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Development and validation of a new scoring system to determine the necessity of small-bowel endoscopy in obscure gastrointestinal bleeding

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ABSTRACT

Background: Small bowel capsule endoscopy (SBCE) is the recommended first-line procedure for obscure gastrointestinal bleeding (OGIB). However, a method for predicting the necessity of subsequent double-balloon endoscopy (DBE) has not been established.
Aims: We aimed to develop a new scoring system that predicts the necessity of DBE in OGIB.
Methods: A retrospective study was performed in 330 patients who underwent SBCE for OGIB at Nagoya University Hospital. The enrolled patients were randomly assigned to either a development or a validation dataset. The former was used to construct a prediction scoring system to assess the necessity of DBE using independent predictors selected by logistic regression. The diagnostic yield of the prediction model was assessed using the validation dataset.
Results: Multivariate logistic regression analysis of the development dataset identified OGIB type, blood transfusion, and SBCE findings as independent predictors of the necessity of DBE. A prediction score gave an area under the receiver operating characteristics curve of 0.77. The sensitivity, specificity, positive predictive value, and negative predictive value at a cutoff ≥2.5 points were 72.5%, 74.6%, 72.6%, and 74.5%, respectively.
Conclusion: Our scoring system may aid clinicians in deciding when to recommend DBE for patients with OGIB.

1. Introduction

Small bowel capsule endoscopy (SBCE) and double-balloon endoscopy (DBE) are excellent tools for the diagnosis and treatment of obscure gastrointestinal bleeding (OGIB). The diagnostic yields of SBCE and DBE are similar [1]; further, SBCE allows painless endoscopic imaging of the entire small bowel [2] and shows localization of lesions before DBE [3]. The rebleeding rate after a normal capsule examination is very low, and conservative management is appropriate in these patients [4]. Since SBCE has a high negative predictive value (NPV), an SBCE-guided DBE approach has been developed to avoid DBE in patients with low pretest probability for small bowel findings [5]. In addition, SBCE increases the diagnostic and therapeutic yields of DBE [6]. Therefore, several guidelines for the management of small bowel bleeding recommend SBCE as the first-line procedure for diagnosis [7–9].

Although SBCE may be a useful screening tool before DBE in patients with OGIB, it can neither obtain tissue for histology nor provide endoscopic therapy. In addition, the administration of SBCE and interpretation of capsule images are time-consuming, particularly in cases of massive bleeding. SBCE also presents a risk of capsule retention. DBE enables endoscopic procedures such as tissue sampling and hemostasis. OGIB patients occasionally require detailed diagnosis followed by rapid treatment by DBE. However,

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complications such as post-procedure abdominal pain, pancreatitis, bleeding, and small bowel perforation have been associated with the procedure [7]. Furthermore, some lesions, such as small lymphangioma, do not require endoscopic procedures and are reportedly difficult to detect with DBE, even though it is the gold standard diagnostic tool [10].

Although DBE is not always necessary in OGIB patients with positive SBCE findings, a method for predicting the necessity of DBE has not been established. The purpose of this study was to develop a new and simple numerical scoring system that predicts which OGIB patients require DBE on the basis of clinical profiles, laboratory findings, and SBCE results.

2. Materials and methods

2.1. Study population

Of 1139 patients who underwent SBCE at Nagoya University Hospital between June 2004 and December 2015, 386 patients with OGIB were selected. OGIB was defined as overt bleeding or recurrent occult fecal bleeding with iron deficiency anemia of unknown origin, as determined by both conventional esophagogastroduodenoscopy and colonoscopy [11]. Fifty-six patients with lesions outside the small bowel were excluded. Therefore, we retrospectively collected data for 330 referral patients by reviewing their medical records and conducting telephone interviews.

Patients with OGIB were classified as having ongoing overt bleeding (bleeding documented within 48 h of SBCE administration), previous overt bleeding (last episode of bleeding occurring >48 h before SBCE), or occult bleeding (anemia with a positive fecal occult blood test). Patients with overt rebleeding were defined as having hematochezia, melena, and hematemesis. Patients with occult rebleeding were defined as having progressive anemia (drop in hemoglobin of >2 g/dL) [12].

2.2. SBCE procedure

Patients were examined using the PillCam SB (SB, SB2, or SB3; Medtronic Japan Co., Ltd, Tokyo, Japan), which measures 26×11 mm and is propelled by peristalsis. The technical procedures and evaluations of capsule images have been described previously [1]. Patients who experienced incomplete SBCE or complete SBCE with poor small bowel visibility underwent DBE without a second SBCE, and their SBCE findings were evaluated within the range observed with SBCE.

2.3. DBE procedures

Our DBE system (Fujifilm Co., Ltd, Tokyo, Japan) consisted of a video endoscope with an inner diameter biopsy channel of 2.8 mm (EN-450T5) or 3.2 mm (EN-580T), a flexible overtube, and a balloon controller. Details of the insertion method have been described elsewhere [13]. An oral or anal approach for the first examination was selected on the basis of medical history or SBCE results, such as transit time and lesion localization. The cutoff values used for route selection for DBE equated to half of the small bowel transit time in the SBCE complete examination [14]. Further, the localization map in the workstation, a computer system, was used to interpret SBCE images to estimate small bowel location [15]. The preparation for both approaches has been described previously [1]. Patients enrolled in the database were always advised to undergo DBE due to the possibility of false-negative findings with SBCE. Patients were only followed-up with SBCE if they refused to undergo DBE or if they were in very poor general condition. Patients with positive SBCE and negative first examination with DBE received a second DBE with the opposite approach.

2.4. Data analysis

We used a split-sample approach to develop and validate the new scoring system for predicting the necessity of DBE. Enrolled patients were randomly divided into two datasets at a ratio of 2:1 [16,17]. The development dataset was used to develop our predictive scoring model, which was subsequently tested on the validation dataset. Patients in the development dataset were classified as DBE necessary or DBE unnecessary. The DBE-necessary group included patients in whom (1) the SBCE diagnosis differed from the DBE diagnosis, (2) the SBCE diagnosis was confirmed histologically or morphologically by DBE, (3) the final diagnosis could be confirmed only by SBCE but DBE procedures such as hemostasis or tattooing were required, and (4) rebleeding occurred within six months when DBE was not performed. The DBE-unnecessary group included patients in whom (1) the final diagnosis could be confirmed only by SBCE and no DBE procedures were required, (2) rebleeding did not occur within six months after SBCE when DBE was not performed, and (3) no lesion was detected with DBE.

The gold standard in this study was a diagnosis made with DBE. When only SBCE was performed, the final diagnosis was made on the basis of the SBCE result and a six-month follow-up of the clinical course. SBCE findings that explained patient symptoms and resulted in a change in therapeutic management were considered diagnostically positive. SBCE findings included bleeding sources such as vascular lesions (angiodysplasia, arteriovenous malformation, and active bleeding), erosion, tumors, ulcers, and others (e.g., parasitic disease, diverticula).

2.5. Statistical analysis

All analyses were performed with the SPSS statistical software package, version 23 (SPSS Japan, Tokyo). Categorical variables were presented as percentages and were compared with the chi-square test. Numerical variables were summarized as medians. The nonparametric Mann–Whitney U test was used when appropriate for between-group comparisons. For all analyses, a two-sided P value <0.05 indicated statistical significance.

Univariate analysis was performed to determine whether baseline characteristics differed between the DBE-necessary and DBE-unnecessary groups. The lowest blood hemoglobin level was chosen for analysis. To identify the independent predictors of necessary DBE, we constructed multivariate logistic regression models using the variables selected by the univariate analysis.

Multivariate logistic regression analysis was performed using stepwise logistic regression with forward selection and backward elimination. A P value <0.05 was required for entry into the model, and a P value >0.05 resulted in elimination. Results were expressed as odds ratios with 95% confidence intervals (CIs). The discriminatory capacity of the model was assessed using the area under the receiver operating characteristics (ROC) curve. The goodness of fit of the regression model was tested with the Hosmer–Lemeshow test, for which a P value >0.05 indicated a lack of deviation between the model and the observed event rate [18].

To enhance the usefulness of our risk stratification for use in clinical settings, we created a simple scoring model based on the logistic coefficients for each of the multivariable predictors of the necessity of DBE. We rounded the logistic coefficients to the nearest integer and assigned them as points to indicate the presence of each covariate. The sum of all points was calculated as the DBE score for each patient.

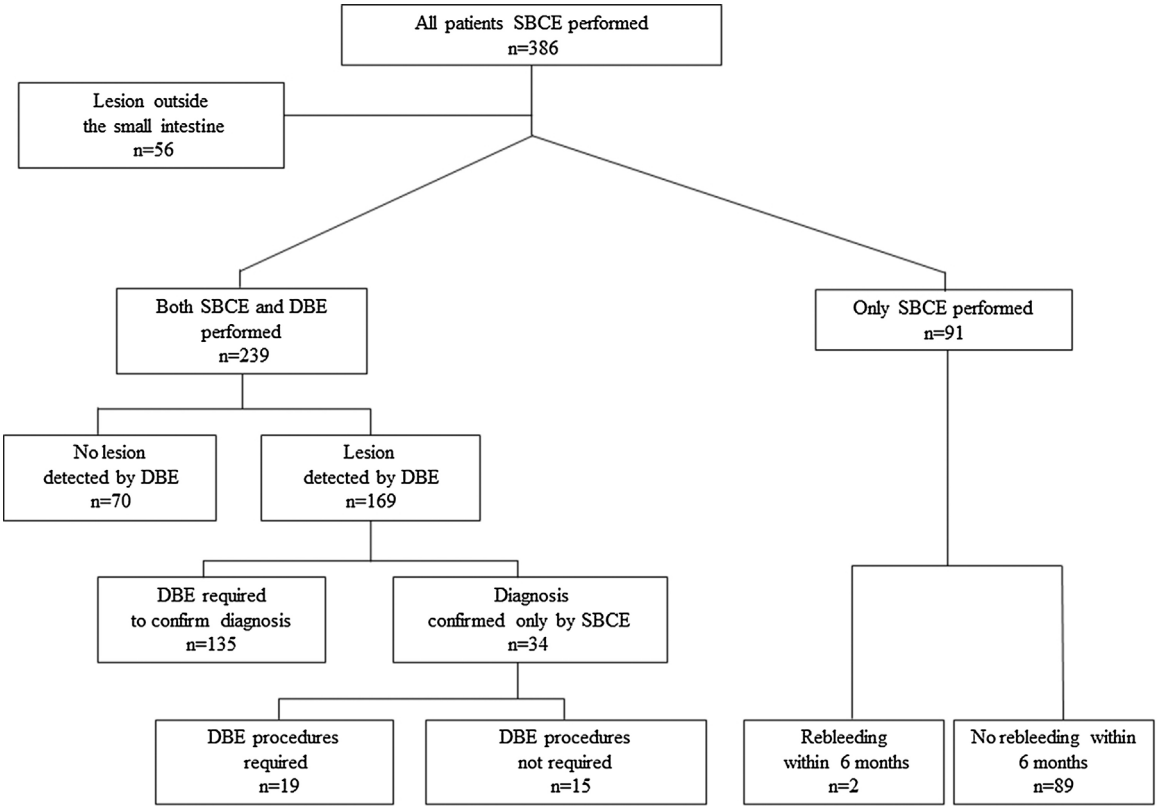

Fig. 1. Patients and group distribution. SBCE, small bowel capsule endoscopy; DBE, double-balloon endoscopy.

3. Results

3.1. Characteristics and clinical outcomes of patients

The patients and group distributions are shown in Fig. 1. A total of 330 OGIB patients who underwent SBCE and/or DBE were analyzed. Of these patients, 239 underwent both SBCE and DBE, and 91 underwent only SBCE. The median follow-up period of patients who underwent only SBCE was 13.3 months (range, 0.7–136.5 months). The success rate of complete SBCE with good small bowel visibility was 80% (264 of 330). No lesions were detected with DBE in 70 patients. The diagnosis of OGIB made with SBCE differed from that made with DBE (n = 45) or was confirmed with DBE (n = 90) in 135 patients. Of 34 patients whose final diagnoses could be confirmed with SBCE alone, 19 required DBE procedures. Of 91 patients who underwent only SBCE, two patients experienced rebleeding within six months after SBCE. Of 107 patients who had normal SBCE findings, 55 underwent DBE and 52 received no further examination. Thirteen of 107 patients and 12.1% of patients with negative SBCE results experienced rebleeding.

Table 1 shows the baseline characteristics and clinical outcomes of patients in the development and validation datasets. Of the 330 total patients, 156 (47%) required DBE and 111 (34%) had taken oral anticoagulants. The median blood hemoglobin level was 6.9 (range, 2.0–16.4), and 173 (52%) patients underwent blood transfusion. SBCE findings included 120 vascular lesions: 67 were attributed to bleeding, 50 to angiodysplasia, and three to arteriovenous malformations. Other SBCE findings consisted of three cases of suspected diverticula and one case of parasitic disease. Of 107 patients with normal SBCE findings, 21 (20%) required DBE. The final diagnoses of these SBCE-negative, DBE-necessary patients were seven cases of angiodysplasias, five cases of diverticula, five cases of ulcers, three cases of varices, and one case of polyps. No significant differences were found between the development and validation datasets.

3.2. Predictive model for the necessity of DBE

In the development dataset, univariate analysis identified five variables (cardiovascular disease, OGIB type, blood transfusion, blood hemoglobin level, and SBCE findings) as significant predictors of the necessity of DBE (Table 2). These variables were included in the stepwise forward logistic regression analysis. OGIB type, blood transfusion, and SBCE findings proved to be independent predictors of the necessity of DBE (Table 3). The Hosmer–Lemeshow statistic was not significant ($P = 0.89$).

A simple scoring system was devised to enhance the utility of the risk stratification by approximating the information from the logistic coefficients of the logistic regression analysis. OGIB types were categorized and assigned scores of 0, 1, or 2. Blood transfusion was given a score of 0 or 1. SBCE findings were also categorized and assigned scores of 0, 1, 2, or 4 (Table 4). This scoring system yielded a maximum additive score of 7.

The necessity of DBE in each category of the development dataset is shown in Supplementary Fig. S1 in the online version at DOI:10.1016/j.dld.2017.08.036. Necessity increased in a stepwise manner with increasing DBE score. The area under the ROC curve was 0.81 (95% CI, 0.75–0.86). At a cutoff of 2.5 points, the sensitivity and specificity of the prediction of DBE necessity were 74.3% and 76.5%, respectively. For simplicity, two risk strata were identified: low necessity (scores of 0–2, which comprised 52.3% of patients) and high necessity (scores of 3 or more, which comprised 47.7% of patients).

The validation dataset was then used to assess the accuracy of the scores for identifying the need for DBE. The median score for the

Table 1
Baseline characteristics and clinical outcome.

	Development dataset (n = 220)	Validation dataset (n = 110)	*P* value
Age, years			
Median, range	68, 4–97	68, 12–92	0.386
Sex			
Male/female	125/95	60/50	0.695
Past history of OGIB			
Presence/absence	106/114	48/62	0.435
Comorbidity, no. patients (%)			
Diabetic mellitus	38 (17.3)	16 (14.5)	0.528
Cardiovascular disease	66 (30.0)	25 (22.7)	0.163
Chronic renal disease	19 (8.64)	7 (6.36)	0.470
Chronic liver disease	18 (8.18)	13 (11.8)	0.286
Hematologic disease	6 (2.73)	4 (3.64)	0.650
Medication used, no. (%)			
Oral anticoagulants	74 (33.6)	37 (33.6)	1.000
NSAIDs	65 (29.5)	34 (30.9)	0.799
OGIB type, no. patients (%)			0.293
Ongoing overt bleeding	48 (21.8)	22 (20.0)	
Previous overt bleeding	134 (60.9)	61 (55.5)	
Occult bleeding with anemia	38 (17.3)	27 (24.5)	
Time between bleeding and DBE, day			
Median, range	20, 0–106	17, 1–76	0.668
Time between SBCE and DBE, day			
Median, range	2, 0–89	1, 0–96	0.882
Blood transfusion			
Yes/no	113/107	60/50	0.585
Necessity of DBE			
Necessary/not necessary	105/115	51/59	0.815
Blood hemoglobin level, g/dL			
Median, range	6.7, 3.1–15.9	7.3, 2.0–16.4	0.203
SBCE findings, no. (%)			0.362
Normal	74 (33.6)	33 (30.0)	
Vascular lesion	83 (37.7)	37 (33.6)	
Erosion	23 (10.5)	15 (13.6)	
Tumor	10 (4.55)	9 (8.18)	
Ulcer	29 (13.2)	13 (11.8)	
Others	1 (0.45)	3 (2.73)	

OGIB, obscure gastrointestinal bleeding; NSAIDs, non-steroidal anti-inflammatory drugs; DBE, double-balloon endoscopy; SBCE, small bowel capsule endoscopy.

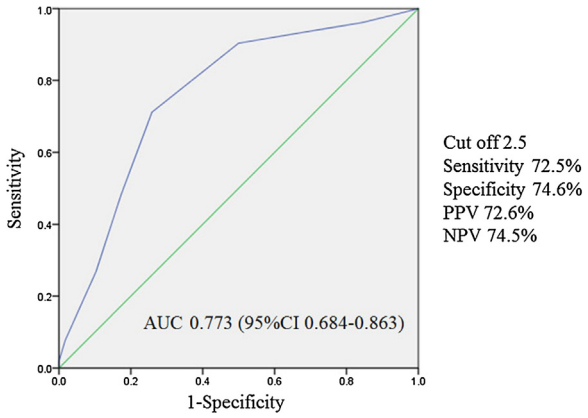

Fig. 2. Receiver operator characteristics analysis of double-balloon endoscopy score. PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver-operating characteristic curve; CI, confidence interval.

validation dataset population was 2 (range, 0–7), and the necessity of DBE according to the simple scoring model is shown in Supplementary Fig. S1 in the online version at DOI:10.1016/j.dld.2017.08.036. DBE was necessary for 71.2% of those in the high-necessity group and 24.1% in the low-necessity group. The area under the ROC curve was 0.77 (95% CI, 0.68–0.86) for the scoring model, which indicated good discrimination (Fig. 2). For a cutoff of 2.5 points, the sensitivity, specificity, positive predictive value, and NPV were 72.5%, 74.6%, 72.6%, and 74.5%, respectively.

Thirty-three patients in the validation dataset had normal SBCE findings (Supplementary Table S1 in the online version at DOI:10.1016/j.dld.2017.08.036). When their scores were ≥ 3 points, the sensitivity, specificity, positive predictive value, NPV, and score accuracy were 33.3%, 96.3%, 66.7%, 86.7%, and 84.8%, respectively.

In patients with scores of 0–2, 14 (24%) required DBE despite their low scores (Supplementary Table S2 in the online version at DOI:10.1016/j.dld.2017.08.036). Ten of 14 patients had SBCE findings that differed from the final diagnosis. SBCE findings in four patients were normal (their final diagnoses were two cases of anastomotic ulcers and two cases of angiodysplasias) and those in the remaining six patients were erosions (their final diagnoses were four cases of angiodysplasias, one case of varices, and one case of intestinal tuberculosis). Twelve of 14 patients had jejunal lesions.

4. Discussion

To our knowledge, this is the first study to develop and validate a simple scoring model to predict the necessity of DBE in patients with OGIB. Our principal findings were that (1) OGIB patients for whom DBE should be recommended can be accurately identified using clinical and SBCE findings, (2) the new prediction model will enable clinicians to make appropriate clinical decisions for OGIB patients with normal SBCE findings, and (3) OGIB type, blood transfusion, and SBCE findings are predictors of DBE outcome in OGIB.

Our scoring system for predicting the necessity of DBE in patients with OGIB may help clinicians determine whether or not DBE should be performed. In patients with scores of ≥ 3, our model

Table 2
Comparison between double-balloon endoscopy necessary patients and double-balloon endoscopy unnecessary patients in the development dataset.

	DBE necessary (n = 105)	DBE unnecessary (n = 115)	*P* value
Age, years			
Median, range	68, 13–97	68, 4–90	0.888
Sex			
Male/female	62/43	63/52	0.524
Past history of OGIB			
Presence/absence	56/49	50/65	0.144
Comorbidity, no. patients (%)			
Diabetic mellitus	21 (20)	17 (14.5)	0.307
Cardiovascular disease	39 (37.1)	27 (23.5)	0.027
Chronic renal disease	11 (10.5)	8 (6.96)	0.353
Chronic liver disease	9 (8.57)	9 (7.83)	0.840
Hematologic disease	2 (1.90)	4 (3.48)	0.474
Medication used, no. (%)			
Oral anticoagulants	41 (39.0)	33 (28.7)	0.105
NSAIDs	32 (30.5)	33 (28.7)	0.772
Type of OGIB, no. patients (%)			<0.001
Ongoing overt bleeding	35 (33.3)	13 (11.3)	
Previous overt bleeding	60 (57.1)	74 (64.3)	
Occult bleeding with anemia	10 (9.52)	28 (24.3)	
Time between bleeding and DBE, years			
Median, range	23, 1–106	17.5, 0–87	0.830
Time between SBCE and DBE, years			
Median, range	2, 0–89	2, 0–63	0.574
Blood transfusion			
Yes/no	68/37	45/70	<0.001
Blood hemoglobin level, g/dL			
Median, range	6.2, 3.4–14	7, 2.3.1–15.9	<0.001
SBCE findings, no. (%)			<0.001
Normal	15 (14.3)	59 (51.3)	
Vascular lesion	60 (57.1)	23 (20.0)	
Erosion	6 (5.71)	17 (14.8)	
Tumor	9 (8.57)	1 (0.870)	
Ulcer	15 (14.3)	14 (12.2)	
Others	0 (0)	1 (0.870)	

DBE, double-balloon endoscopy; OGIB, obscure gastrointestinal bleeding; NSAIDs, non-steroidal anti-inflammatory drugs; SBCE, small bowel capsule endoscopy.

identified those who would benefit from DBE with high accuracy (73.6%).

False-positive SBCE results can occur in patients with OGIB. One study found that 26% (50/193) of OGIB patients with positive SBCE findings had negative findings following subsequent DBE [19]. In our validation dataset, 12.7% (14/93) of patients who underwent both SBCE and DBE had negative DBE findings despite having positive SBCE findings. In cases of false-positive SBCE results, 42.9% (6/14) patients had a DBE score <3 points and could dispense with DBE. Therefore, our scoring model can identify such false-positive SBCE cases to reduce the burden and cost of DBE.

Patients with negative SBCE results can reportedly be managed safely with watchful waiting because the NPV of normal SBCE findings remains high [9]. In our validation dataset, 82% of SBCE-negative patients did not require DBE and could be managed without any further invasive procedures during a six-month follow-up. However, SBCE has a reported false-negative rate of 11% for small bowel findings [20]. Moreover, Postgate et al. reported significant small-bowel lesions that were missed by capsule endoscopy [21]. Hence, DBE should be performed, including consideration of total enteroscopy, in SBCE-negative patients who are highly suspected of having a small bowel lesion.

It has been reported that a greater need for red blood cell transfusion and overt bleeding are associated with a higher rebleeding rate in SBCE-negative cases [22]. Our scoring model identified patients who would benefit from DBE with high accuracy (84.8%) when the DBE score cutoff value was set to 3 (which reflects cases with ongoing overt bleeding and those needing blood transfusion). Therefore, DBE is necessary in patients with a DBE score of 3 even if they have normal SBCE findings.

Furthermore, age (>70 years) is a reported risk factor for rebleeding in SBCE-negative cases [23]. Our validation dataset contained four SBCE-negative patients with scores <3 who needed DBE, three of whom were older than 70 years. Therefore, careful follow-up is recommended for elderly patients even when SBCE findings are normal and the DBE score is <3.

A few studies have identified factors associated with OGIB patients who have a higher probability of successful detection and therapy with DBE. Hussan et al. [24] reported that predictors of DBE outcomes included smaller blood transfusion requirements, absence of esophagogastroduodenoscopy and colonoscopy findings, and the performance of more than one DBE per day per endoscopist. These characteristics were associated with negative diagnostic and therapeutic DBE yields. However, the analysis did not include SBCE findings, and the sample size was too small to be reliable (n = 55). Our study showed that OGIB type, blood transfusion, and SBCE findings were independent predictors of the necessity of DBE.

Previous studies have reported that, compared with occult bleeding, ongoing overt bleeding is more likely to yield positive SBCE results, which increases the diagnostic yield of DBE [25–27]. Of the positive SBCE findings in our study, tumors contributed to a higher score (4 points), and 16 of 19 patients (84%) with SBCE tumor findings were classified into the DBE-necessary group because their diagnoses were confirmed with biopsy or morphological analysis during DBE. The need for DBE biopsy or morphological data in the diagnosis of tumorous lesions may explain why SBCE tumor findings contributed to a high score.

There were 14 patients (24%) in the low-necessity group of the validation dataset who required DBE despite their low scores. Such cases could decrease the diagnostic accuracy of the DBE score (Supplementary Table S2 in the online version at DOI:10.1016/j.dld.2017.08.036). Ten of 14 patients in whom SBCE findings differed from the final diagnosis were thought to have false-negative SBCE

Table 3
Multivariable logistic regression analyses for predicting the necessity of double-balloon endoscopy in the development dataset.

	Logistic coefficient (β)	SE	Odds ratio	95% CI	
				Lower	Upper
OGIB type					
Occult bleeding with anemia	Reference				
Previous overt bleeding	0.832	0.480	2.299	1.491	14.83
Ongoing overt bleeding	1.548	0.586	4.702	0.897	5.892
Blood transfusion	0.759	0.332	2.136	1.114	4.096
SBCE findings					
Normal	Reference				
Vascular lesion	2.017	0.399	7.513	3.439	16.41
Erosion	0.494	0.578	1.638	0.527	5.091
Tumor	3.970	1.137	52.98	5.703	492.1
Ulcer	1.432	0.489	4.188	1.607	10.91
Others	−21.00	40192	0.000	0.000	

CI, confidence interval; OGIB, obscure gastrointestinal bleeding; SBCE, small bowel capsule endoscopy.

Table 4
Double-balloon endoscopy score.

Variable	0	1	2	3	4
OGIB type	Occult	Previous	Ongoing		
Blood transfusion	No	Yes			
SBCE findings	Normal Erosion Others	Ulcer	Vascular lesion[a]		Tumor

OGIB, obscure gastrointestinal bleeding; SBCE, small bowel capsule endoscopy.
[a] Vascular lesion consists of angiodysplasia, arterio-venous malformation, and bleeding.

findings. The false-negative rate of SBCE is reportedly high for the proximal jejunum because of its rapid transit [21,28]. Since nine lesions in the patients with false-negative findings were located in the jejunum, lesion location might be associated with mismatches between the clinical need for DBE and that predicted by our model. The SBCE diagnosis matched the DBE diagnosis in the four patients who had different clinical and predicted needs for DBE (Supplementary Table S2 in the online version at DOI:10.1016/j.dld.2017.08.036). The types of OGIB in these patients were occult bleeding (three patients) and overt bleeding without blood transfusion (one patient), and their scores might have been low because of the small amount of bleeding in one episode.

Our scoring model may not precisely predict the necessity of DBE in patients with proximal jejunal lesions and a small amount of bleeding. However, repeat SBCE may be beneficial and may increase the diagnostic yield even when the results of the initial study are negative [29]. A prospective study supported this finding, particularly when bleeding changed from occult to overt or when hemoglobin decreased by $\geq 4 g/dL$ [30]. Hence, in patients with low scores (0–2 points), careful follow-up, including a second-look SBCE, should be considered.

This retrospective study had several limitations, including the possibility of selection bias, such as loss to follow-up and learning curves for SBCE and DBE. Further, there were only two rebleeding cases among patients who underwent only SBCE. There were no cases in which clinically significant small bowel lesions were detected or rebleeding occurred after six months of follow-up. Therefore, we defined DBE-necessary cases as those in which rebleeding occurred within six months after patients underwent only SBCE. However, rebleeding risk may reportedly extend past the six-month follow-up period [31]. Yung et al. also reported that the majority of rebleeding occurs within the first two years after SBCE [32]. Moreover, it was reported that significant small-bowel pathology may be missed by SBCE [21]. Therefore, the low rebleeding rate in patients who underwent only SBCE might have been affected by selection bias, such as loss to follow-up. Furthermore, the fact that we always advised patients to undergo DBE even when their SBCE findings were negative might also affect the low risk of rebleeding and any missing significant pathology in patients who underwent only SBCE. We also had cases (20%) in which total endoscopy with SBCE was not successful and evaluation of SBCE findings could not be completed. This may also have biased our analysis. In addition, drug-related selection bias might also be present because patients who were on anticoagulants/antiplatelet drugs at baseline but stopped taking such medications following OGIB were not excluded from the study. More stringent external validation involving completely new data from other institutions would allow further assessment of the generalizability of the proposed scoring model. Furthermore, the time between bleeding and DBE did not differ significantly between the DBE-necessary and DBE-unnecessary groups. Therefore, this factor was not included in the DBE score. However, the variation in time between bleeding onset and evaluations such as SBCE and DBE may have biased our analysis. Finally, we did not demonstrate whether our scoring model was useful for preventing rebleeding or reducing mortality from OGIB.

Despite these limitations, we believe that the results of this study are meaningful because the scoring system can help clinicians accurately determine which patients should undergo DBE, thereby reducing the burden and cost of DBE to patients.

In conclusion, our predictive model based on patient characteristics and SBCE findings accurately predicted the necessity of DBE in patients with OGIB and should prove valuable for clinicians who need to determine whether or not to recommend DBE to OGIB patients.

Conflict of interest
None declared.

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Supplementary Table 1.

Score and double-balloon endoscopy necessity in **patients with normal small bowel capsule endoscopy findings in the validation dataset.**

	DBE necessary	DBE not necessary	Total
Score			
≥3 point	2	1	3
0-2 point	4	26	30
Total	6	27	33

DBE, double-balloon endoscopy.

Supplementary Table 2.

Characteristics of patients who required double-balloon endoscopy despite low score.

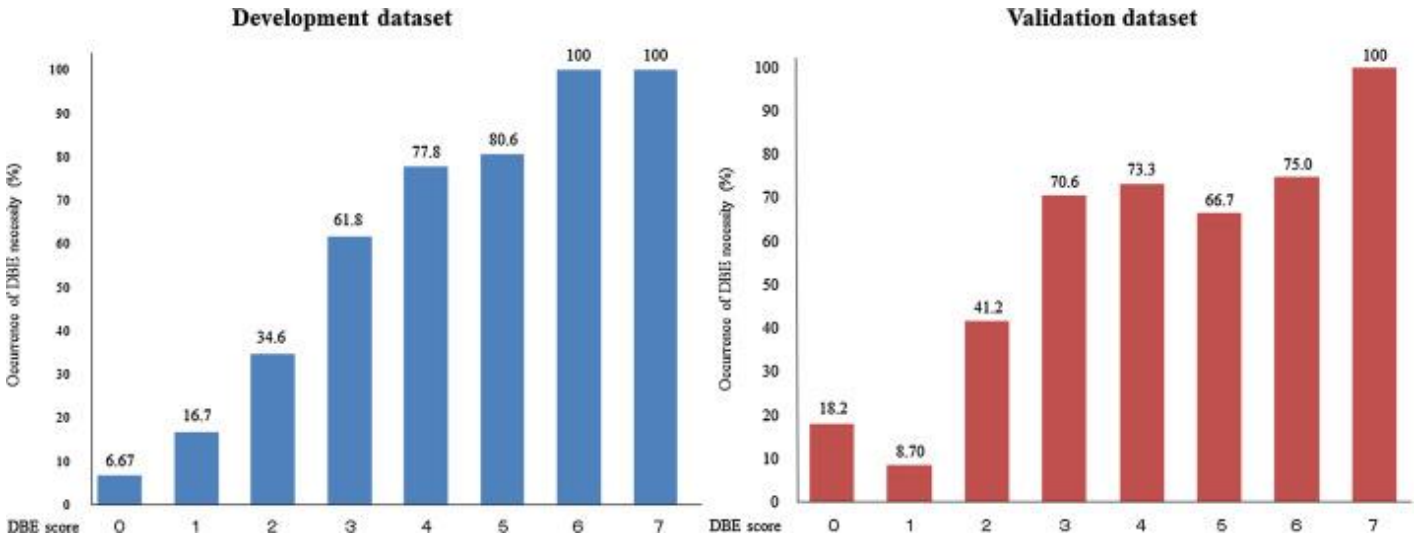
ID	Score	OGIB type	Blood transfusion	SBCE findings	Final diagnosis	Location	DBE procedure
1	0	FOB	No	Normal	Angiodysplasia[a]	Jejunum	Coagulation
2	0	FOB	No	Erosion	Anastomotic ulcer[a]	Jejunum	None
3	1	Previous	No	Normal	Anastomotic ulcer[a]	Jejunum	Medication
4	1	Previous	No	Erosion	Angiodysplasia[a]	Jejunum	Coagulation
5	2	FOB	No	Angiodysplasia	Angiodysplasia	Jejunum	Coagulation
6	2	FOB	No	Vascular lesion	AVM	Jejunum	Operation
7	2	Previous	Yes	Erosion	Angiodysplasia[a]	Jejunum	Coagulation
8	2	Previous	Yes	Erosion	Varices[a]	Jejunum	None
9	2	Previous	No	Ulcer	NSAIDs ulcer	Ileum	Biopsy
10	2	Ongoing	No	Normal	Angiodysplasia[a]	Jejunum	Coagulation
11	2	Previous	Yes	Erosion	Tuberculosis[a]	Jejunum	Biopsy
12	2	Previous	Yes	Normal	Angiodysplasia[a]	Ileum	Coagulation
13	2	FOB	Yes	Ulcer	Tuberculosis	Jejunum	Biopsy
14	2	previous	Yes	Erosion	Angiodysplasia[a]	Jejunum	None

[a] SBCE false-negative case

OGIB, obscure gastrointestinal bleeding; SBCE, small bowel capsule endoscopy; DBE, double-balloon endoscopy;

FOB, fecal occult blood; AVM, arterio-venous malformation; NSAIDs, non-steroidal anti-inflammatory drugs.

(Ms. Ref. No.: DLD-17-27)



Supplementary Figure 1.

Double-balloon endoscopy scoring model evaluated for correspondence with the necessity of double-balloon endoscopy in the development and validation datasets. DBE, double-balloon endoscopy.