471.
16. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the ulcerative colitis endoscopic index of severity (UCEIS). *Gut*. 2012;61:535–542.
17. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. *Gastroenterology*. 2013;145:987–995.
18. Saigusa K, Matsuoka K, Sugimoto S, et al. Ulcerative colitis endoscopic index of severity is associated with long-term prognosis in ulcerative colitis patients treated with infliximab. *Dig Endosc*. 2016;28:665–670.
19. Arai M, Naganuma M, Sugimoto S, et al. The ulcerative colitis endoscopic index of severity is useful to predict medium- to long-term prognosis in ulcerative colitis patients with clinical remission. *J Crohns Colitis*. 2016;10:1303–1309.
20. Rey JF, Ladas S, Alhassani A, et al; ESGE Guidelines Committee. European Society of Gastrointestinal Endoscopy (ESGE). Video capsule endoscopy: update to guidelines (may 2006). *Endoscopy*. 2006;38:1047–1053.
21. Leighton JA, Rex DK. A grading scale to evaluate colon cleansing for the pillcam COLON capsule: a reliability study. *Endoscopy*. 2011;43:123–127.
22. Theede K, Holck S, Ibsen P, et al. Level of fecal calprotectin correlates with endoscopic and histologic inflammation and identifies patients with mucosal healing in ulcerative colitis. *Clin Gastroenterol Hepatol*. 2015;13:1929–1936.e1.