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Predicting Therapeutic Intervention for Patients with Quiescent Crohn's Disease Using the Small Bowel Capsule Endoscopy Score

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Keywords
Small bowel capsule endoscopy · Crohn's disease activity in capsule endoscopy · Capsule endoscopy · Crohn's disease activity index · Crohn's disease · Small bowel

Abstract
Introduction: Small bowel (SB) capsule endoscopy (SBCE) is a sensitive modality for screening the entire SB of patients with Crohn's disease (CD); however, the prognostic impact of the results is unclear. We evaluated the ability of the SBCE score to predict therapeutic intervention for patients with CD and SB lesions without clinical symptoms as well as negative C-reactive protein (CRP) levels. ***Methods:*** Fifty-six patients who underwent a patency evaluation and had a CD activity index (CDAI) score <150 mg/dL and CRP level <0.5 mg/dL were included. Twenty-one and 35 patients had CD classified as Montreal classifications L1 and L3, respectively. The initial SBCE scores were subsequently grouped according to the presence or absence of intervention based on cutoff values. We examined whether the scores could predict the need for therapeutic intervention at 1 year, 2 years, and 5 years. The CD activity in capsule endoscopy (CDACE) score was used as the SBCE score. ***Results:*** The median observation period was 1,326 days. Twenty-one patients received therapeutic intervention. There were significant differences between patients with and without treatment intervention according to the CDACE cutoff value of 420 at 1 year, 2 years, and 5 years. Significant differences between patients with Montreal classification L1 with and without intervention were observed at 1 year and 2 years. The CDACE score was moderately and strongly correlated with the Lewis score and capsule endoscopy CDAI score, respectively (Spearman rank correlation coefficient: $\rho = 0.6462$ and $\rho = 0.9199$, respectively; $p < 0.0001$). ***Conclusion:*** A CDACE score ≥420 is predictive of intervention after 1 year for patients with CD, a CDAI score <150, and a CRP level <0.5 mg/dL. A larger study with a prospective design is necessary to validate our findings.

Introduction

Crohn's disease (CD) is a chronic, progressive, and destructive inflammatory disease characterized by the accumulation of intestinal damage caused by repeated inflammation in the small bowel (SB) and colon. The accumulation of intestinal damage leads to various complications such as stenosis and abscess formation [1, 2]; therefore, early diagnosis and appropriate therapeutic intervention are important. Lesions of the small intestine are found in approximately 80% of

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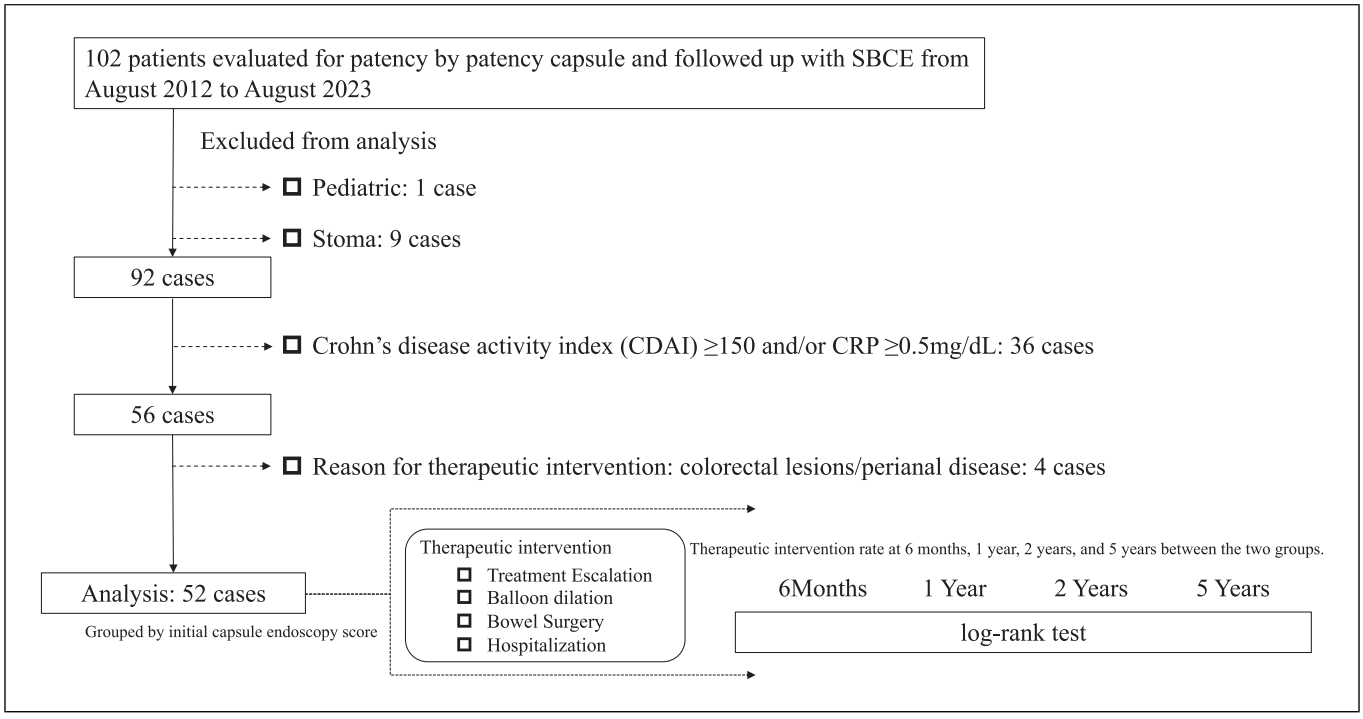

Fig. 1. Study profile. CDAI, Crohn's disease activity index; SBCE, small bowel capsule endoscopy.

patients in Japan [3]. SB involvement in CD is a prognostic factor for intervention; however, it is difficult to accurately assess with the Crohn's disease activity index (CDAI), which is used to determine disease activity in CD. Furthermore, C-reactive protein (CRP) is unlikely to reflect disease activity [4]; therefore, it is important to evaluate SB lesions accompanying CD using an objective and measurable modality.

SB capsule endoscopy (SBCE) is sensitive and capable of screening lesions throughout the SB; additionally, the Lewis score (LS) [5] and capsule endoscopy Crohn's disease activity index (CECDAI) score are commonly used as SBCE scores for CD [6]. Although the LS and CECDAI score have good correlation [7–10], they may not always reflect the effects of stenotic lesions or the extent of inflammation [10]. Therefore, the authors proposed the Crohn's disease activity in capsule endoscopy (CDACE) score as a new score that focuses more on inflammation by clarifying inflammation and stenosis, which are characteristics of intestinal lesions with CD [11]. The CDACE score is correlated with other SBCE scores [11, 12]. However, the impact of the CDACE score on clinical practice remains unclear. The primary aim of this study was to evaluate whether the CDACE score can predict therapeutic intervention for patients with CD and SB lesions without clinical symptoms as well as negative CRP levels.

Methods

This was a retrospective study of patients with CD with Montreal classification L1 or L3 who attended Tokyo Women's Medical University between August 2012 and August 2023 and were evaluated using SBCE to determine the presence of SB lesions. The inclusion criteria were asymptomatic CD with a CDAI score <150 and CRP level <0.5 mg/dL. Pediatric patients (younger than 15 years) and those with stoma extensions were excluded. Patients whose colorectal lesions or hemorrhoids were the reason for treatment intervention after SBCE were also excluded.

The maximum observation period after SBCE was 5 years. After the initial SBCE, patients underwent blood tests and an evaluation of clinical symptoms every 2–3 months as outpatients. SBCE was also performed at the discretion of the attending physician (median, two SBCE procedures; interquartile range [IQR], one to three SBCE procedures) during the observation period. During the observation period, therapeutic intervention was defined as intensified medical therapy, balloon dilation, bowel surgery, or hospitalization because of SB lesions. Patients were grouped according to the cutoff value of the CDACE score, which was determined using the Youden index. The scores that could predict intervention at 6 months, 1 year, 2 years, and 5 years were examined. In this study, before the patients underwent SBCE, they were evaluated using a patency capsule to confirm SB patency. As a secondary endpoint, the correlation between the CDACE score and LS or CECDAI score was examined. We also examined the LS and CECDAI score to determine their ability to predict therapeutic intervention at 6 months, 1 year, 2 years, and 5 years.

Table 1. Clinical characteristics

n	52
Male patients, *n* (%)	32 (61.5)
Age, years	35.5 (27–47)
Disease duration, months (%)	105 (18.8–171)
Montreal classification, *n* (%)	
A1/A2/A3	11 (21.2)/30 (57.7)/11 (21.1)
B1/B2/B3	21 (40.4)/21 (40.4)/10 (19.2)
L1/L2/L3	21 (40.4)/0 (0)/31 (59.6)
Perianal disease, *n* (%)	16 (30.8)
Previous intestinal surgery, *n* (%)	27 (51.9)
Smoking, no/current/past, *n* (%)	40 (76.9)/7 (13.5)/5 (9.6)
Medication, *n* (%)	
5ASA	41 (78.8)
Elemental diet	23 (44.2)
PSL	4 (7.7)
AZA	8 (15.4)
Anti-TNF-α inhibitor	23 (44.2)
IL-12/23p40 inhibitor	2 (3.8)
Integrin inhibitor	0 (0)
Biologics, 0/1/2/3, *n* (%)	25 (48.1)/22 (42.3)/4 (7.7)/1 (1.9)
SBCE score	
LS	8 (0–225)
CECDAI	6 (2–10)
CDACE	420 (210–730)
Hb, g/dL	13.7 (12.2–14.6)
Plt, $\times 10^4/\mu L$	23.9 (21.1–27.9)
Alb, g/dL	4.3 (4.1–4.4)
CRP, mg/dL	0.09 (0.04–0.21)
CDAI	64 (44–95)

Unless otherwise indicated, the data are presented as the median (IQR). 5ASA, 5-aminosalicylic acid; Alb, albumin; AZA, azathioprine; CDACE, Crohn's disease activity in capsule endoscopy; CDAI, Crohn's disease activity index; CECDAI, capsule endoscopy Crohn's disease activity index; CRP, C-reactive protein; Hb, hemoglobin; IL, interleukin; Plt, platelet; PSL, prednisolone; SBCE, small bowel capsule endoscopy; TNF, tumor necrosis factor.

Table 2. Reason for and description of therapeutic intervention

	Reason for intervention, *n* (%)		SBCE	Observational period, days	Intervention, *n* (%)			
					nonbiologics	biologics	EBD	surgery
No intervention	N/A		3 (2–4)	1,825 (1,366–1,825)	N/A			
Intervention	Clinical symptoms	3 (14.3)	1 (1–2)	298 (146–833)	1 (33.3)	1 (33.3)	0	1 (33.3)
	Biomarker	6 (28.6)	1 (1–2)	326 (167–616)	4 (66.7)	2 (33.3)	0	0
	Endoscopic findings	12 (57.1)	1 (1–1)	162 (58–403)	4 (33.3)	5 (41.7)	3 (25)	0

Unless otherwise indicated, the data are presented as the median (IQR). EBD, endoscopic balloon dilation; N/A, not applicable; SBCE, small bowel capsule endoscopy.

Table 3. Differences in patient backgrounds based on the presence or absence of therapeutic intervention

	No treatment (absence) (n = 31)	Treatment (presence) (n = 21)	p value
Hb, g/dL	13.8 (12.9–14.6)	12.7 (11.7–14.6)	0.2472
Plt, $\times 10^4/\mu L$	23.9 (20.7–28.8)	24.2 (21.2–27.5)	0.9109
Alb, g/dL	4.3 (4.1–4.4)	4.3 (3.9–4.5)	0.8659
CRP, mg/dL	0.08 (0.03–0.22)	0.09 (0.06–0.2)	0.4835
CDAI	61 (48–80)	64 (43–107)	0.8012
LS	0 (0–8)	225 (68–2,581)	<0.0001
CECDAI	3 (0–6)	10 (6–15)	<0.0001
CDACE	210 (0–620)	632 (471–886)	<0.0001
Stenosis (presence), n (%)	3 (9.7)	10 (47.6)	0.0031
SBCE examination during the observation period	3 (2–4)	1 (1–1)	<0.0001
No patency as determined by the capsule, n (%)	3 (9.7)	5 (23.8)	0.2440

Unless otherwise indicated, the data are presented as the median (IQR). Alb, albumin; CDACE, Crohn's disease activity in capsule endoscopy; CDAI, Crohn's disease activity index; CECDAI, capsule endoscopy Crohn's disease activity index; CRP, C-reactive protein; Hb, hemoglobin; Plt, platelet; SBCE, small bowel capsule endoscopy.

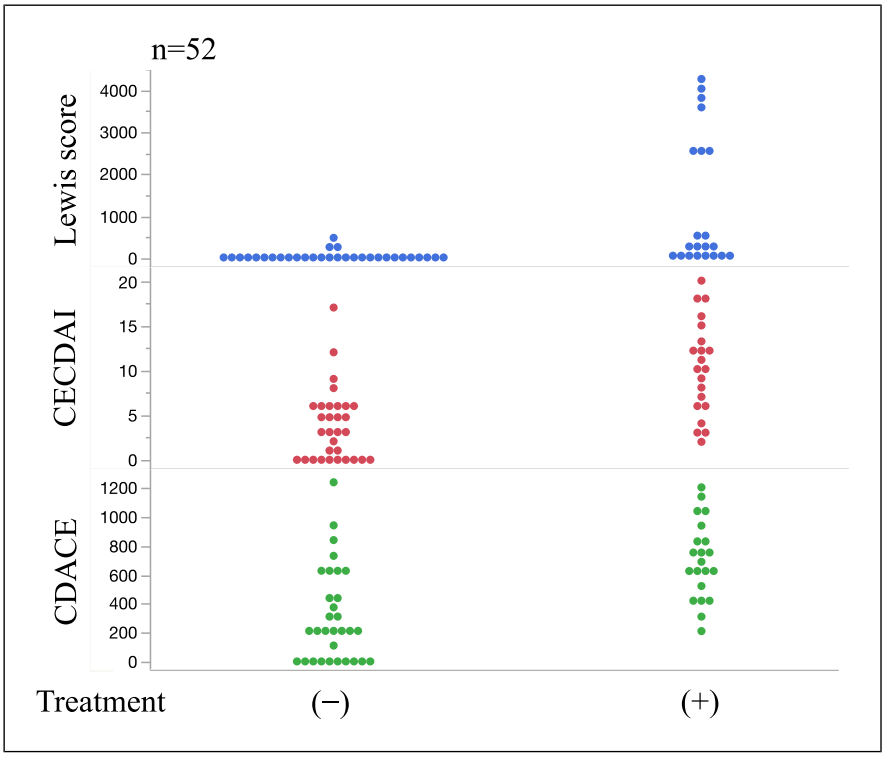

Fig. 2. Differences in the capsule endoscopic score based on the presence or absence of therapeutic intervention. CDACE, Crohn's disease activity in capsule endoscopy; CECDAI, capsule endoscopy Crohn's disease activity index.

The CDACE score is based on the results of a visual assessment of the inflammatory status of the small intestine and the presence of stenosis [11]. Using the progress indicator function of RAPID (software used to analyze SBCE), the SBCE images of the SB were divided into quartiles (25%, 50%, and 75% percentiles). The severity of inflammation was graded using the following 5-point scale for each quartile: 0, normal mucosa; 1, edema/redness; 2, erosions/aphthae (<0.5 cm); 3, irregular/round ulcers (0.5–2 cm); and 4, longitudinal ulcers, large ulcers, and paving stone changes. The scores of each of these quartiles were summed to obtain an

Table 4. Differences in patient backgrounds based on a CDACE score ≥420

	CDACE score <420 (n = 23)	CDACE score ≥420 (n = 29)	p value
Hb, g/dL	14.1 (13.1–14.6)	13.2 (11.7–14.6)	0.2454
Plt, $\times 10^4/\mu L$	22.8 (20.1–25.6)	25.7 (22.8–28.8)	0.0357
Alb, g/dL	4.3 (4.1–4.6)	4.3 (4.1–4.4)	0.8201
CRP, mg/dL	0.07 (0.03–0.15)	0.11 (0.06–0.24)	0.1373
CDAI	69 (51–111)	63 (43–86)	0.4227
LS	0 (0–8)	196 (0–1,544)	0.0004
CECDAI	1 (0–3)	9 (6–12.5)	<0.0001
CDACE	210 (0–210)	632 (621–890)	<0.0001
Stenosis (presence), n (%)	1 (4.4)	12 (41.4)	0.0029
Observation period	1,825 (1,367–1,825)	445 (169–1,349)	<0.0001
SBCE examinations during the observation period	3 (2–4)	1 (1–2)	0.0026
No patency determined by the capsule, n (%)	4 (17.4)	8 (27.6)	0.5132

Unless otherwise indicated, the data are presented as the median (IQR). Alb, albumin; CDACE, Crohn's disease activity in capsule endoscopy; CDAI, Crohn's disease activity index; CECDAI, capsule endoscopy Crohn's disease activity index; CRP, C-reactive protein; Hb, hemoglobin; Plt, platelet; SBCE, small bowel capsule endoscopy.

Table 5. Cutoff values for each SBCE score for predicting therapeutic intervention

	Cutoff value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy	AUC
CDACE	420	90.5 (75.5–97.2)	67.7 (57.6–72.3)	65.5 (54.7–70.4)	91.3 (77.7–97.5)	76.9 (64.8–82.4)	82.1
LS	143	71.4 (56.6–80)	90.3 (80.3–96.2)	83.3 (66.1–93.4)	82.4 (73.2–87.7)	82.7 (70.7–89.7)	81
CECDAI	7	71.4 (56.2–81.4)	87.1 (76.8–93.9)	78.9 (62.1–90)	81.8 (72.1–88.2)	80.8 (68.4–88.8)	84.4

AUC, area under the curve; CDACE, Crohn's disease activity in capsule endoscopy; CDAI, Crohn's disease activity index; CECDAI, capsule endoscopy Crohn's disease activity index; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; SBCE, small bowel capsule endoscopy.

inflammation score (range: 0–16). Then, the range score was calculated as the number of significant scores of the aforementioned quartiles (range: 0–4). The stenosis score was calculated as follows: 0, none; 1, single passage; 2, multiple passages; and 3, no passage (range, 0–3). The CDACE score was calculated using the following formula: CDACE score = inflammation score × 100 + range score × 10 + stenosis score (range: 0000–1,643). Specifically, the first two digits of the score (from left to right) denote the severity of SB inflammation, the third digit defines the extent of SB inflammation, and the fourth digit denotes the presence or absence of stenosis. Furthermore, the result of the first and second digits divided by the third digit represents the severity of inflammation.

Statistical Analysis

Numerical data are expressed as the median and IQR. Wilcoxon's test was used for the univariate analysis of background factors. $p < 0.05$ was considered significant. The cutoff value of each score was calculated based on the receiver-operating characteristic curve, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were determined. Predictions of treatment intervention at 6 months, 1 year, 2 years, and 5 years were determined using the log-rank test and survival time analysis. Spearman's rank correlation coefficient was used to analyze the correlations among the CDACE score, LS, and CECDAI score. JMP statistical analysis software (version 11; SAS, Cary, NC, USA) was used for all analyses.

Results

A flowchart of the patients included in this study is shown in Figure 1. Of 102 eligible patients, 52 were included in the analysis. Thirty-two (61.5%) patients were male. The median age at the time of examination and the disease duration were

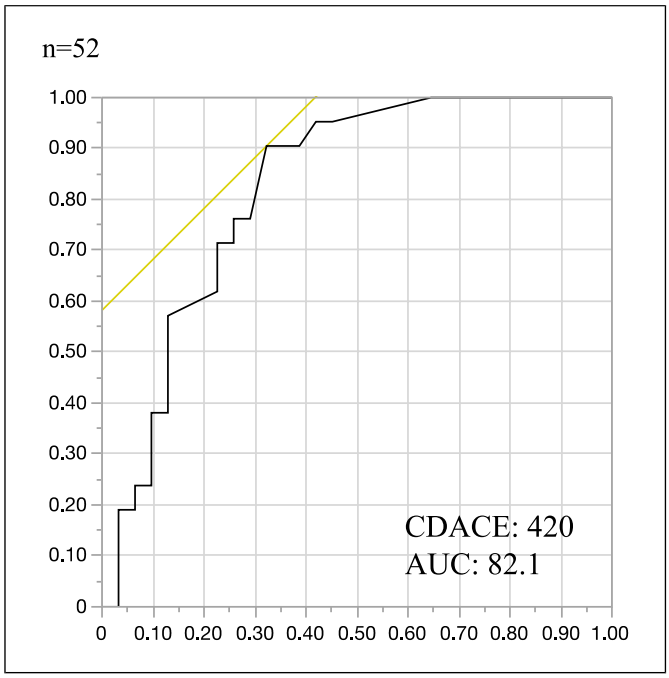

Fig. 3. CDACE score cutoff value. The initial CDACE scores were subsequently grouped by cutoff values established using the Youden index based on the presence or absence of therapeutic intervention for SB lesions. AUC, area under the curve; CDACE, Crohn's disease activity in capsule endoscopy.

35.5 years (IQR, 27–47 years) and 105 months (IQR, 18.8–171 months), respectively. Twenty-one (40.4%) patients had CD with Montreal classification L1, and 31 (59.6%) patients had CD with Montreal classification L3. During the first SBCE examination, the median CRP level, CDAI score, LS, CECDAI score, and CDACE score were 0.09 mg/dL (IQR, 0.04–0.21 mg/dL), 64 mg/dL (IQR, 44–95 mg/dL), 8 mg/dL (IQR, 0–225 mg/dL), 6 mg/dL (2–10 mg/dL), and 420 mg/dL (210–730 mg/dL), respectively (Table 1). The median observation period of the 52 patients was 1,326 days (IQR, 290–1,825 days), and 21 (40.4%) patients received therapeutic intervention for SB lesions during a maximum follow-up of 5 years. Therapeutic intervention was performed for three (14.3%) patients with worsening clinical symptoms, six (28.6%) patients with worsening biomarkers, and 12 (57.1%) patients with endoscopic (SBCE or balloon-assisted enteroscopy) findings that indicated the need for intervention. Interventions performed based on endoscopic findings included endoscopic balloon dilation for 3 patients (Table 2). There were no significant differences in serological markers at the beginning of the observation period for patients with and without treatment intervention; however, the SBCE scores for both patient groups differed significantly at the time of the initial SBCE examination (Table 3 and Fig. 2). The intervention group had significantly greater stenosis (no intervention group vs. intervention group: 3 patients [9.7%] vs. 10 patients [47.6%]; $p = 0.0031$). Interventions comprised nonbiological treatment (42.9%), biological treatment (38.1%), endoscopic balloon dilation (14.3%), and surgery (4.7%). During the 5-year follow-up period, the patency capsule evaluation indicated that 8 patients lost patency; however, there was no statistically significant difference between the intervention and no intervention groups.

Based on the initial SBCE results of the 21 patients who required treatment intervention, at the beginning of the observation period, a CDACE score of 420 was used as the cutoff value for predicting treatment intervention. There was no significant difference in serological markers, except for the platelet level, at the beginning of the observation period for patients with and without a CDACE score ≥420; however, the SBCE scores for both patient groups differed significantly at the time of the initial SBCE examination (Table 4).

Using a cutoff value of 420, the area under the curve (AUC) for predicting intervention over the course of 5 years was 82.1 (sensitivity, 90.5%; specificity, 67.7%; PPV, 65%; NPV, 91.3%) (Table 5; Fig. 3). This cutoff value was not significantly different at 6 months ($p = 0.0592$); however, it was significantly different at 1 year ($p = 0.0009$), 2 years ($p = 0.0002$), and 5 years ($p < 0.0001$) (log-rank test) (Fig. 4). Significant differences in the presence or absence of treatment intervention were observed at 1 year ($p = 0.0009$) and 2 years ($p = 0.0002$) for patients with CD with Montreal classification L1 (Fig. 5).

The CDACE score was moderately correlated with the LS and strongly correlated with the CECDAI score (Spearman rank correlation coefficient: $\rho = 0.6462$ and $\rho = 0.9199$, respectively; $p < 0.0001$) (Fig. 6). The LS and CECDAI score were moderately correlated (Spearman rank correlation coefficient: $\rho = 0.6252$; $p < 0.0001$) (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000538468). Using a cutoff value of 143 for the LS at the beginning of the observation period, the AUC was 81 (sensitivity, 71.4%; specificity, 90.3%; PPV, 83.3%; NPV, 82.4%) (Table 5; online suppl. Fig. 2). This cutoff value was not significantly different at 6 months ($p = 0.0782$) but was significantly different at 1 year ($p = 0.0002$), 2 years ($p < 0.0001$), and 5 years ($p < 0.0001$) (online suppl. Fig. 3). Additionally, using a cutoff value of 7 for the CECDAI score at the beginning of the observation period, the AUC was 84.4 (sensitivity, 71.4%; specificity,

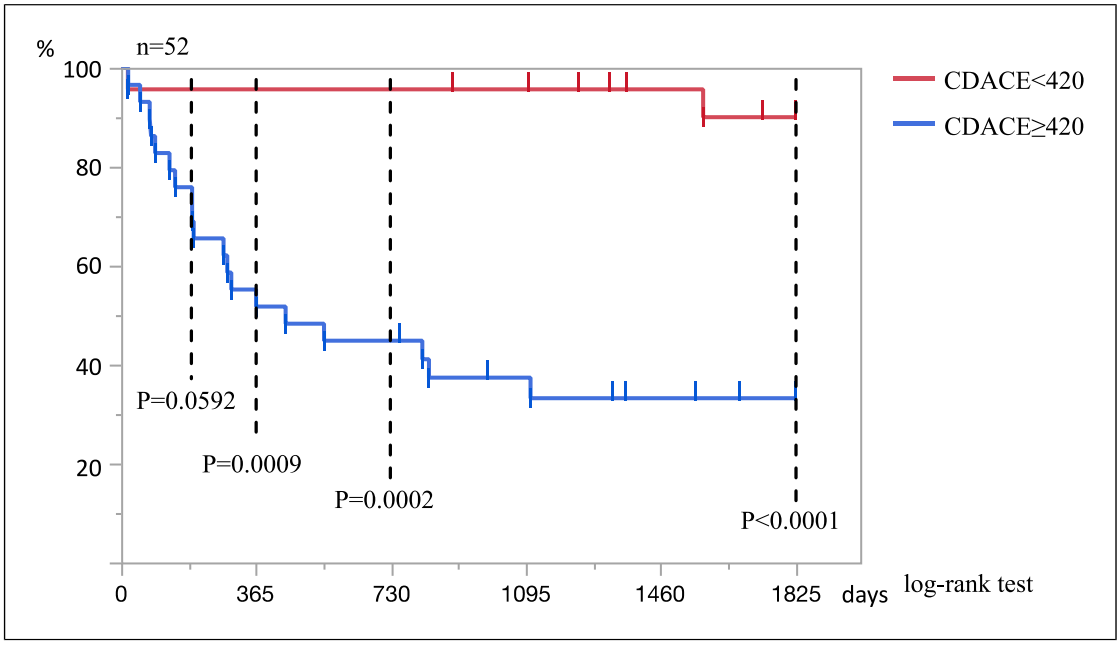

Fig. 4. Comparison of the therapeutic interventions for small intestinal lesions in patients with Crohn's disease (CD) with Montreal classification L1 or L3. CDACE, Crohn's disease activity in capsule endoscopy.

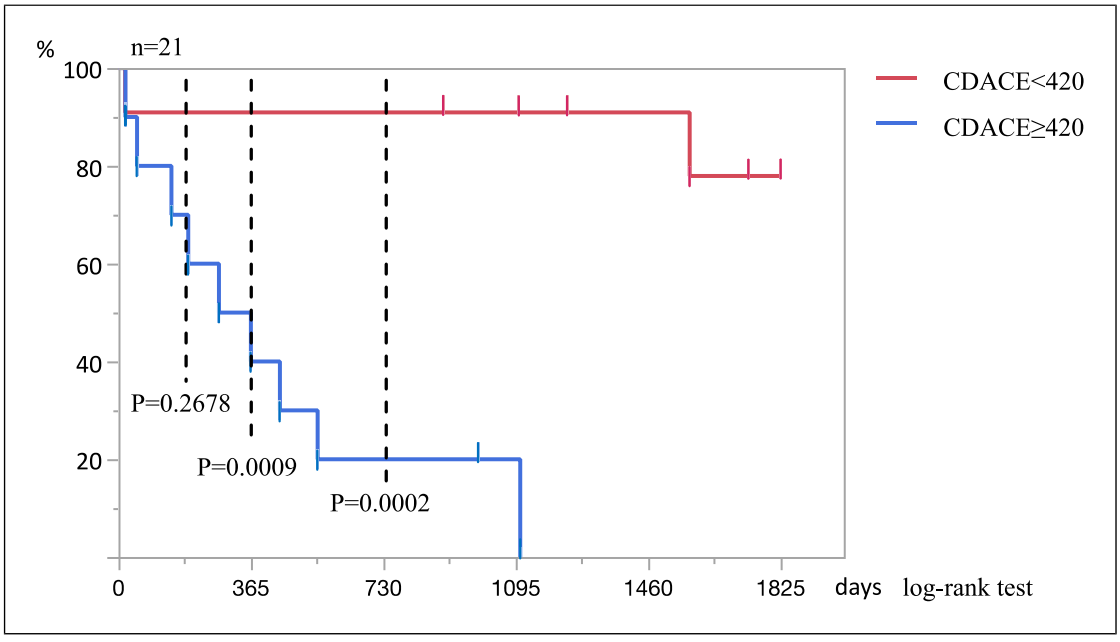

Fig. 5. Comparison of patients with Crohn's disease (CD) with Montreal classification L1 with and without therapeutic interventions for small intestinal lesions. CDACE, Crohn's disease activity in capsule endoscopy.

87.1%; PPV, 78.9%; NPV, 81.8%) (Table 5; online suppl. Fig. 2). This cutoff value was used to group the patients according to the need for treatment intervention. Significant differences were observed at 6 months ($p = 0.0148$), 1 year ($p = 0.0003$), 2 years ($p < 0.0001$), and 5 years ($p < 0.0001$) (log-rank test) (online suppl. Fig. 3).

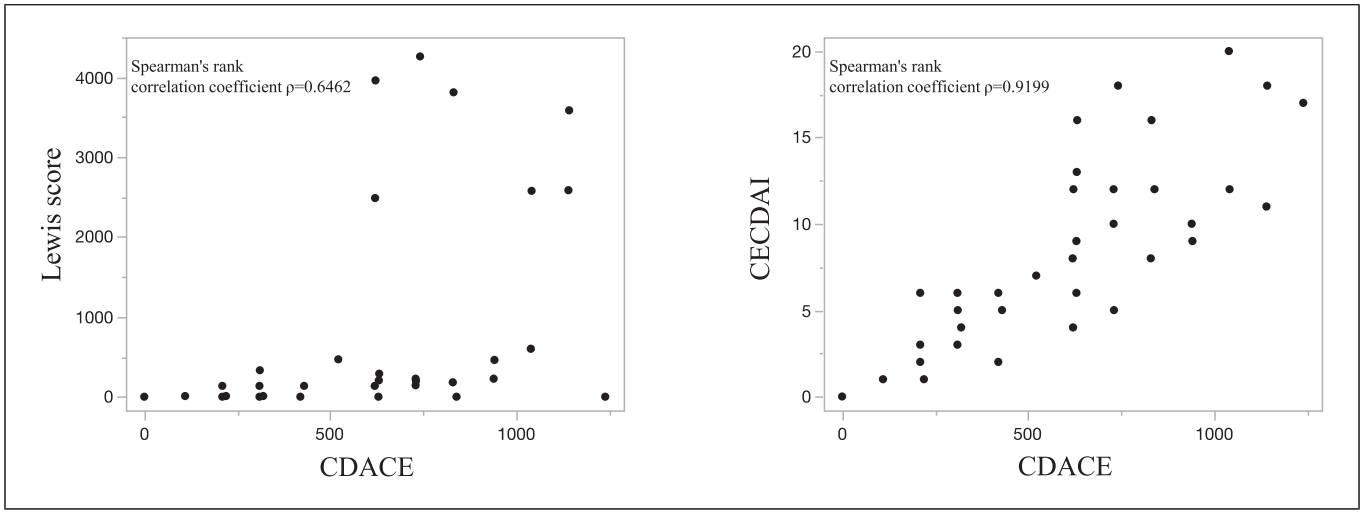

Fig. 6. Correlation of the CDACE score with the LS and CECDAI. CDACE, Crohn's disease activity in capsule endoscopy; CECDAI, capsule endoscopy Crohn's disease activity index.

Discussion

Scoring the endoscopic findings contributed to the objective understanding of the pathophysiology of disease and evaluation of treatment efficacy. Disease control during the early stage of CD decreases the risk of disease progression [13], indicating the importance of a treat-to-target approach for CD [14]. In this context, it has become clear that a treat-to-target approach combining the endoscopic assessment of disease activity and adjustment of medical therapy is likely to improve the prognosis [15]. The use of SBCE plays an important role in the CD prognosis. Additionally, SBCE is useful for the diagnosis of CD and the evaluation and follow-up of the disease status [16]. The European Society of Gastrointestinal Endoscopy recommends the use of capsule endoscopy scores, such as the LS and CECDAI score, for long-term evaluation of CD activity [17].

Several studies have reported that SBCE scores could predict the prognosis [18–20]. A baseline LS ≥350 predicts disease relapse (increase in baseline CDAI score >70, CDAI score >150, and therapeutic intervention) at 24 months [18]. An LS ≥270 and prognostic nutritional index score <45 are also associated with a higher risk of CD-related emergency hospitalization [19]. Furthermore, a CECDAI score cutoff value of 4 is predictive of therapeutic intervention [20].

During the present study, we used our previously reported CDACE score [11] to predict the need for therapeutic intervention for patients with CD and SB lesions without clinical symptoms as well as negative CRP levels. The CDACE score is correlated with the LS and CECDAI score, and similar results have been reported by other centers; therefore, these results are considered reproducible [12]. The CDACE score cutoff of 420 was significantly predictive of therapeutic intervention for SB lesions after 1 year. This result was similar when restricted to CD with SB involvement. However, the previously used LS and CECDAI score were also prognostic; however, only the CECDAI score predicted relapse at 6 months for the entire population and had the highest AUC (84.4 with a cutoff value of 7).

Interestingly, the correlation between the CDACE and CECDAI scores was very good; however, the CDACE score had higher sensitivity and a higher NPV, and the CECDAI score had higher specificity and a higher PPV. High specificity and PPVs were also observed with the LS. These results suggest that although any score can be used to predict therapeutic intervention, for the purpose of stratifying the risk of therapeutic intervention for SB lesions, a CDACE score <420 may be superior for screening because of its high sensitivity and high NPV. However, because of the low PPV of CDACE, this score may not indicate immediate therapeutic intervention for patients with CD without clinical symptoms as well as negative CRP levels. Therefore, it should be considered as an indicator for more careful monitoring and follow-up.

Additionally, the CDACE score is determined based on the visualization of the state of inflammation and the presence or absence of stenosis in the SB. The presence

or absence of stenosis can be determined using the CDACE score; therefore, it may be superior for providing an understanding of the pathophysiology of CD, which comprises structural damage in the form of inflammation and stenosis.

This study had some limitations. First, this was a retrospective study comprising a small number of patients at a single institution; therefore, it was not clear whether these methods improved the prognosis. Prospective, observational, and interventional studies are necessary. Second, the indications for therapeutic intervention for the SB were determined by an individual physician, and there were no clear criteria. Although the CDAI score has been used as a criterion during previous studies [19], SB lesions were not used as a criterion during this study because the CDAI score often does not reflect the presence of lesions. Therefore, the SBCE results may have indicated the need for therapeutic intervention. Third, the inclusion of patients was limited to those with SB lesions that could be detected using SBCE, which may have introduced selection bias.

In conclusion, a CDACE score ≥420 had high sensitivity and a high NPV; therefore, it may be useful for predicting intervention at 1 year for patients with CD with a CDAI score <150 and a CRP level <0.5 mg/dL. However, a larger study with a prospective design is necessary to validate our findings.

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Statement of Ethics

The study protocol was approved by the Human Ethics Review Committee of our university on October 18, 2023 (approval No.: 2023-0077). Informed consent was obtained from all patients using the opt-out method because of the retrospective design of the study. The opt-out informed consent protocol allowed for the use of participant data for research purposes. This consent procedure was reviewed and approved by Tokyo Women's Medical University Human Ethics Review Committee (approval No.: 2023-0077; date of decision: October 18, 2023).

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

T.O.: study concept and design. M.K., S.M., A.I., M.Y., and T.O.: data acquisition. T.O.: statistical analysis and drafting of the first version of the manuscript. T.O., S.N., and K.T.: critical revision and approval of the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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