Pediatr Gastroenterol Hepatol Nutr. 2023 Jul;26(4):181-192
https://doi.org/10.5223/pghn.2023.26.4.181
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Original Article

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Predictors of Small Bowel Transit Time for Capsule Endoscopy in Children with Inflammatory Bowel Disease

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OPEN ACCESS

Received: Aug 13, 2022
1st Revised: Apr 3, 2023
2nd Revised: Jun 5, 2023
Accepted: Jun 8, 2023
Published online: Jul 5, 2023

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ABSTRACT

Purpose: The development of assistive devices has allowed for the performance of capsule endoscopy in children. Anticipating the capsule's transit time could affect the efficacy of the investigation and potentially minimize the fasting period. This study determined the predictors of small bowel transit time for small-bowel capsule endoscopy in children and adolescents with inflammatory bowel disease.
Methods: We retrospectively examined children and adolescents with inflammatory bowel disease who underwent capsule endoscopy by the age 18 at a Japanese tertiary care children's hospital. Small bowel transit time predictors were analyzed using multiple regression with explanatory variables.
Results: Overall, 92 patients, aged 1–17 years, with inflammatory bowel disease (63 Crohn's disease and 29 ulcerative colitis cases) were examined for factors affecting small bowel transit time. In the simple regression analysis, diagnosis, age, height, weight, serum albumin, general anesthesia, and small intestine lesions were significantly associated with small bowel transit time. In the multiple regression analyses, serum albumin (partial regression coefficient: −58.9, p=0.008), general anesthesia (partial regression coefficient: 127, p<0.001), and small intestine lesions (partial regression coefficient: 30.1, p=0.037) showed significant associations with small bowel transit time.
Conclusion: Hypoalbuminemia, the use of general anesthesia for endoscopic delivery of the capsule, and small intestine lesions appeared to be predictors of prolonged small bowel transit time in children and adolescents with inflammatory bowel disease. Expecting the finishing time may improve examination with a fasting period reduction, which benefits both patients and caregivers.

Keywords: Capsule endoscopy; General anesthesia; Hypoalbuminemia; Inflammatory bowel disease; Small bowel transit time; Child

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Funding
This study was supported by a National Grant-in-Aid for the National Center for Child Health and Development (grant number 2019A-3 [to KA]) and a Health and Labour Sciences Research Grant for Research on Intractable Disease (grant number 20FC0201 [to KA]) from the Japanese Ministry of Health, Labour and Welfare. The study sponsors had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or decision to submit the paper for publication.

Conflict of Interest
The authors have no financial conflicts of interest.

INTRODUCTION

Since small intestinal capsule endoscopy (SBCE) was first approved by the Food and Drug Administration (FDA) in 2001, it has been widely utilized in the field of gastroenterology as a safe, accurate, and non-invasive strategy for evaluating small intestinal mucosa [1].The evolution of capsule endoscopy has been remarkable, with improved optics, wider vision angle, increased dynamic imaging speeds, extended battery life, advanced real-time viewing, and updated hardware and software. PillCam SB is an FDA-approved capsule endoscopy that uses the Given Imaging (Yoqneam, Israel) platform. Although it was approved for use in children as young as 2 years old [2], case reports have demonstrated uneventful use in children as young as 8 months old and weighing as little as 7.9 kg [3]. The patency capsule (PC) has enabled the use of capsule endoscopy in patients with Crohn's disease that may be complicated with stenotic small-bowel lesions. Furthermore, a capsule delivery device (AdvanCE; US Endoscopy) has made the endoscopic delivery of capsules into the stomach or duodenum possible for those who cannot swallow them. The use of the PC and capsule-delivering device has been reported with success [4-6]. However, the small bowel transit time (SBTT) of capsule endoscopy that could affect the prediction of the test's duration has not been well studied.

By determining the SBTT, an efficient examination with a fasting period reduction and expectation of finishing time would benefit patients and their caregivers. Therefore, this study aimed to determine the predictors of SBTT in children and adolescents with inflammatory bowel disease (IBD).

MATERIALS AND METHODS

Patients

This study was a cross-sectional study including patients with IBD who underwent SBCE from 2011 to 2016 at a tertiary care children's hospital in Japan. Patients who underwent SBCE for non-IBD reasons, such as scrutiny of anemia or chronic diarrhea, and those without sufficient data were excluded from this study. None of the patients examined this time had been previously diagnosed with IBD, underwent surgery, or had their capsule endoscopy re-examined for reassessment during long-term hospitalization. As preparation, patients took approximately 20 mL/kg of isotonic magnesium citrate at least 2 hours after dinner the day before the exam. Patients who took extra magnesium citrate after the placement of SBCE were also excluded since it could have affected SBTT.

Patient demographics and clinical data

Patient demographics, including diagnosis, age at SBCE, and sex, were recorded. Baseline clinical variables within 1 week before SBCE, including growth parameters (weight, height), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin (Alb) were collected. Furthermore, the general anesthesia used for the endoscopic delivery of the capsule and small intestine lesions (SILs) found during capsule endoscopy were also checked. SILs were categorized into three groups: no findings, aphthous ulcers, and ulcers. Aphthous ulcers were defined as shallow ulcers or erosions with round or oval white moss surrounded by red scabs, while ulcers were defined as larger and deeper lesions.

https://doi.org/10.5223/pghn.2023.26.4.181

Methods of capsule placement

In children who were unable to swallow the capsule (n=27), we used two different endoscopic capsule delivery methods. In the first four patients, the capsule was delivered to the duodenum endoscopically using a polyp snare or foreign body retrieval basket, Roth Net (STERIS), with reference to previous reports [7-9]. In the subsequent 23 children, the AdvanCE delivery device was used in the same manner [10-12]; the capsule was placed in the stomach and duodenum in 12 and 15 cases, respectively. The oldest child who could not swallow the capsule and required device assistance was a 13-year-old girl.

Small bowel transit time

The imaging data were downloaded to the working station and reviewed by staff pediatric gastroenterologists. SBTTs in minutes were calculated as the duration of time from the first duodenal image or release of the capsule into the duodenum using endoscopic delivering devices to the first image of the cecum.

Statistical analyses

Statistical analyses were performed using IBM Statistics for Windows (version 24.0; SPSS Inc.). First, the descriptive summary statistics were reported for all study patients. We assessed individual demographic and clinical variables to determine if they were significantly associated with SBTT status using a univariate and single regression analysis. Then, we performed multiple regression analyses using coefficients that showed a significant association in the single regression analysis. As a subgroup analysis, the same one was performed with a group of Crohn's disease patients associated with SIL. In this analysis, all cases except for those missing values were examined as a complete-case analysis. Finally, a *t*-test was used to compare the two groups. A *p*-values<0.05 indicated statistical significance.

This study was approved by the Institutional Review Board (study #2020-336) and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013). The requirement for written informed consent was waived because of the study's retrospective design.

RESULTS

Overall, 151 capsule endoscopies were performed in 99 patients between June 2011 and December 2016, and we excluded non-IBD cases and those with date defects or incomplete data with capsules remaining in the stomach during the examination. Thus, 92 procedures were included in this study (**Fig. 1**). The clinical backgrounds of these cases are summarized in **Table 1**.

There were 63 Crohn's disease and 29 ulcerative colitis cases. The male-to-female ratio was 55:37, and the median age at procedure was 12.05 years (interquartile range [IQR]: 10.22–14.40 years, minimum age: 1.73 years, maximum age: 17.76 years). The median height was 145.00 cm (IQR: 131.75–157.25 cm, minimum height: 72.00 cm, maximum height: 180.00 cm), and the median weight was 34.00 kg (IQR: 26.00–46.95 kg, minimum weight: 9.00 kg, maximum weight: 80.00 kg). Endoscopic delivery of the capsule was performed under general anesthesia or through intravenous sedation, mainly in patients who were smaller in size or unable to swallow the capsule. The endoscopically delivered group (403.11±133.20 minutes) had significantly longer SBTT than the orally swallowed group (244.60±113.20 minutes) (p<0.05).

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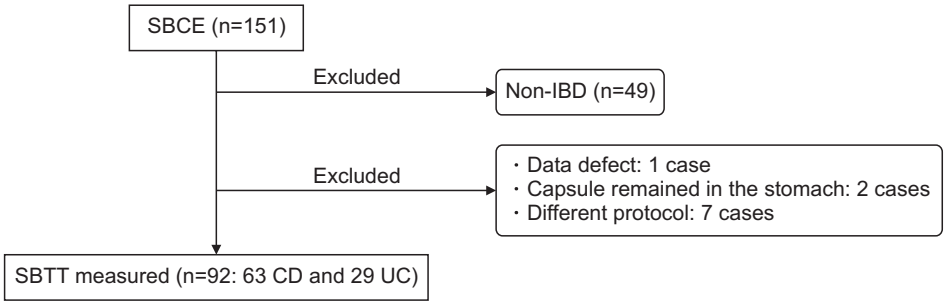

Fig. 1. Flow diagram of patients included for SBTT analysis.
SBTT: small bowel transit time, SBCE: small-bowel capsule endoscopy, IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis.

Table 1. Clinical background of patients who underwent small bowel capsule endoscopy

Characteristic	Value (n=92)
Mean age (yr)	12.05 (1–17)
Diagnosis	
CD	63 (68.5)
UC	29 (31.5)
Sex	
Male	55 (59.7)
Female	37 (40.3)
Height (cm)	145.00 (131.75–157.25)
Weight (kg)	34.00 (26–46.95)
SBTT (min)	277.50 (203.25–349.75)
ESR (mm)	23.50 (12–37)
CRP (mg/dL)	0.11 (0–0.50)
Alb (g/dL)	3.80 (1.8–4.2)
General anesthesia	
Yes	27 (29.3)
No	65 (70.7)
Repetitive studies	2 times: 10 cases 3 times: 5 cases 4 times: 1 case
Cases using delivery device	
AdvanCE delivery device	23 cases
Snare/net	4 cases

Values are presented as mean (range), number (%), or median (interquartile range).
CD: Crohn's disease, UC: ulcerative colitis, SBTT: small bowel transit time, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Alb: albumin.

First, we performed a single regression analysis using each variable as a factor affecting SBTT. For the blood tests and CRP, ESR, and Alb analyses, data from the day of the examination or within 1 week before the examination were used. For the presence of SIL, 54, 11, and 27 cases had no findings, aphthous ulcers, and ulcers, respectively. The SIL in the Crohn's disease-only group consisted of 27, 10, and 26 cases with no findings, aphthous ulcers, and ulcers, respectively.

Single regression analysis showed a negative correlation with diagnosis (b=0.046, p=0.041), age (b=0.119, p<0.001), height (b=0.127, p<0.001), weight (b=0.128, p<0.001), and Alb (b=0.259, p<0.001). Conversely, a positive correlation was shown with the presence or absence of general anesthesia (b=0.310, p<0.001) and SIL (b=0.160, p<0.001), but not sex (b=0.015, p=0.247), ESR (b=0.018, p=0.200), or CRP (b=0.009, p=0.372) (**Fig. 2**, **Table 2**).

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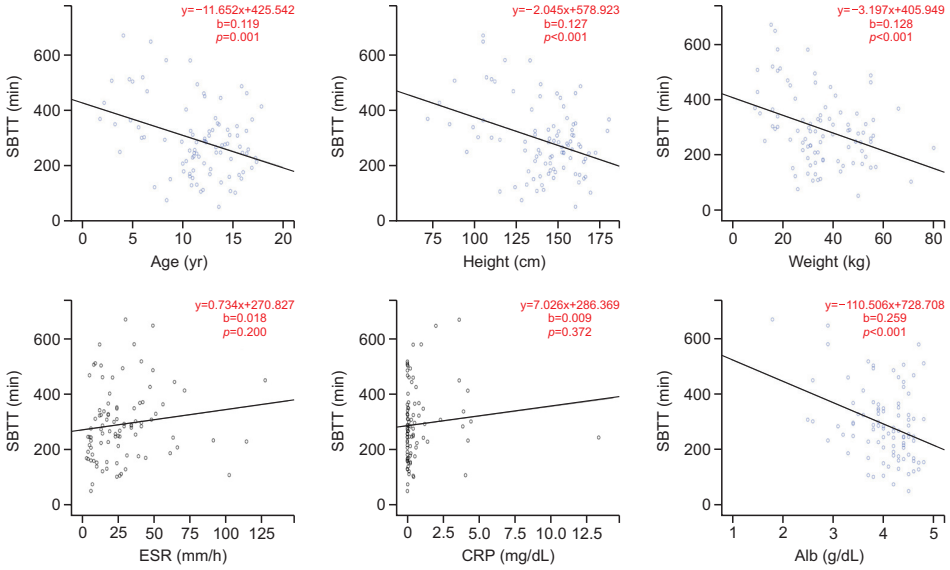

Fig. 2. Single regression analysis of each variable against SBTT. The coefficient of determination is represented by b, and those statistically significant are indicated in blue.
SBTT: small bowel transit time, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Alb: albumin.

Table 2. Single regression analysis of each variable against SBTT

Model	Non-standardization factor		*p*-value
	b	SE	
Constant	310.238	16.089	<0.001
Diagnosis	−59.479	28.656	0.041
Constant	270.827	20.952	<0.001
ESR	0.734	0.569	0.200
Constant	425.542	40.532	<0.001
Age	−11.652	3.343	0.001
Constant	286.369	14.719	<0.001
CRP	7.026	7.828	0.372
Constant	304.418	17.495	<0.001
Sex	−32.148	27.587	0.247
Constant	728.708	78.916	<0.001
Alb	−110.506	19.724	<0.001
Constant	578.923	80.368	<0.001
Height	−2.045	0.564	<0.001
Constant	245.123	13.472	<0.001
Generalanesthesia	157.988	24.869	<0.001
Constant	405.949	33.927	<0.001
Weight	−3.197	0.878	<0.001
Constant	250.532	15.943	<0.001
SIL	57.97	14.018	<0.001

SBTT: small bowel transit time, b: partial regression coefficient, SE: standard error, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, Alb: albumin, SIL: small intestine lesion.

Furthermore, a multiple regression analysis was performed using each factor that had a significant association in the single regression analysis. Regarding height, the variance inflation factor (VIF) was high (VIF=9.781) (**Table 3**), and multicollinearity to other variables was expected; thus, diagnosis, age, weight, Alb, general anesthesia, and SIL were selected as independent variables. It showed a positive correlation with general anesthesia (partial regression coefficient: 127.00, $p<0.001$) and SIL (partial regression coefficient: 30.1, $p=0.037$) and a negative correlation with Alb (partial regression coefficient: −58.9, $p=0.008$) (**Fig. 3**, **Table 4**).

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Table 3. Multiple regression analysis of each variable against SBTT

Model	Non-standardization factor		*p*-value	Collinearity statistics		*R*	R^2	Adjusted R^2	Estimated SE
	b	SE		Tolerance	VIF				
Constant	452.740	160.073	0.006						
Diagnosis	−5.010	26.386	0.850	0.737	1.358				
Age	−0.374	7.847	0.962	0.123	8.146				
Height	−0.137	1.459	0.925	0.102	9.781				
Weight	1.082	1.657	0.516	0.192	5.203				
Alb	−59.027	21.728	0.008	0.662	1.510				
Generalanesthesia	127.194	33.923	<0.001	0.464	2.156				
SIL	30.336	14.409	0.038	0.671	1.490				
1 Coefficient						0.666	0.444	0.397	100.917

SBTT: small bowel transit time, b: partial regression coefficient, SE: standard error, VIF: variance inflation factor, Alb: albumin, SIL: small intestine lesion.
Only height shows high multicollinearity with a VIF, 9.781.

Table 4. Multiple regression analysis excluding height against SBTT

Model	Non-standardization factor		*p*-value	Collinearity statistics		*R*	R^2	Adjusted R^2	Estimated SE
	b	SE		Tolerance	VIF				
Constant	441.453	105.493	<0.001						
Diagnosis	−5.576	25.543	0.828	0.777	1.287				
Age	−0.878	5.708	0.878	0.229	4.361				
Weight	1.012	1.474	0.494	0.240	4.171				
Alb	−58.920	21.571	0.008	0.664	1.506				
Generalanesthesia	127.594	33.460	<0.001	0.471	2.122				
SIL	30.188	14.239	0.037	0.679	1.472				
1 Coefficient						0.666	0.444	0.404	100.327

SBTT: small bowel transit time, b: partial regression coefficient, SE: standard error, VIF: variance inflation factor, Alb: albumin, SIL: small intestine lesion.
Excluding height reduces each VIF and multicollinearity.

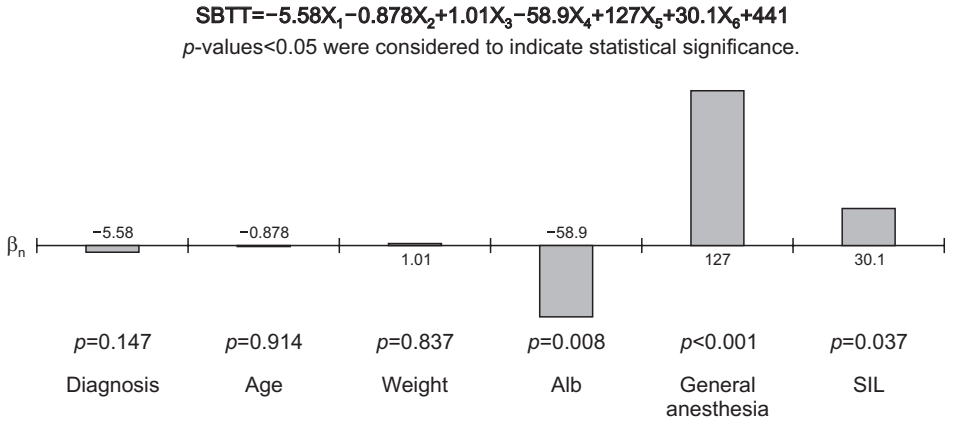

Fig. 3. Regression coefficient of each clinical background characteristic of the patients.
Data that cannot be quantified are replaced with dummy variables, and multiple regression equations are created (X_1=diagnosis [UC=0, CD=1], X_2=age [year], X_3=weight [kg], X_4=Alb [g/dL], X_5=general anesthesia [No=0, Yes=1], X_6=SIL [no findings=0, aphthous ulcers=1, ulcers=2]). Alb, general anesthesia, and SIL are significantly associated with small bowel transit time.
SBTT: small bowel transit time, CD: Crohn's disease, UC: ulcerative colitis, Alb: albumin, SIL: small intestine lesion.

Further, when a subgroup analysis was performed in the Crohn's disease-only group (n=63) using the same method, the single regression analysis showed similar results (age: b=0.184, *p*<0.001, height: b=0.167, *p*=0.001, weight: b=0.201, *p*<0.001, Alb: b=0.256, *p*<0.001, general anesthesia: b=*0.304*, *p*<0.001, SIL: b=0.182, *p*<0.001) (**Table 5**), and the results of the multiple regression analysis—excluding heights with high VIF (VIF=10.554) (**Table 6**)—were similar

https://doi.org/10.5223/pghn.2023.26.4.181

Table 5. Single regression analysis of each variable against SBTT (only Crohn's disease)

Model	Non-standardization factor		*p*-value
	b	SE	
Constant	476.974	47.523	<0.001
Age	−14.536	3.914	<0.001
Constant	306.572	19.018	<0.001
CRP	3.936	8.603	0.649
Constant	326.026	22.013	<0.001
Sex	−39.786	34.945	0.259
Constant	720.758	90.907	<0.001
Alb	−105.562	23.060	<0.001
Constant	645.038	97.040	<0.001
Height	−2.406	0.688	0.001
Constant	257.643	17.655	<0.001
Generalanesthesia	157.786	30.579	<0.001
Constant	456.881	40.468	<0.001
Weight	−4.151	1.059	<0.001
Constant	248.419	22.917	<0.001
SIL	62.816	17.036	<0.001
Constant	303.198	26.158	<0.001
ESR	0.237	0.660	0.721

SBTT: small bowel transit time, b: partial regression coefficient, SE: standard error, CRP: C-reactive protein, Alb: albumin, SIL: small intestine lesion, ESR: erythrocyte sedimentation rate.

Table 6. Multiple regression analysis of each variable against SBTT (only Crohn's disease)

Model	Non-standardization factor		*p*-value	Collinearity statistics		*R*	R^2	Adjusted R^2	Estimated SE
	b	SE		tolerance	VIF				
Constant	441.587	207.393	0.038						
Age	−1.484	9.485	0.876	0.127	7.893				
Height	0.043	1.908	0.982	0.095	10.554				
Weight	0.421	2.336	0.858	0.156	6.404				
Alb	−53.191	25.654	0.043	0.659	1.518				
Generalanesthesia	113.710	45.582	0.016	0.392	2.549				
SIL	34.325	16.743	0.045	0.768	1.301				
1 Coefficient						0.144	0.021	0.005	135.698

SBTT: small bowel transit time, b: partial regression coefficient, SE: standard error, VIF: variance inflation factor, Alb: albumin, SIL: small intestine lesion. Similar to the primary analysis, the subgroup analysis also shows high multicollinearity in height.

to those of the main analysis. Furthermore, a significant correlation was observed with Alb (partial regression coefficient: −53.2, p=0.040), general anesthesia (partial regression coefficient: 114, p=0.014), and SIL (partial regression coefficient: 34.4, p=0.038) (**Table 7**).

Regarding adverse events, none of the 92 cases examined had capsule retention in the small bowel and were all safely examined. Two cases were excluded because the capsule remained in the stomach during the test; however, the capsules were subsequently excreted. Therefore, there were no adverse events, such as retention.

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Table 7. Multiple regression analysis excluding height against SBTT (only Crohn's disease)

Model	Non-standardization factor		*p*-value	Collinearity statistics		*R*	R^2	Adjusted R^2	Estimated SE
	b	SE		Tolerance	VIF				
Constant	445.162	132.101	0.001						
Age	−1.350	7.336	0.855	0.208	4.806				
Weight	0.450	1.931	0.817	0.225	4.452				
Alb	−53.241	25.332	0.040	0.664	1.506				
Generalanesthesia	113.589	44.865	0.014	0.398	2.513				
SIL	34.404	16.231	0.038	0.803	1.245				
1 Coefficient						0.665	0.443	0.394	105.89

SBTT: small bowel transit time, b: partial regression coefficient, SE: standard error, VIF: variance inflation factor, Alb: albumin, SIL: small intestine lesion.
Similar to the main analysis, Alb, general anesthesia, and SIL are significantly associated with small bowel transit time.

DISCUSSION

Predictors of SBTT of the SBCE have not been well studied. Herein, we set variables focused on anthropometric data, disease characteristics, laboratory values, and external factors that might affect the luminal diameter of the small bowel and peristalsis. Our study demonstrated that hypoalbuminemia, the use of general anesthesia for the endoscopic delivery of the capsule, and SIL were the strongest factors that affected the prolongation of SBTT.

Jansen et al. [13] reported that general anesthesia might affect the SBTT of the capsule, and our results were consistent with this finding. Furthermore, hypoalbuminemia could result in edematous thickening of the intestinal wall, which would narrow the intestinal lumen and dysregulate the peristalsis. Additionally, certain drugs used in general anesthesia could slow down the peristalsis by various mechanisms. Our hospital uses anesthetics, including sevoflurane and propofol, for endoscopy, and it is presumed that the decrease in peristalsis was caused by suppression of the nerves that control it or direct suppression of the muscle movements in the intestinal tract. In an animal study, propofol suppressed bronchospasm in pigs by reducing the release of tachykinin involved in muscle contraction, and the authors predicted the effect of suppressing intestinal peristalsis by reducing the release of tachykinin in the intestine [14].

Similarly, a report comparing the inhibitory effect of sevoflurane and propofol on intestinal peristalsis stated that the inhibitory effect of sevoflurane was stronger [15]. Thus, anesthetics are considered to have an inhibitory effect on intestinal peristalsis. Furthermore, SILs, observed as erosions or ulcers by SBCE, may interfere with the smooth passage of capsules mechanically and functionally, prolonging SBTT. In a previous report, the SBTT of the capsule was longer in the group with small intestinal ulcers than in the group with no endoscopic lesions, and 61.9% of the group with small intestinal ulcers included patients with IBD [16]. In this study, SILs were also identified as an important factor that prolongs SBTT, and it was assumed that patients with IBD, especially those with SIL, have longer SBTT than healthy individuals. Height and age consequences remain to be fully investigated. We hypothesized that the small luminal diameter of younger and shorter children would negatively affect SBTT. However, in this analysis, age and height were not significantly associated with SBTT; the slowed or dysregulated peristalsis may have affected SBTT more than the luminal length or diameter. Therefore, well-coordinated peristalsis is a very important factor for the smooth passage of a capsule; however, in the multiple regression model, the coefficient of determination was not as high as R^2=0.444, and unmeasured factors may have affected the results (**Table 3**).

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A subgroup analysis was also performed for the Crohn's disease group, in which a longer SBTT was expected due to SILs. Although inflammatory markers, such as CRP and ESR, might have affected the SBTT, no association was found between inflammatory markers and the SBTT. Some patients with Crohn's disease, especially those with SIL, had undergone multiple SBCEs, and autocorrelation may have affected the results.

Predicting the SBTT could lead to an efficient examination with minimum dietary restriction and potentially reduce the anxiety and burden of patients, caregivers, and managing physicians.

Retention of the capsule has been reported in several studies [17-19]. In adults, capsule retention rates range from 0.75 to 21% in cases of known stricture [20-25]. In addition, in a meta-analysis that evaluated the retention of capsule endoscopes, the capsule retention rate associated with suspected occult and/or overt small-bowel bleeding was 2%, established IBD was 8.3%, and suspected IBD was 3.6%. Notably, prior PC or computed tomography/magnetic resonance enterography, to exclude intestinal strictures, lowered the capsule retention rate to 2.7% (95% confidence interval, 1.1–6.4%); PC would have definitely benefited patients who underwent SBCE [18]. Studies evaluating capsule retention in children reported a retention rate of 0–3.6%, similar to that in adults [8,26-34]. Furthermore, a Japanese group reported their experience with 183 cases of SBCE that did not have any incidences of capsule retention, and the use of PC appeared to lower the risk of retention in pediatric cases [35].

The use of an assistive device for children and infants who cannot swallow the capsules has become standard practice. The potential of mucosal damage and technical difficulty of releasing the capsule using a self-made assistive device with a snare or a net has been a concern [9,36-38]. Therefore, evaluating the patency with AdvanCE and PC appears to be a relatively safe and efficient method for infants and young children who require SBCE. Our study completion rate of examinations was similar to that reported in pediatric cases [39,40].

Our study has some limitations. We used laboratory data collected within 1 week of SBCE, which could have resulted in selection bias, especially in patients with changing conditions. In addition, some patients were examined multiple times to assess the disease state, and autocorrelation may have occurred. Although the presence or absence of general anesthesia was strongly associated with SBTT, the type and dose of anesthetic and time of general anesthesia were not examined.

In conclusion, capsule endoscopy is feasible even in young and small children using PC and endoscopic delivering devices. The multiple regression analyses revealed that hypoalbuminemia and SIL are associated with prolonged SBTT; SIL can cause hypoalbuminemia, and its effect on SBTT should be carefully noted. Predicting the SBTT in children with IBD would improve the quality of the procedural experience for the patients, caregivers, and clinicians. However, future research is needed to further validate our findings of factors that predict SBTT in children with IBD.

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