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Title	Usefulness of transabdominal ultrasonography for assessing ulcerative colitis : a prospective, multicenter study
Author(s)	Kinoshita, Kenji; Katsurada, Takehiko; Nishida, Mutsumi et al.
Citation	Journal of gastroenterology, 54(6), 521-529 https://doi.org/10.1007/s00535-018-01534-w
Issue Date	2019-06
Doc URL	https://hdl.handle.net/2115/78260
Rights	The final publication is available at link.springer.com
Type	journal article
File Information	J Gastroenterol_54_521.pdf



Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Usefulness of Transabdominal Ultrasonography for Assessing Ulcerative Colitis: A Prospective, Multicenter Study

Short title: Transabdominal US for ulcerative colitis

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Abstract

Background and Aims: Transabdominal ultrasonography (US) has been reported to be a useful tool for evaluating ulcerative colitis (UC), but with less well-established data than for Crohn's disease. This prospective multicenter study aimed to establish the usefulness of US for assessing disease extent and activity of UC, comparing with colonoscopy (CS).

Methods: Altogether, 173 consecutive patients with UC were prospectively enrolled, among whom 156 were eligible for this study. All patients underwent US and CS within 2 days at five facilities. We divided the colon into six segments and examined each segment and the rectum using US and CS. US severity was graded as 1–4 regarding bowel wall thickness, stratification, and ulceration. CS severity was also graded to 1–4 according to Matts' endoscopic classification. Concordance between US and CS grades for all colonic segments was analyzed using kappa statistics. US and CS findings were also compared with the clinical disease activity index (CAI) and histological grade using Spearman's correlation coefficient.

Results: We showed moderate concordance between US and CS grades in all colonic segments (weighted $\kappa = 0.55$). Concordance was rated moderate for each colonic segment but only slight for the rectum. The US grade was significantly correlated with the CAI score ($r = 0.40$, $p<0.0001$) and histological grade ($r = 0.35$, $p<0.0001$).

Conclusions: This prospective multicenter study showed moderate concordance between US and CS for assessing the disease activity of UC. Hence, US may be used more generally for evaluating UC in daily clinical practice.

Keywords: Ulcerative Colitis; Transabdominal ultrasonography; Colonoscopy

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by alternating periods of remission and relapse.(1, 2). To monitor the clinical course and treatment response in patients with UC, accurate assessment of disease extent and disease activity is crucial. Currently, colonoscopy is regarded as the most accurate, objective measure of colorectal inflammation. (3). Colonoscopy has limitations, however, such as cost, inconvenience, and invasiveness, making it unsuitable for frequent monitoring. It also presents the risk of complications (e.g., perforation) or aggravation of disease activity in severe UC. (4, 5). Therefore, a noninvasive method for assessing disease extent and activity of patients with UC is needed, especially for those suspected to have severe UC.

Although computed tomography (CT) is widely used to evaluate patients with IBD, it subjects patients to repeated radiation exposure, placing them at an increased risk of developing a malignancy.(6, 7) Magnetic resonance imaging (MRI) can assess disease activity in IBD patients with high sensitivity and specificity using oral contrast agents and intravascular agents.(8, 9) MRI has a diagnostic accuracy similar to that of CT and has the major advantage of not imparting ionizing radiation.(10) MRI also has several disadvantages, however, such as limited availability, relatively high cost, and a time-consuming examination.

Transabdominal ultrasonography (US) has several advantages, including being radiation-free, non-invasive, and cost-effective, as well as offering real-time scanning. (11, 12) During the last decade, US has been regarded as an important imaging modality for the diagnosis and follow-up of IBD, especially Crohn’s disease. (13-19) Although several studies have evaluated the accuracy of US for assessing UC compared with colonoscopy, (20-24) its role in addressing UC is less well established than for Crohn's disease. Most of the aforementioned studies were retrospective, however, and were performed at a single center with only a limited number of expert sonographers.

Thus, US has not yet come into general, widespread use for assessing UC. The aim of this prospective, multicenter study was therefore to evaluate the usefulness of US for assessing UC, compared with colonoscopy.

2. Material and Methods

2.1. Patients

All consecutive patients with an established diagnosis of ulcerative colitis were prospectively recruited at five facilities in Japan from June 2013 to September 2016. All eligible patients were at least 20 years of age. Patients were excluded from the study if they had acute complications such as severe bleeding or a toxic megacolon. Patients who had histologically proved cytomegalovirus colitis were also excluded. Patients underwent a complete clinical evaluation and laboratory investigations.

Colonoscopy (CS) and US were performed within 2 days of each other. Clinical disease activity was evaluated by the Rachmilewitz clinical activity index (CAI) and classified as inactive, mild, moderate, or severe disease.(25). The variables of the Rachmilewitz CAI include bowel frequency, blood in stool, general well-being, abdominal pain, body temperature >38.0°C, erythrocyte sedimentation rate >50 mm/h, and hemoglobin level <10.0 g/dl. Disease severity was defined as follows: score 0-2 = inactive disease; score 3-4 = mild disease; score 5-7 = moderate disease; score ≥ 8 = severe disease. C-reactive protein was also evaluated.

The institutional review board or ethics committee at each facility approved the study protocols. All patients gave written informed consent. This trial is registered at the UMIN Clinical Trial Registry as UMIN 000012354.

2.2. Transabdominal US

US was performed by 24 sonographers from different facilities using several US machines (Xario XG, Aplio 400, Aplio 500, Aplio XG; Toshiba Medical Systems Corp., Otawara, Japan). The median period of experience of the operators was 8 years (range 1–38 years). Sonographic findings and images were double-checked by experienced sonographers when US was performed by those who

had <3 years of experience. We used colonic cleansing when US and CS were performed on the same day. Otherwise, 8 h of fasting was required for the US examination.

Patients generally remained supine during the examinations or were moved to the decubitus position as needed. First, a convex transducer (frequency 3.5–6.0 MHz) was used, followed by a high-frequency liner-array transducer (7.5 MHz) for detailed evaluation if needed. The colon and rectum were sequentially assessed, first locating the hepatic flexure and then scanning the ascending colon toward the cecum, identifying the terminal ileum and Bauhin's valve. The examination proceeded to the sagittal plane of the midline to identify the transverse colon located on the caudal side of the gastric antrum. The probe was then rotated 90° to trace the transvers colon to the hepatic flexure and splenic flexure. The descending colon was identified on the left back side. Finally, the colon was traced from the sigmoid colon to the rectum, which was visualized through the urinary bladder.

We divided the colon into six segments (cecum, ascending colon, right-sided transverse colon, left-sided transverse colon, descending colon, sigmoid colon) and then examined each segment and the rectum. Bowel wall thickness was defined as the distance from the central hyperechoic line of the mucosa to the outer hyperechoic margin of the wall. It was considered abnormal if it was ≥4 mm.(26) US severity was graded on a 1–4 scale based on previously reported data and our preliminary study (11, 27, 28) (Figure 1). Before starting the study, sonographers of each facility attended four sessions on consensual interpretation of US grading and standardization of US techniques. All sonographers, who were blinded to CS findings, initially performed US examinations and assigned grades. All still images and movie clips were analyzed and interpreted in a consensus manner by two registered sonographers at Hokkaido University Hospital (MN, SO) who had 30 and 9 years, respectively, of experience in US. They were aware of the UC diagnosis but were blinded to the patients' clinical information, CS findings, and other sonographers' US assessments.

2.3. Colonoscopy

CS were performed by nine expert endoscopists who had each performed at least 2000 colonoscopies, before entering the trial. CS was performed with standard colonoscope (Olympus, Japan). Polyethylene glycol-based bowel preparation was provided to the patients. For patients with severe UC, flexible sigmoidoscopy without bowel preparation was performed to avoid the risk of bowel perforation. To allow comparison with US, six colonic segments and the rectum were also examined by CS. In each segment, disease activity was assessed according to the Matts' endoscopic classification (CS grades 1–4) (29) (Figure 2), as follows: Grade 1, remission; Grade 2, mild activity; Grade 3, moderate activity; Grade 4, severe activity. All endoscopic findings were evaluated by three experienced gastroenterologists (TK, RO, KK), each with more than 4 years of CS experience. They were blinded to the patient's clinical information and US findings.

2.4. Histopathological examination

Biopsy specimens were obtained from each segments and graded histologically according to the Matts' grading system as follows(29): Grade 1, normal appearance; Grade 2, some infiltration of the mucosa or lamina propria with round cells or polymorphonuclear cells; Grade 3, much cellular infiltration of the mucosa, lamina propria, and submucosa; Grade 4, presence of crypt abscesses with much infiltration of all layers of the mucosa; Grade 5, mucosal ulceration, erosion, or necrosis with cellular infiltration of some or all layers.

2.5. Statistical analysis

Concordance between US and CS grades was assessed for all colonic segments using kappa (κ) statistics. To determine the usefulness of evaluating the disease activity of each patient, the

maximum US and CS grades were analyzed in each patient, which were also compared by κ statistics. Correlation between US grade, endoscopic grade, histological grade, and disease activity index were calculated using Spearman's correlation coefficient. The visualization rate of each colonic segment by CS and US were calculated using the McNemar test. The κ values were interpreted as follows, as proposed by Landis and Koch(30): κ ≤0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; 0.81–1.00, almost perfect agreement. The level of significance was set at $p<0.05$. For data analysis, we used SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA) and Bell Curve for Excel (version 2.11; Social Survey Research Information Corp., Tokyo, Japan). To verify the reproducibility of US grading, interobserver agreement was calculated using κ statistics between interpretations of each sonographer and two consensus readers (MN, SO) considering the US grade.

3. Results

Among the 173 consecutive UC patients who were initially enrolled in this study, 16 patients had not undergone US and CS examinations within 2 days of each other, and 1 patient was <20 years old. As these patients did not meet the inclusion criteria, they were excluded, leaving 156 patients eligible for the study. The demographic, clinical, and biological parameters of this study population are shown in Table 1. Among the study group, 136 patients (87.2%) underwent US and CS on the same day. Total colonoscopy was achieved in 145 patients (92.9%). Colonoscopy was incomplete in 11 patients (7.1%) because of disease severity or insufficient preparation of the colon. US depicted almost all colonic segments except the rectum (Table 2). US could depict colonic segments better than CS, although it depicted the rectum rather poorly ($p<0.0001$). A total of 1026 colonic segments were examined by CS and US.

As shown in Table 3, we achieved moderate concordance between US and CS maximum grades in each patient (weighted $\kappa = 0.50$). The overall concordance between US and CS grades in colonic segments were also moderate (weighted $\kappa = 0.55$) (Table4). The concordance in each colonic segment was in moderate agreement, whereas in the rectum there was slight agreement (Figure 3).

There was a significant correlation between the US maximum grade and CAI score ($r = 0.40$, $p<0.0001$) in each patient, although weak correlation was found between US grade and histological grade in all colonic segments ($r = 0.35$, $p<0.0001$). A moderate correlation was found between the CS maximum grade and CAI score ($r = 0.65$, $p<0.0001$) and the CS grade and histological grade ($r = 0.51$, $p< 0.0001$). CS grade was better correlated with the CAI score and histological grade than was the US grade.

The interobserver agreement between the consensus readers (MN, SO) and each sonographer was almost perfect for US maximum grade in each patient [weighted $\kappa = 0.81$; 95% confidence interval (CI) 0.72–0.90] and was substantial for all colonic segments (weighted $\kappa = 0.73$,

95% CI 0.65–0.80).

4. Discussion

US has been recently proposed as a useful tool for detecting the anatomical location and assessing disease activity of UC.(18, 23, 31, 32) Maconi et al reported that the degree of bowel wall thickness (BWT) measured by US in affected colon was significantly correlated with the degree of clinical, biochemical, and endoscopic activity of UC.(31) Other US parameters reported to be useful in UC include the loss of stratification in the bowel wall and the increased vascularity shown by color Doppler examination.(33, 34). Contrast-enhanced ultrasonography (CEUS) was also reported to be a useful technique to assess the activity of UC quantitatively by analyzing the bowel wall enhancement pattern with intravenous contrast agent administration.(35, 36).

There are few previous prospective US studies that evaluated patients with UC. Parente et al. (21) prospectively evaluated patients with moderate to severe UC and defined the US grade according to the maximum BWT and the degree of intramural blood flow. They reported high concordance between US and CS grades at various follow-up periods (weighted $\kappa = 0.76–0.90$). In another prospective study comparing US and CS in pediatric patients with UC, the authors assessed BWT, increased vascularity, loss of normal stratification, and loss of haustra and then defined the US score considering these variables.(20) They reported that the US score was strongly correlated with both endoscopic ($r = 0.94$) and clinical ($r = 0.90$) activity of the disease. These prospective studies, however, were conducted at a single center and examined by only a limited member of expert gastroenterologists.

To our knowledge, this is the first prospective multicenter studies that compared US with CS for assessing UC. We showed moderate concordance between the US and CS grades in all colonic segments and the maximum grade for each patient (weighted $\kappa = 0.55$ and 0.50, respectively). We demonstrated that US had moderate accuracy for evaluating disease activity and severity for patients with UC even in multicenter evaluations.

In our study, US could visualize almost all colonic segments except the rectum, whereas total CS could not be performed in 11 (7.1%) patients. These results suggest that US might be a useful tool for evaluating severe, extended colitis when CS poses the risk of complications. The clinical activity score and histological grade also showed significant correlation with the US grade (r = 0.40 and 0.35, respectively), which agreed with previously reported data.(18, 31, 37, 38).

To standardize commonly used US parameters, we defined US grade according to the BWT, analyzing stratification of the bowel wall and disruption of the mucosal and submucosal layers (indicating ulceration in the tract). These parameters were used in our preliminary study, which showed substantial correlation between US and CS grades when assessing UC (r = 0.67)(28). We did not evaluate increased vascularity of the bowel wall because Doppler US is dependent on the acquisition parameters of US machine settings (e.g., pulse repetition frequency, velocity range, color gain), which could limit reproducibility.

To improve the accuracy of US grading, before starting this study, all sonographers attended four sessions on the consensual interpretation of US grading and standardization of US techniques. Our study showed that interobserver agreement between central readers and each sonographer was good for the US maximum grade for each patient and for the US grade in all colonic segments (weighted $\kappa = 0.81$ and 0.73, respectively). This result indicated that the US parameters used for our US grading might have good reproducibility for assessing UC.

Concordance between US and CS grades were moderate in this study, which was less than that of similar studies.(20, 21). The moderate concordance between US and CS grades when assessing UC could be due to several factors. First, we included US evaluation of the rectum because the rectum is the most affected part of the tract in UC. Concordance between US and CS grades in the rectum was in fair agreement (weighted $\kappa = 0.33$), which confirmed the low US accuracy for disease confined to the rectum(39). Second, our US grading trended to take milder grades than the

CS grades. For example, 59 patients had a CS grade of 3 or 4, whereas only 32 patients had a US grade of 3 and 4. Based on this result, it can be assumed that in cases where the colonic wall was extended by the bowel preparation, US may have difficulty evaluating wall stratification. Therefore, some patients with moderate to severe UC might be graded as having milder disease by US. Also, in some patients with severe disease, a superficial ulcer may be missed by US, which would result in fewer patients being assessed as US grade 4. We believe that these conditions comprise a possible limitation of our US grading.

This study has several strengths. It was a prospectively performed, multicenter study. Also, all patients underwent CS, which is regarded as the gold standard. CS and US findings were interpreted independently by readers who were blinded to the patients' clinical information and the results of other examinations.

There are also several limitations in this study. We had a relatively small proportion of patients with moderate to severe disease (15.8%). In addition, 20 patients (12.8%) did not undergo US and CS on the same day, which may have affected the results. Finally, our study did not evaluate blood flow signals or enhancement patterns of contrast-enhanced Ultrasonography. To enhance the moderate accuracy of our US grading, we might need to make some adjustments, including to these parameters.

In conclusion, the results of our prospective, multicenter study show that—after further standardizing the US techniques and interpretation of US grading—that transabdominal US may be an alternative method for evaluating UC, even when evaluated by ordinarily skilled sonographers. According to these results and the advantages of being radiation-free and non-invasive, we suggest that more general and widespread use of US could be applied in day-to-day clinical practice. It could be considered as first choice examination for the assessment and follow-up of patients with UC.

Funding

None.

Acknowledgment

The authors would like to thank all the endoscopists and sonographers who participated in this study. We thank Nancy Schatken, BS, MT(ASCP), from Edanz Group (www.edanzediting.com) for editing a draft of this manuscript.

Conflict of interest statement

The authors declare no conflicts of interest associated with this manuscript. Professor Naoya Sakamoto received lecture fees from Bristol Myers Squibb and Janssen Pharmaceutical, grants and endowments from MSD and Chugai Pharmaceutical Co., and a research grant from Gilead Sciences.

Authors' contributions

All authors contributed equally. All authors approved the final version of the manuscript as submitted.

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Figure 1. (A) US grade 1: normal thickness of the colonic wall (arrows). (B) US grade 2: thickened mucosa and submucosa without hypoechoic change of the submucosa (arrows). (C) US grade 3: thickened mucosa and submucosa with loss of stratification. (D) US grade 4: bowel wall thickness with loss of stratification and irregular mucosa (arrows) or hyperechogenic areas in the mucosa (arrowheads), which suggest ulceration.

Figure 2. (A) Matts grade 1: normal. (B) Matts grade 2: mild granularity of the mucosa with mild contact bleeding. (C) Matts grade 3: marked granularity and edema of the mucosa, contact bleeding, and spontaneous bleeding. (D) Matts grade 4: severe ulceration of the mucosa with hemorrhage.

Figure 3. Concordance rate between US and CS grade and 95% confidence intervals for each colonic segment. A-colon, ascending colon; Right-T-colon, right-sided transverse colon; Left-T-colon, left-sided transverse colon; D-colon, descending colon; S-colon, sigmoid colon.

Table 1 Demographic and clinical characteristics of patients with UC (n=156)

Age (years), mean (SD)	43.9 (17.0)
Male sex	98 (62.8)
Disease extension	
Proctitis (E1)	33 (21.1)
Left-sided colitis (E2)	46 (29.5)
Extensive colitis (E3)	77 (49.4)
Rachmilewitz clinical disease activity, median (range)*	2 (0-20)
Inactive	83 (59.2)
Mild	25 (17.9)
Moderate	18 (12.9)
Severe	14 (10.0)
Concomitant medications	
Mesalazine	148 (94.9)
Oral or intravenous corticosteroids	28 (17.9)
Azathioprine or 6-mercaptopurine	32 (20.5)
Tumor necrosis factor-α antagonists	9 (5.8)

Tacrolimus	9 (5.8)
Cytapheresis	4 (2.6)
C-reactive protein (mg/dl), median (range)	0.06 (0.01-14.03)

Results are given as the number (%) unless otherwise stated.

*Data for the CAI score were missing for 16 patients.

Table 2 Visualization rate in each colonic segment examined by US and CS

Colonic segment	**CS**	**US**	**p**
Cecum	145 (92.9)	153 (98.1)	0.039
Ascending colon	145 (92.9)	154 (98.7)	0.022
Right T-colon	145 (92.9)	156 (100)	0.001
Left T-colon	146 (93.9)	154 (98.7)	0.008
Descending colon	148 (94.9)	156 (100)	0.008
Sigmoid colon	155 (99.4)	156 (100)	1.000
Rectum	156 (100)	146 (93.6)	0.002
All segments	1040 (95.2)	1075 (98.4)	<0.0001

Results are the number (%).

US, ultrasonography; CS, colonoscopy; Right T-colon, right-sided transverse colon; Left T-colon, left-sided transverse colon

Table 3 Concordance between US and CS maximum grades in each patient

	CS grade				
US grade	1	2	3	4	Total no.
1	2	18	1	0	21
2	7	67	21	8	103
3	0	1	5	10	16
4	0	2	5	9	16
Total no.	9	88	32	27	156
Weighted κ	0.50		ASE: 0.072	95% CI: 0.36-0.65	

ASE, average squared error; CI, confidence interval.

Table 4 Concordance between US and CS grades, all colonic segments

	CS grade				
US grade	1	2	3	4	Total no.
1	434	155	13	4	606
2	115	167	47	21	350
3	1	15	12	18	46
4	0	4	9	11	24
Total no.	550	341	81	54	1026
Weighted κ	0.55		ASE: 0.026	95% CI: 0.50-0.60	

ASE, average squared error; CI, confidence interval.

Figure 1.

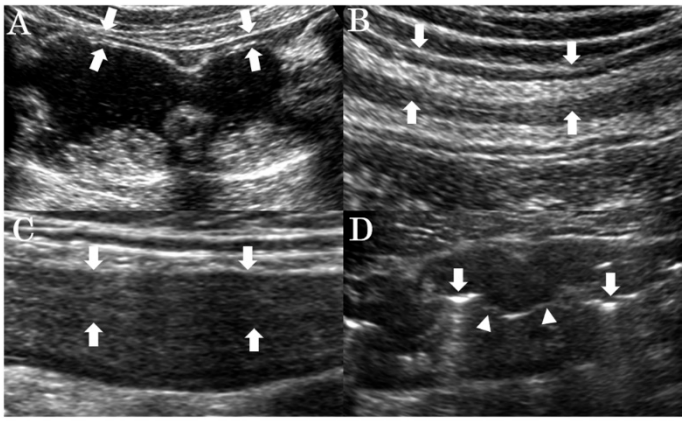


Figure 2.

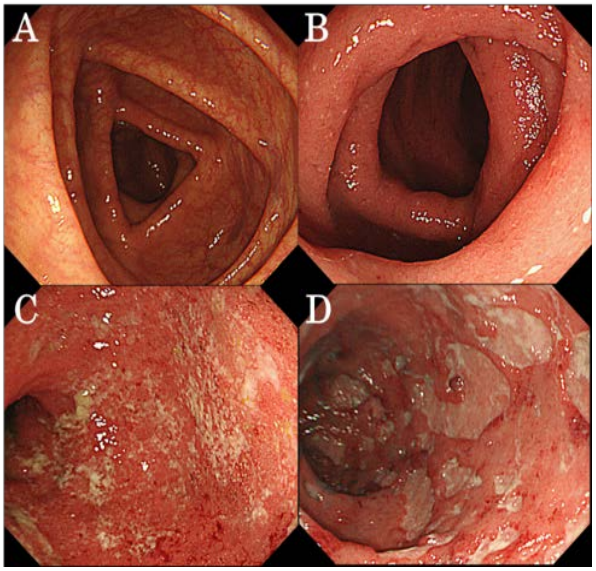
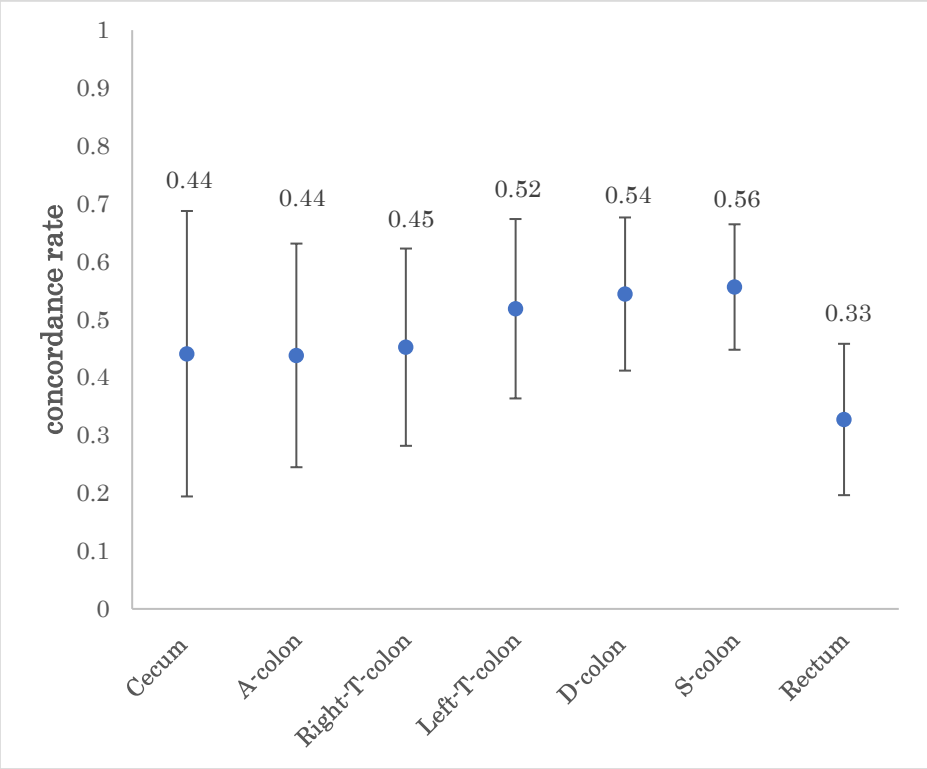


Figure 3.


concordance rate
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.44
0.44
0.45
0.52
0.54
0.56
0.33
Cecum
A-colon
Right-T-colon
Left-T-colon
D-colon
S-colon
Rectum