

## A newly proposed endoscopic score system to evaluate the entire small bowel and predict the prognosis in Crohn's disease

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### ABSTRACT

Small bowel stenosis in patients with Crohn's disease leads to abdominal symptoms and can affect prognosis. The Simple Endoscopic Score for Crohn's Disease for the large bowel has been applied to the small bowel; however, stenosis scoring may be overestimated since it has a long diameter. This retrospective study aimed to devise a new endoscopic scoring system including the small bowel and evaluate whether it predicts the prognosis of Crohn's disease. The study included 103 patients with Crohn's disease at our hospital. We modified the Simple Endoscopic Score for Crohn's Disease and proposed a new scoring system; the modified applied Simple Endoscopic Score for Crohn's Disease was created by subtracting one point for stricture from the Simple Endoscopic Score for Crohn's Disease. Receiver operating characteristic curve analysis was performed to assess the accuracy of the modified applied score for Crohn's disease in predicting disease worsening within 1 year. Results were validated using the log-rank test. For the modified applied score, the area under the receiver operating characteristic curve for disease worsening within 1 year in 57 cases was 0.850. When the cutoff score was set to 9 points, the sensitivity and specificity were 72.7% and 80.6%, respectively. The log-rank test showed a significant difference ( $P = 0.027$ ) in the risk of worsening within 1 year between the low (<9 points) and high ( $\geq 9$  points) score groups. Thus, a higher modified applied Simple Endoscopic Score for Crohn's Disease may be associated with a significantly increased risk of disease worsening within 1 year.

Keywords: Crohn's disease, balloon-assisted endoscopy, small bowel, scoring, prognosis

#### Abbreviations:

SES-CD : Simple Endoscopic Score for Crohn's Disease

MASES-CD : modified applied Simple Endoscopic Score for Crohn's Disease

CD : Crohn's disease

MH : mucosal healing

SBCE : small bowel capsule endoscopy

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DBE : double-balloon endoscopy

ROC : receiver operating characteristic

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## INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease that causes inflammation and swelling of digestive tract tissues, resulting in abdominal pain, severe diarrhea, fatigue, weight loss, and malnutrition. Persistent inflammation can lead to ulcers, stenosis, abscess formation, and intestinal perforation, necessitating surgery. Targeting is currently being proposed as a treatment strategy for CD. This concept was introduced as a therapeutic target for rheumatoid arthritis<sup>1</sup> and has been proposed for CD since 2015.<sup>2</sup> Endoscopic mucosal healing (MH) is among the most important goals of CD treatment, and the MH status has been reported to reduce the risk of long-term relapse.<sup>3-6</sup> However, the definition of MH differed from that in the previous studies, and MH rates for CD have been reported to range from 3%–84%.<sup>7-11</sup>

More than 70% of patients with CD have small bowel lesions,<sup>12</sup> and evaluation of the entire small bowel is essential for optimal treatment. Balloon-assisted endoscopy and small bowel capsule endoscopy (SBCE) are currently the primary modalities used to evaluate the entire small bowel mucosa. SBCE is well tolerated and examines the entire small bowel only once in patients with gastrointestinal tract patency. There are several endoscopic scoring systems for SBCE to evaluate the entire small bowel, including the Lewis score, Capsule Endoscopy Crohn's Disease Activity Index, and Crohn's Disease Activity in Capsule Endoscopy.<sup>13,14</sup> However, scoring is limited because of the risk of capsule retention,<sup>15</sup> and therefore, patients with severe intestinal stenosis cannot undergo SBCE. It has been reported that patients who were able to undergo SBCE have better intestinal prognoses.<sup>16</sup>

The Simple Endoscopic Score for Crohn's Disease (SES-CD) has been the most frequently used method for evaluating colonic mucosa in clinical studies.<sup>17</sup> It is based on the ulcer size, extent of the ulcerated and affected surface, and stenosis and ranges from 0 to 3 for each of the five segments—ileum, right colon, transverse colon, left colon, and rectum. Balloon-assisted endoscopy is the gold standard for evaluating the entire small bowel mucosa and allows endoscopic scoring of CD by modifying the SES-CD. Morise et al assessed MH of the small bowel in CD using a modified SES-CD, in which the evaluation was extended up to 80 cm away from the ileocecal valve using double-balloon endoscopy (DBE).<sup>18</sup> Takenaka et al extended the scoring for the ileum to 300 cm for the length in single-balloon endoscopy and proposed a new scoring system, applied SES-CD, in which less than 5 points led to a better prognosis.<sup>19</sup> However, the jejunum does not have a score; therefore, a gold standard endoscopic scoring system to assess all small bowel lesions has not yet been established.

In our hospital, small bowel evaluation for CD is usually performed through an entire small bowel observation with oral and anal approaches to DBE. In this study, we proposed a new scoring system for balloon-assisted endoscopy to evaluate all small bowel lesions in patients with CD. We used a training set prepared from the DBE database and validated the score for predicting the intestinal prognosis of CD, extracting cases presenting with disease activity within 1 year.

## MATERIALS AND METHODS

*Ethics statements*

This retrospective study was approved by the Ethics Committee of the Nagoya University Hospital (ID: 2015-0466). The study was conducted in compliance with the principles of the Declaration of Helsinki.

*Patients*

In clinical practice, we usually evaluate the entire small bowel mucosa using a combination of oral DBE on the first day and anal DBE on the third day post-admission. EN-580T or EN-580XP (FUJIFILM, Tokyo, Japan) was used for each DBE as previously described.<sup>20</sup> CO<sub>2</sub> was used for airflow. The marking clip was placed at the deepest point of the oral DBE, and the anal DBE was subsequently approached. We reviewed the DBE database and medical charts to determine patient eligibility for this study. The inclusion criteria were patients with CD who underwent DBE for the evaluation of disease activity and those in whom the entire small bowel could be visualized with DBE. The exclusion criteria were patients for whom the entire small bowel could not be evaluated with endoscopy and those treated with immunosuppressants for comorbidities other than CD.

A random number was generated, and the 103 patients were allocated to training and validation cohorts. These patients were divided using a random number table in a 6:4 ratio, with 57 in the training and 46 in the validation cohorts.

*Data analysis*

We used the previously applied SES-CD,<sup>19</sup> which divided the small bowel into three sections for reference. However, it has been suggested that the effect of small bowel stenosis on scoring is relatively low.<sup>19</sup> In addition, we encountered a number of patients with CD in whom the DBE endoscope passed through jejunal stenoses. On the basis of such published evidence<sup>6,19</sup> and clinical experience, we modified the applied SES-CD at the point of stenosis and created a new scoring system, the modified applied SES-CD (MASES-CD), which assigned a zero point to the stenosis through which the endoscope could pass and one point to the stenosis through which the endoscope could not pass (Tables 1A and 1B). The sample split method was used to

**Table 1A** Applied SES-CD (aSES-CD)

Definitions of endoscopic score				
Variables	0	1	2	3
A: Size of ulcers, cm	None	0.1–0.5	0.5–2.0	>2
B: Ulcerated surface, %	None	<10	10–30	>30
C: Affected surface, %	Unaffected segment	<50	50–75	>75
D: Presence of stenosis	None	Single, can be passed	Multiple, can be passed	Cannot be passed
Definitions of endoscopic segmentation				
Terminal ileum (TI)	≤10 cm from the ileocecal valve			
Proximal ileum (PI)	10–300 cm from the ileocecal valve			
Jejunum (J)	The proximal part, excluding the section defined as the proximal ileum			

SES-CD: Simple Endoscopic Score for Crohn's Disease

**Table 1B** New scoring system, modified applied SES-CD (MASES-CD)

Definitions of endoscopic score				
Variables	0	1	2	3
A: Size of ulcers, cm	None	0.1–0.5	0.5–2.0	>2
B: Ulcerated surface, %	None	<10	10–30	>30
C: Affected surface, %	Unaffected segment	<50	50–75	>75
<b>D: Presence of stenosis</b>	<b>None or can be passed</b>	<b>Cannot be passed</b>		
Definitions of endoscopic segmentation				
Terminal ileum (TI)	≤10 cm from the ileocecal valve			
Proximal ileum (PI)	10–300 cm from the ileocecal valve			
Jejunum (J)	The proximal part, excluding the section defined as the proximal ileum			

MASES-CD: modified applied Simple Endoscopic Score for Crohn's Disease

develop and validate the MASES-CD. The primary endpoint was a reliable indicator for predicting disease exacerbation within 1 year. The secondary endpoint was the cutoff value for the score predicting disease exacerbation within 1 year.

### Definitions

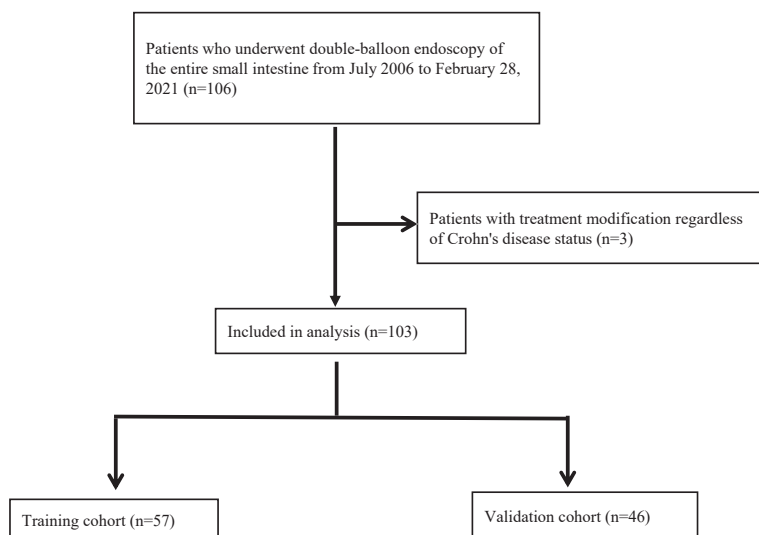
Exacerbation was defined as worsening abdominal pain, fever, or bloody stools that the attending physician judged, thus requiring a change in treatment.

### Statistical analyses

For the testing cohort, receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminative abilities of C-reactive protein level, Crohn's Disease Activity Index, applied SES-CD, and MASES-CD for CD within 1 year. The cutoff value of the MASES-CD was determined from the ROC analysis. The MASES-CD was validated by comparing the risk of exacerbation between patients with high and low scores using the log-rank test. The areas under the curve for each score were compared using DeLong's test. Continuous variables were compared using the Mann–Whitney U test. Fisher's exact test was used to compare the categorical variables.  $P < 0.05$  denoted statistical significance. All statistical analyses were performed using SPSS statistical software v28.0 (IBM Corp, Chicago, Illinois, USA).

## RESULTS

Of all the patients with CD who regularly received clinical consultation at Nagoya University Hospital between July 2006 and February 2021, a total of 106 patients whose entire small bowel was successfully evaluated using DBE were eligible for the study. Three patients with comorbidities such as immunoglobulin A nephropathy and systemic lupus erythematosus, which required frequent volume adjustments of steroids or immunomodulators, were excluded from this study. Finally, 103 patients with CD were included (Fig. 1).



**Fig. 1** Flow diagram of the study

The characteristics of the patients allocated to the training and validation cohorts are shown in Table 2. No significant differences were found between the two groups. MASES-CD was scored to predict exacerbation of CD within 1 year.

**Table 2** Characteristics of patients in the training and validation cohorts

	Training cohort (n=57)	Validation cohort (n=46)	<i>P</i> -value
Age, years (range)	39 (19–78)	39 (16–67)	0.845*
Sex (M:F)	43:14	39:7	0.326**
Disease duration, years	9 (0.1–40)	8 (0–41)	0.668*
CD type (Ileal/Ileocolonic: colonic)	56:1	43:3	0.322**
Surgical history, %	25 (44)	25 (54)	0.326*
Exacerbation within 1 year, %	13 (23)	9 (20)	0.81**
Treatment before DBE, n (%)			
5-ASA	37 (65)	33 (72)	0.527**
Steroid	7 (12)	6 (13)	0.775**
Immunomodulator	12 (21)	8 (17)	0.803**
Biologics (IFX: ADA: UST)	7:11:3	8:10:3	0.795**

CD: Crohn's disease

5-ASA: 5-aminosalicylate

DBE: double-balloon endoscopy

IFX: infliximab

ADA: adalimumab

UST: ustekinumab

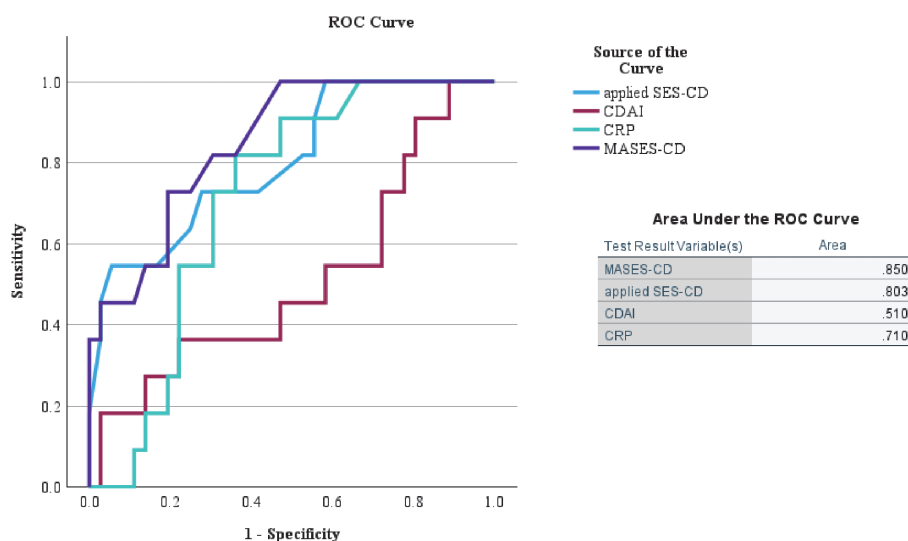
\* The Mann–Whitney U test was used.

\*\* Fisher's exact test was used.

*Discrimination ability of scores*

The distribution of each score for SES-CD and the total number of points are shown in the Supplemental Figure. Out of 57 patients, 56 had small bowel lesions, and the SES-CD score was a reference for the new scoring that evaluated the whole small bowel.

ROC curves were generated for the training cohort using these curves as clinical indicators of existing CD. The areas under the curve for Crohn's Disease Activity Index, C-reactive protein, applied SES-CD, and MASES-CD for CD exacerbation were 0.510, 0.710, 0.803, and 0.850, respectively. MASES-CD had the highest area under the curve among the indicators (Fig. 2), and the cutoff value for MASES-CD was determined from the ROC analysis to be 9 points, with a sensitivity of 72.7% and specificity of 80.6%. The distributions of MASES-CD and applied SES-CD for the 57 cases are shown in Figure 3. The maximum total scores were 22 and 38 points for MASES-CD and applied SES-CD, respectively. In many cases, the MASES-CD provided a lower score than the applied SES-CD. During the training phase, five patients with stenosis assigned 2 or more points for the applied SES-CD showed MH, and none of them had any progression within 1 year. For the validation phase, seven patients who had MH with stenosis were assigned 2 or more points by applying SES-CD, and one patient had an exacerbation within 1 year (Table 3).



**Fig. 2** ROC curves for scores in the training cohort

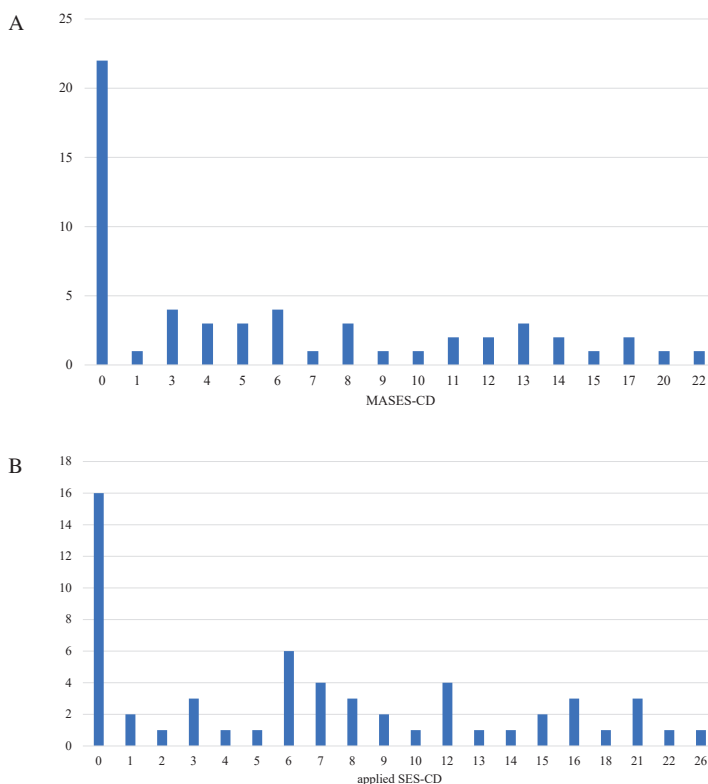
ROC: receiver operating characteristic

CRP: C-reactive protein

CDAI: Crohn's Disease Activity Index

SES-CD: Simple Endoscopic Score for Crohn's Disease

MASES-CD: modified applied Simple Endoscopic Score for Crohn's Disease



**Fig. 3** Distribution of 57 cases assessed by the MASES-CD and applied SES-CD in the training set  
**Fig. 3A:** Distribution of 57 cases assessed by the MASES-CD in the training set.  
**Fig. 3B:** Distribution of 57 cases assessed by applied SES-CD in the training set.  
 SES-CD: Simple Endoscopic Score for Crohn’s Disease  
 MASES-CD: modified applied Simple Endoscopic Score for Crohn’s Disease

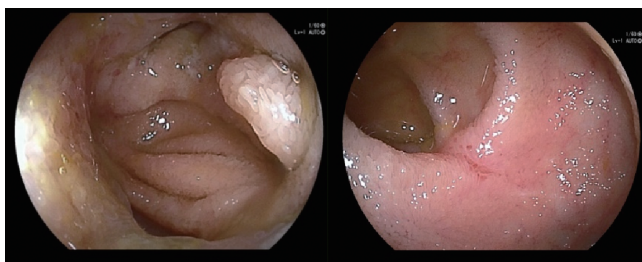
**Table 3** One-year prognosis of patients with mucosal healing and multiple stenoses

No	Age	Sex	Disease duration (years)	Disease type	Stenosis number	Applied SES-CD (stenosis score)	MASES-CD (stenosis score)	Worsening within 1 year
Training phase								
1	59	M	40	Ileal	6	6 (6)	0 (0)	Negative
2	59	M	0.1	Ileocolonic	2	2 (2)	0 (0)	Negative
3	66	M	21	Ileocolonic	6	6 (6)	0 (0)	Negative
4	35	M	3	Ileocolonic	6	6 (6)	0 (0)	Negative
5	31	M	9	Ileal	5	5 (5)	1 (1)	Negative
Validation phase								
1	16	M	1	Ileal	2	2 (2)	0 (0)	Negative
2	31	M	2	Ileal	2	2 (2)	0 (0)	Negative
3	23	M	1	Ileal	2	2 (2)	0 (0)	Negative
4	35	M	8	Ileal	4	4 (4)	0 (0)	Negative
5	36	M	1	Ileal	4	4 (4)	0 (0)	Negative
6	26	M	3	Colonic	2	2 (2)	2 (2)	Negative
7	44	M	20	Ileocolonic	4	4 (4)	0 (0)	Positive

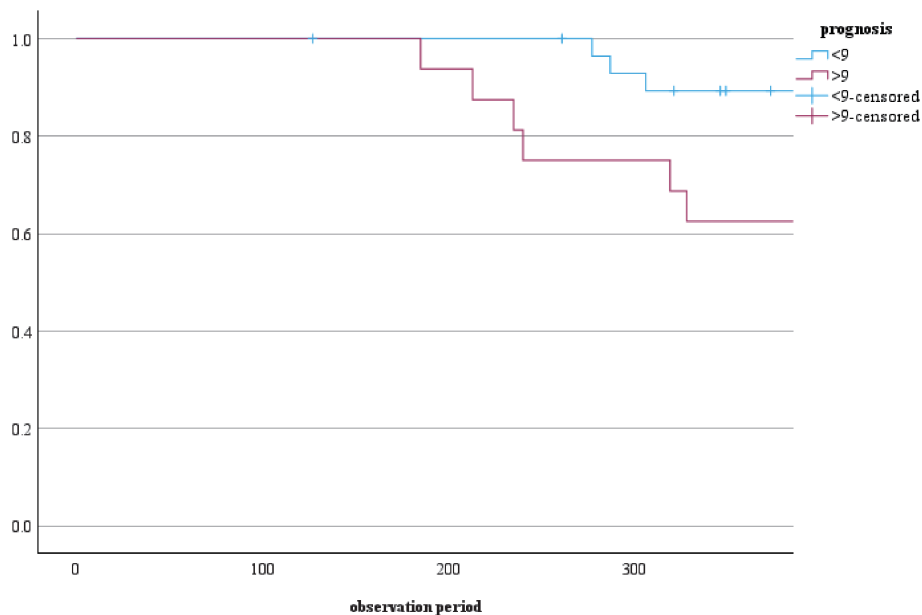
SES-CD: Simple Endoscopic Score for Crohn’s Disease

MASES-CD: modified applied Simple Endoscopic Score for Crohn’s Disease

Endoscopic images of the patients with MASES-CD gap and applied SES-CD are shown in Figure 4. Part of the lumen was complicated by stenosis in the images; however, no inflammatory signs were observed. The SES-CD and MASES-CD scores were 2 and 0, respectively. For the validation cohort, patients with higher MASES-CD scores (>9 points) had a significantly higher risk of disease exacerbation within 1 year ( $P = 0.027$ ; Fig. 5). The area under the ROC curve for the validation phase was 0.56 for both applied SES-CD and MASES-CD (Fig. 6).



**Fig. 4** A case of point dissociation between applied SES-CD and MASES-CD  
 SES-CD: Simple Endoscopic Score for Crohn's Disease  
 MASES-CD: modified applied Simple Endoscopic Score for Crohn's Disease

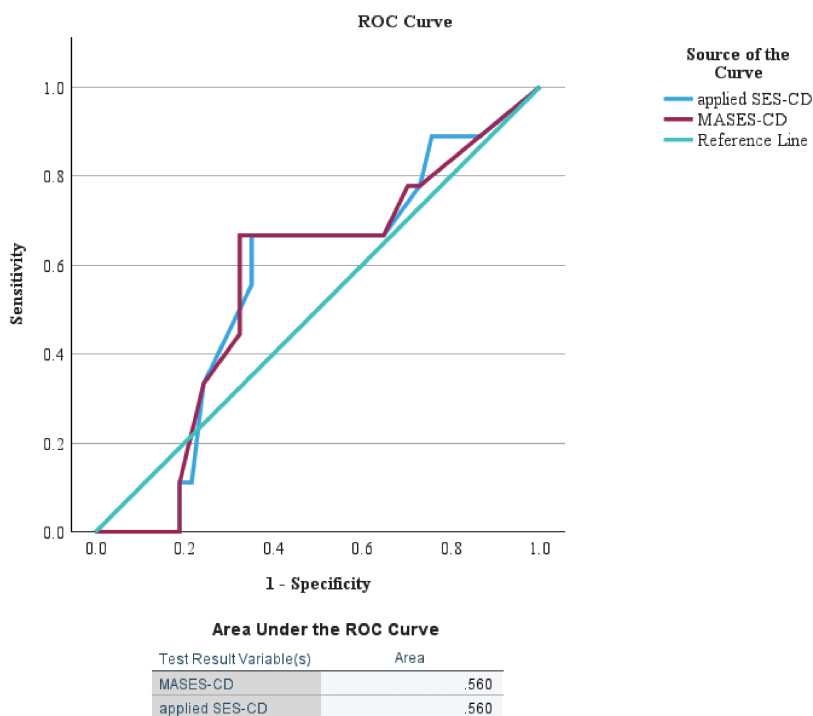


**Overall Comparisons**

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.921	1	.027

**Fig. 5** Kaplan–Meier scores for exacerbation within 1 year stratified by MASES-CD  
 MASES-CD: modified applied Simple Endoscopic Score for Crohn's Disease





**Fig. 6** ROC curves for scores in the validation cohort

ROC: receiver operating characteristic

SES-CD: Simple Endoscopic Score for Crohn's Disease

MASES-CD: modified applied Simple Endoscopic Score for Crohn's Disease

## DISCUSSION

Recurrent relapse and remission of CD can lead to intestinal stenosis, abscesses, and fistulas and ultimately require surgery. The therapeutic goals of CD include improving the inflammatory response in blood sampling and endoscopic MH.<sup>7</sup> Endoscopic MH has been reported to be useful in maintaining long-term remission. However, we often encounter cases where MH has not yet been achieved. Furthermore, there is no established endoscopic scoring system for evaluating CD activity, including small bowel lesions.

Therefore, in this study, we selected patients who could undergo an endoscopic examination of the entire small intestine and created a score for disease exacerbation within a short period of 1 year. The optimal timing of intensified treatment in patients who do not achieve MH remains unclear. Although SES-CD has been used to evaluate small bowel lesions,<sup>19</sup> predicting the long-term outcome of CD may not be possible.

Several scores are used to evaluate small bowel lesions in CD, such as the Crohn's Disease Endoscopic Index of Severity,<sup>21</sup> Maria score,<sup>22</sup> and Lewis score; however, some are complicated.<sup>23</sup> Although the SES-CD is simple to calculate and easy to use in actual clinical practice, the accuracy of ROC analysis of the existing applied SES-CD<sup>19</sup> may be low for small bowel evaluation, especially in patients with jejunal lesions. Therefore, in this study, we created a new scoring system including evaluation of the jejunum to identify patients who could require readmission or intensification of treatment within 1 year and evaluated the effectiveness of the score.

As Takenaka et al reported,<sup>6</sup> stenosis alone may have little impact on patient prognosis; therefore, this study evaluated stenosis based on whether the endoscope could pass through the lumen. The proportion of patients with CD, including those with small bowel lesions, was 96% (99/103), higher than previously reported.<sup>12</sup> The same score may have been used for both small and large bowel lesions when the scoring system was created. In addition, the new MASES-CD can predict the one-year prognosis of patients with CD.

We have shown that MASES-CD is more useful than applied SES-CD for predicting CD exacerbations within 1 year. The stenosis score of the conventional SES-CD may have overestimated the effect of stenosis on the passage of the endoscope because the digested material in the small bowel passes through as a gruel, which has no significant effect on the stenosis. This could be one of the reasons why the area under the curve was higher for the small intestine with a stenosis score of 0/1 for MASES-CD compared with applied SES-CD. On the contrary, the conventional SES-CD may be more effective for the stenosis score in the colorectum to predict the prognosis because fecal material passes through the large intestine. In addition, there have been advances in the balloon dilation technique for small bowel stenosis in DBE and an increase in published guidelines for balloon dilation within the last 10 years.<sup>24</sup> The management of small bowel stenosis has been updated, and the stenosis score may not affect the intestinal prognosis compared with other scores. Therefore, we consider MASES-CD useful for patients with active jejunal lesions and the small bowel-dominant type of CD. It was ultimately necessary to determine whether the combined scoring of the small bowel and SES-CD, which we examined in this study, was effective.

This study had some limitations. This was a single-center retrospective study, and the cases were selected from patients who underwent DBE, many of whom had small bowel lesions. However, many patients with CD have small bowel lesions, and we believe there is a need to develop scoring for whole small bowel evaluation.

We also believe that the MASES-CD score used in this study will help identify patients who need enhanced treatment, especially those who can be examined for the entire small bowel. Although an accumulation of cases is necessary, the treatment course of patients with a poor prognosis may be improved by intensifying treatment; this should be studied prospectively in the future.

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### *Author contributions*

Conception and design: Tanaka H, Nakamura M, Yamamura T; analysis and interpretation of data: Tanaka H, Nakamura M, Maeda K, Sawada T, Ishikawa E, Furukawa K; drafting of the article: Tanaka H, Nakamura M; statistical analysis: Uchida G, Mizutani Y, Iida T; critical revision of the article for important intellectual content: Yamao K, Ishikawa T, Honda T, Hirose T, Uetsuki K, Ishizu Y; final approval of the article: Kawashima H.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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*Data availability statement*

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

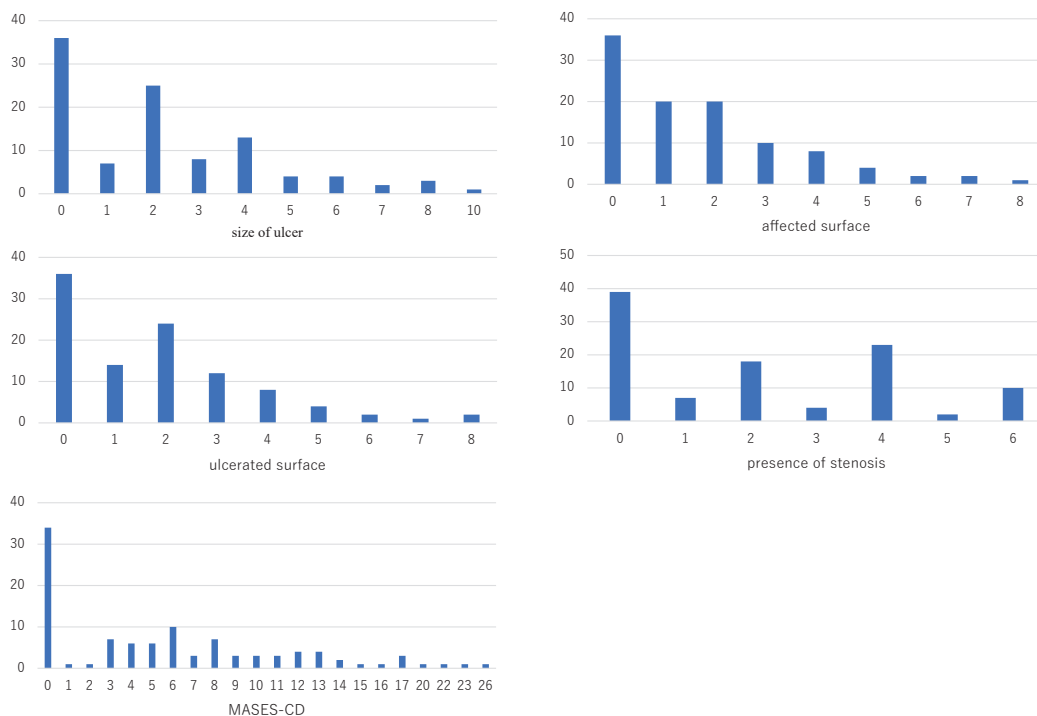
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### SUPPLEMENTAL INFORMATION



#### Supplemental Figure

MASES-CD: Modified Applied Simple Endoscopic Score for Crohn's Disease