

## Risk factors for bleeding after endoscopic submucosal dissection of colorectal neoplasms

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### Abstract

**AIM:** To investigate the risk factors for delayed bleeding following endoscopic submucosal dissection (ESD) treatment for colorectal neoplasms.

**METHODS:** We retrospectively reviewed the medical records of 317 consecutive patients with 325 lesions who underwent ESD for superficial colorectal neoplasms at our hospital from January 2009 to June 2013. Delayed post-ESD bleeding was defined as bleeding that resulted in overt hematochezia 6 h to 30 d after ESD and the observation of bleeding spots as

confirmed by repeat colonoscopy or a required blood transfusion. We analyzed the relationship between risk factors for delayed bleeding following ESD and the following factors using univariate and multivariate analyses: age, gender, presence of comorbidities, use of antithrombotic drugs, use of intravenous heparin, resected specimen size, lesion size, lesion location, lesion morphology, lesion histology, the device used, procedure time, and the presence of significant bleeding during ESD.

**RESULTS:** Delayed post-ESD bleeding was found in 14 lesions from 14 patients (4.3% of all specimens, 4.4% patients). Patients with episodes of delayed post-ESD bleeding had a mean hemoglobin decrease of 2.35 g/dL. All episodes were treated successfully using endoscopic hemostatic clips. Emergency surgery was not required in any of the cases. Blood transfusion was needed in 1 patient (0.3%). Univariate analysis revealed that lesions located in the cecum ( $P = 0.012$ ) and the presence of significant bleeding during ESD ( $P = 0.024$ ) were significantly associated with delayed post-ESD bleeding. The risk of delayed bleeding was higher for larger lesion sizes, but this trend was not statistically significant. Multivariate analysis revealed that lesions located in the cecum (OR = 7.26, 95%CI: 1.99-26.55,  $P = 0.003$ ) and the presence of significant bleeding during ESD (OR = 16.41, 95%CI: 2.60-103.68,  $P = 0.003$ ) were independent risk factors for delayed post-ESD bleeding.

**CONCLUSION:** Location in the cecum and significant bleeding during ESD predispose patients to delayed post-procedural bleeding. Therefore, careful and additional management is recommended for these patients.

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**Key words:** Adverse event; Bleeding; Colorectal neo-

plasms; Endoscopic submucosal dissection; Hemorrhage

**Core tip:** Endoscopic submucosal dissection (ESD) has recently been accepted as an effective treatment for colorectal neoplasms, but the risk factors for bleeding following ESD have not been elucidated. We analyzed the relationship between delayed post-ESD bleeding and various factors related to ESD for colorectal neoplasms. The rate of delayed post-ESD bleeding was 4.3%, and univariate and multivariate analyses showed that the location of lesions in the cecum and the presence of significant bleeding during ESD were significantly associated with delayed post-ESD bleeding. Therefore, patients with these risk factors should be carefully managed with additional interventions if necessary.

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## INTRODUCTION

Endoscopic resection (ER) is an effective and safe procedure for the treatment of superficial colorectal neoplasms because this procedure is minimally invasive and provides good clinical outcomes<sup>[1-3]</sup>. Conventional endoscopic mucosal resection (EMR) is widely performed, but this procedure is often inadequate for *en bloc* resection in cases involving large tumors, tumors in difficult locations, or poor tumor elevation after submucosal injection, which results in a high rate of local recurrence<sup>[4-6]</sup>. Endoscopic submucosal dissection (ESD) was initially developed for early gastric cancers, and it is a highly effective and safe treatment. Furthermore, ESD has a high *en bloc* resection rate, regardless of tumor size or location<sup>[7,8]</sup>. ESD has recently been accepted as an effective endoscopic treatment for superficial colorectal neoplasms<sup>[9,10]</sup>.

ER is associated with a low but significant rate of serious adverse events, including delayed post-procedural bleeding. The rate and risk factors of post-procedural bleeding after conventional polypectomy and EMR have been examined previously<sup>[11,12]</sup>, but investigations into the risk factors for delayed bleeding following ESD treatment for superficial colorectal neoplasms are lacking.

Delayed post-ESD bleeding can result in serious adverse effects that can increase morbidity and hospital admissions and require additional expenditures for medical resources and procedures, such as endoscopy, rarely for angiography, or surgical interventions and/or blood transfusions. Therefore, an understanding of the risk factors for delayed bleeding following ESD for colorectal neoplasms is important to avoid this complication. The

present study determined the incidence of delayed bleeding following ESD and identified the clinical factors that are associated with this adverse event.

## MATERIALS AND METHODS

### Patients

A total of 319 patients (who had 327 colorectal neoplasms) underwent ESD at the Cancer Institute Hospital (Tokyo, Japan) between January 2009 and June 2013. The indications for ESD were defined according to the guidelines proposed by the Japanese Colorectal ESD Standardization Implementation Working Group (Table 1). Two patients were excluded because they had undergone emergency surgical repair for bowel perforation. Therefore, the medical records of 325 colorectal neoplasms in 317 patients were reviewed retrospectively.

### ESD procedure and post-procedural treatment

Patients with multiple lesions received multiple ESD procedures on different days to treat each lesion separately. Antiplatelet and/or anticoagulant drugs were discontinued for 7 d before and after treatment if patients were considered low risk for thromboembolism. Intravenous heparin was administered to patients considered high risk for thromboembolism until 6 h before ESD, and then restarted on first post-procedural day if hemostasis was confirmed by stable vital signs and laboratory data.

Expert endoscopists, who were certified by the Japanese Society of Gastrointestinal Endoscopy, performed ESD. All patients were treated under sedation with midazolam and pethidine hydrochloride. Submucosal injections of 10% glycerol and 5% fructose in normal saline solution (Glycerol®; Chugai Pharmaceutical, Tokyo, Japan) and undiluted 0.4% sodium hyaluronate (MucoUp®; Johnson and Johnson, New Brunswick, NJ, United States) were administered to lift the mucosa. Circumferential incisions and all lesion dissections were performed using endoscopic knives. Carbon dioxide insufflation was used. Endoscopic hemostasis during ESD was achieved whenever active bleeding occurred using hemostatic forceps (FD-411QR; Olympus, Tokyo, Japan) and an electrosurgical unit (ERBE-ICC200 or ERBE-VIO300D; Erbe Elektromedizin, Tübingen, Germany) in the 80-W, soft coagulation mode. Hemostatic clips (EZ Clip; Olympus) were used when hemostasis could not be achieved using hemostatic forceps alone. Endoscopic hemostasis using hemostatic forceps was performed if bleeding occurred on the artificial ulcer after resection of the lesion.

Patients without adverse events began drinking water on the first postoperative day and eating soft food on the second postoperative day. All patients were discharged on postoperative days 4-5. Patients were informed to contact our hospital and visit an emergency department immediately if they experienced hematochezia. All patients had visited the outpatient department to confirm their final pathological results within 3 wk after discharge.

**Table 1** Indications for colorectal endoscopic submucosal dissection

Large lesions (diameter > 20 mm) for which endoscopic treatment is indicated but <i>en bloc</i> resection by snare endoscopic mucosal dissection would be difficult
Laterally spreading tumor of the non-granular type, particularly the pseudo-depressed type
Lesions showing a type V I pit pattern
Cancer with submucosal infiltration
Large depressed type tumor
Large lesions of the protruded type suspected to be carcinoma <sup>1</sup>
Mucosal lesions with fibrosis caused by prolapse due to biopsy or peristalsis of the lesions <sup>2</sup>
Local residual early cancer after endoscopic resection
Sporadic localized tumors with chronic inflammation, such as ulcerative colitis

<sup>1</sup>Including laterally spreading tumors of the granular type consisting of large nodules; <sup>2</sup>Caused by biopsy or peristalsis of the lesion (prolapse).

### Data analysis

Delayed post-ESD bleeding was defined as bleeding that resulted in overt hematochezia 6 h to 30 d after ESD and the observation of bleeding spots as confirmed by repeat colonoscopy or the requirement of a blood transfusion.

The risk factors for delayed post-ESD bleeding were assessed from data based on patient-, treatment-, and lesion-related variables. The patient-related factors included age, gender, presence of comorbidities (*e.g.*, hypertension, diabetes mellitus, hyperlipidemia, cardiovascular disease, liver cirrhosis, and chronic renal failure), use of antithrombotic drugs (including anticoagulants and/or antiplatelet drugs), and the use of intravenous heparin. The lesion-related factors were the size of the resected specimen and the size, location, and morphology of the lesions [protruded type (I s, I sp, I p), depressed type (II c), laterally spreading tumor granular type (LST-G), or laterally spreading tumor nongranular type (LST-NG)]. Histology was sub-classified as serrated lesion, adenoma, intra-mucosal adenocarcinoma, submucosal minutely invasive adenocarcinoma (SM invasion < 1000  $\mu$ m), or submucosal deeply invasive adenocarcinoma (SM invasion  $\geq$  1000  $\mu$ m). The treatment-related factors were the device used [needle type (Hook/Flush/Dual/B knife), scissor type (SB knife Jr)], procedure time, and the presence of significant bleeding during ESD.

The procedure time was defined as the interval between submucosal injection and the completion of specimen resection. Significant bleeding during ESD was defined as active bleeding during the procedure that resulted in the use of endoscopic hemostatic clips because hemostasis could not be achieved using hemostatic forceps alone.

### Ethics

This study was conducted in accordance with the Declaration of Helsinki, and the Institutional Review Board of our hospital approved the study protocol.

### Statistical analysis

Univariate analysis was performed using Fisher's exact test or the  $\chi^2$  test for associations between the categorical variables and delayed post-ESD bleeding. The Mann-Whitney *U*-test was used for associations between the continuous variables and delayed post-ESD bleeding. Variables with a *P* value < 0.1 in univariate analysis were considered potential risk factors, and these variables were entered into multivariate logistic regression analysis. OR with 95% CIs quantified the extent of the association. A *P* < 0.05 was considered significant for all tests. All analyses were performed using the SPSS statistical software package (IBM SPSS statistic version 19.0; IBM, New York, United States).

## RESULTS

### Patient baseline and outcomes

The baseline characteristics of the patients are shown in Table 2. A total of 325 lesions from 317 patients were treated with ESD. Post-ESD bleeding was observed in 14 patients (4.3% of all specimens, 4.4% patients). The onset of bleeding occurred between postoperative days 1 and 7 (mean postoperative day, 2.5). Bleeding onset occurred by postoperative day 4 in all cases except for 1. Only 1 patient had more than one bleeding episode (on postoperative days 4 and 7), which required a repeat colonoscopy with endoscopic hemostasis. Patients with episodes of delayed post-ESD bleeding had a mean hemoglobin decrease of 2.35 g/dL (range, 0.8-5.9 g/dL). All patients with hematochezia received a repeat colonoscopy without bowel preparation. All hemorrhagic episodes were successfully treated using endoscopic hemostatic clips, and no cases required surgical intervention. Only 1 patient needed a blood transfusion (0.3% of all specimens, 0.3% of patients); this patient had overt hematochezia and a hemoglobin decrease of 5.9 g/dL. There were no treatment-related deaths.

### Risk factor assessment

Univariate analysis for associations between the various clinical factors and the risk of delayed post-ESD bleeding are shown in Tables 3 and 4. Significant bleeding during the ESD procedure was associated with an increased risk of delayed post-ESD bleeding (*P* = 0.024). Lesions that showed delayed post-ESD bleeding significantly differed from lesions without bleeding in terms of location (*P* = 0.042). The presence of lesions in the cecum was significantly associated with an increased risk of delayed post-ESD bleeding (Table 4; *P* = 0.012). A larger lesion size tended to be associated with bleeding, but this association failed to reach statistical significance (*P* = 0.070).

The results of the multivariate logistic regression analysis are shown in Table 5. This analysis examined lesion size (mm), location in the cecum (yes *vs* no), and significant bleeding during ESD (yes *vs* no). Lesions located in the cecum (OR = 7.26, 95%CI: 1.99-26.55, *P* =

**Table 2** Baseline characteristics of the 325 superficial colorectal neoplasms in 317 patients *n* (%)

Characteristic	<i>n</i>
Patient characteristics	
Number	317
Age (yr)	
Mean $\pm$ SD	65.5 $\pm$ 10.9
Median (range)	67 (29-86)
Gender	
Male	183 (57.7)
Female	134 (42.3)
Comorbidities	
Hypertension	103 (32.5)
Diabetes mellitus	31 (9.8)
Hyperlipidemia	54 (17.0)
Cardiovascular disease	16 (5.0)
Liver cirrhosis	0 (0)
Chronic renal failure	0 (0)
Use of antithrombotic drugs	26 (8.2)
Use of intravenous heparin	5 (1.6)
Lesion characteristics	
Number	325
Lesion size, mm	
Mean $\pm$ SD	34.1 $\pm$ 16.6
Median (range)	30 (7-115)
Location	
Cecum	23 (7.1)
Ascending colon	58 (17.8)
Transverse colon	51 (15.7)
Descending colon	12 (3.7)
Sigmoid colon	59 (18.2)
Rectum	122 (37.5)
Morphology	
Protruded	31 (9.5)
Depressed	4 (1.2)
LST-G	180 (55.4)
LST-NG	110 (33.8)
Histology and depth	
Serrated lesion	5 (1.5)
Adenoma	26 (8.0)
M	249 (76.6)
SM < 1000 $\mu$ m	27 (8.3)
SM $\geq$ 1000 $\mu$ m	18 (5.5)
Resectability	
En bloc resection	284 (87.4)
Complete resection	282 (86.8)
Procedure time, min	
Mean $\pm$ SD	101.0 $\pm$ 80.2
Median (range)	80 (10-630)
Procedure-related adverse events	
Delayed bleeding	14 (4.3)
Patients needed transfusion	1 (0.3)
Death related to the procedure	0 (0)

M: Intra-mucosal adenocarcinoma; SM < 1000  $\mu$ m: Submucosal, minutely invasive adenocarcinoma; SM  $\geq$  1000  $\mu$ m: Submucosal, deeply invasive adenocarcinoma.

0.003) and significant bleeding during ESD (OR = 16.41, 95%CI: 2.60-103.68,  $P$  = 0.003) were independent risk factors for delayed post-ESD bleeding in multivariate logistic regression analysis.

## DISCUSSION

This is the first study to identify risk factors that are as-

**Table 3** Univariate analysis for risk factors of delayed bleeding *n* (%)

Variable	Delayed bleeding	Non-bleeding	<i>P</i> value
Number of patients	14	303	
Number of lesions	14	311	
Patient-related factors			
Median age (yr) (range)	68 (29-79)	67 (31-86)	0.871
Gender (male/female)	7/6	175/124	> 0.999
Comorbidities			
Hypertension	5 (35.7)	103 (33.1)	> 0.999
Diabetes mellitus	1 (7.1)	34 (10.9)	> 0.999
Hyperlipidemia	2 (14.3)	52 (16.7)	> 0.999
Cardiovascular disease	1 (7.1)	17 (5.5)	0.557
Use of antithrombotic drugs	1 (7.1)	27 (8.7)	> 0.999
Use of intravenous heparin	0 (0)	6 (1.9)	> 0.999
Lesion related factors			
Mean size of tumor (mm) (range)	40.9 (20-70)	33.8 (7-115)	0.070
Mean size of specimen (mm) (range)	45.4 (20-75)	38.4 (8-120)	0.142
Location			0.042
Cecum	4 (28.6)	19 (6.1)	
Ascending colon	3 (21.4)	55 (17.7)	
Transverse colon	2 (14.3)	49 (15.8)	
Descending colon	0 (0)	12 (3.9)	
Sigmoid colon	1 (7.1)	58 (18.6)	
Rectum	4 (28.6)	118 (37.9)	
Morphology			0.897
Protruded	1 (7.1)	30 (9.6)	
Depressed	0 (0)	4 (1.3)	
LST-G	9 (64.3)	171 (55.0)	
LST-NG	4 (28.6)	106 (34.1)	
Histology and depth			0.312
Serrated lesion	0 (0)	5 (1.6)	
Adenoma	2 (14.3)	24 (7.7)	
M	8 (57.1)	241 (77.5)	
SM < 1000 $\mu$ m	3 (21.4)	24 (7.7)	
SM $\geq$ 1000 $\mu$ m	1 (7.1)	17 (5.5)	
Treatment-related factors			
Device used			
Needle type <sup>1</sup> /scissor type <sup>2</sup>	12/2	280/31	0.642
Mean procedure time (min) (range)	90.4	101.5	0.965
	(20-180)	(10-630)	
Significant bleeding during ESD	2 (14.3)	4 (1.3)	0.024

<sup>1</sup>Including Flush knife, Dual knife, Hook knife, and B knife; <sup>2</sup>SB knife Jr. LST-G: Laterally spreading tumor granular type; LST-NG: Laterally spreading tumor nongranular type; M: Intra-mucosal adenocarcinoma; SM < 1000  $\mu$ m, submucosal, minutely invasive adenocarcinoma; SM  $\geq$  1000  $\mu$ m, submucosal, deeply invasive adenocarcinoma; ESD: Endoscopic submucosal dissection.

sociated with delayed bleeding following ESD treatment of colorectal neoplasms. Delayed bleeding occurred in 4.3% of all lesions in this study (4.4% of all patients). This finding varies from the published studies on delayed post-ESD bleeding, which ranges between 0% and 12% for colorectal neoplasms<sup>[13-17]</sup>. This wide variation is largely due to differences in study design, patient selection criteria, the operative technique used, and the definition of bleeding. Bleeding occurred within 4 postoperative days in all cases except for 1. Therefore, patients who undergo ESD should be observed carefully for at least 4 d after ESD.

We also discovered that lesions located in the cecum have an increased risk for the development of delayed



**Table 4** Univariate analysis of specific locations in the colon as risk factors for delayed bleeding *n* (%)

Location of the lesions	Delayed bleeding	Non-bleeding	<i>P</i> value
Cecum	4 (28.6)	19 (6.1)	0.012
Ascending colon	3 (21.4)	55 (17.7)	0.722
Transverse colon	2 (14.3)	49 (15.8)	> 0.999
Descending colon	0 (0)	12 (3.9)	> 0.999
Sigmoid colon	1 (7.1)	58 (18.6)	0.479
Rectum	4 (28.6)	118 (37.9)	0.581

bleeding complications (7.3-fold higher) compared to lesions located in other parts of the colon. This result is supported by studies of post-EMR and post-polypectomy bleeding in which delayed bleeding occurred more often in lesions proximal to the hepatic flexure, including the cecum<sup>[18-22]</sup>. This difference may be due to differences in the anatomical structure and physiology of the colon. For example, the submucosal vasculature is easily affected by thermal injury because the intestinal wall of the cecum is thin, and the cecum wall receives higher tension than the other parts of the colon<sup>[21]</sup>. Buddingh *et al*<sup>[18]</sup> suggested that fresh ileal fluids contain bile acids and digestive enzymes that have not been fully resorbed and/or have been inactivated in the colon prior to their transit into the cecum, and these factors underlie the high occurrence of delayed post-polypectomy bleeding in the cecum. These fluids and enzymes are postulated to remove post-polypectomy protective substances in the ulcer site, which damages blood vessels. A previous retrospective study reported that the prophylactic clipping of resection sites after endoscopic resection of large, flat, colorectal lesions was associated with a reduced incidence of delayed post-procedural bleeding<sup>[22]</sup>. The prophylactic closure may reduce the exposure of cecal ulcer sites to bile acids and digestive enzymes. However, this proposed mechanism has not been fully elucidated.

We also found that significant bleeding during the ESD procedure was associated with an increased (16.4-fold) incidence of delayed bleeding compared to cases in which bleeding was easily stopped using only hemostatic forceps during the procedure. Kim *et al*<sup>[23]</sup> also found that immediate post-polypectomy bleeding was significantly correlated with delayed bleeding. Higashiyama *et al*<sup>[24]</sup> reported poor control of bleeding during ESD as an independent risk factor for delayed bleeding in their ESD study on gastric lesions. These authors suggested that the delayed bleeding might be caused by difficulties in the identification of the exposed blood vessel and the failure of coagulation with hemostatic forceps. This failure may be due to the adhesion of the coagula to the ulcer floor immediately after the resection and the occurrence of bleeding during the procedure. However, no prospective trial has been conducted to confirm these reports, and preventive coagulation treatment of the ulcer floor following ESD remains safe and appropriate in gastric ESD. Preventive coagulation treatment using hemostatic forceps for colorectal lesions is rarely performed

**Table 5** Multivariate analysis of risk factors for delayed bleeding

Variable	OR (95%CI)	<i>P</i> value
Lesion size (per mm)	1.02 (0.99-1.05)	0.212
Location in the cecum (yes vs no)	7.26 (1.99-26.55)	0.003
Significant bleeding during ESD (yes vs no)	16.41 (2.60-103.68)	0.003

ESD: Endoscopic submucosal dissection.

after ESD because the muscularis propria of the colon is much thinner and more easily perforated. Accordingly, there may be an association between the lack of hemostasis and/or coagulation treatment and the occurrence of delayed bleeding in cases with bleeding during ESD, which our results suggest. Therefore, hemostasis and/or coagulation treatment should be performed on the bleeding spots during ESD to prevent delayed bleeding complications after the procedure.

The lesion location and bleeding during the ESD procedure were significantly associated with delayed post-ESD bleeding, but no association was found for lesion size. The resection of large lesions exposes larger areas of the submucosa and creates deeper wounds, which suggests that larger lesions are more likely to bleed. However, there is a lack of consensus on the association between lesion size and delayed post-procedural bleeding in the EMR and polypectomy literature. Some reports have shown a significant difference<sup>[23,25]</sup>, some studies have shown a trend without significance<sup>[21]</sup> and some studies have not demonstrated an association<sup>[19,26]</sup>. The resection area is larger in ESD procedures than EMR because of the absence of a size limitation for tumors suitable for *en bloc* ESD resection. The diameter of the largest lesion removed in the present study was 115 mm (mean, 34.1 mm), which is larger than typical EMR procedures. However, significant associations were not found between the size of the lesion and the rate of delayed bleeding in either the univariate or multivariate analyses.

This study has a number of limitations. The study was retrospective in nature. In addition, this study was a single-institution analysis, and future studies are required to replicate our findings at other sites. Finally, the number of subjects enrolled was relatively small. We aim to conduct a multicenter, prospective study with a larger number of subjects in the future.

In conclusion, we found that the rate of delayed post-procedural bleeding following ESD for colorectal neoplasms was 4.3%, and an increased risk of post-procedural bleeding was associated with the presence of lesions in the cecum and significant bleeding events during the ESD procedure. Therefore, additional post-ESD procedures are recommended in patients with these risk factors.

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## COMMENTS

### Background

Endoscopic submucosal dissection (ESD) was initially developed for early gastric cancers, and it is a highly effective and safe treatment. ESD has recently been accepted as an effective endoscopic treatment for superficial colorectal neoplasms. ESD is associated with a small but finite rate of serious adverse events, including delayed post-procedural bleeding. Delayed post-ESD bleeding can result in serious adverse effects that can lead to increased morbidity and require additional medical resources. However, the risk factors for delayed post-ESD bleeding following the treatment of colorectal neoplasms remain unknown.

### Research frontiers

ESD for colorectal neoplasms is not a widely used procedure because of its technical difficulties and the high incidence of severe adverse events, including delayed post-procedural bleeding. ESD for colorectal neoplasms may be performed more safely to determine the incidence of delayed post-ESD bleeding and identify the clinical factors that are associated with this adverse event.

### Innovations and breakthroughs

The rate of delayed post-ESD bleeding was 4.3%, and bleeding occurred within 4 postoperative days in most cases. The increased risk of post-ESD bleeding was significantly associated with the presence of lesions in the cecum and significant bleeding events during the ESD procedure.

### Applications

The study results suggest that patients who undergo ESD should be observed carefully during the 4 d after ESD, and additional post-ESD procedures, such as prophylactic closure of the resection site or hemostasis treatment in the bleeding spots, should be performed in patients with these risk factors.

### Terminology

Delayed post-ESD bleeding: Delayed post-ESD bleeding was defined as bleeding that resulted in overt hematochezia 6 h to 30 d after ESD and the observation of bleeding spots confirmed by repeat colonoscopy or the requirement of blood transfusion. Significant bleeding during ESD: Significant bleeding during ESD was defined as active bleeding during the procedure that resulted in the use of endoscopic hemostatic clips because hemostasis could not be achieved using hemostatic forceps alone.

### Peer review

This is a good descriptive study of the risk factors of delayed bleeding after colorectal ESD. The results are interesting and suggest that location in the cecum and significant bleeding during ESD were the risk factors for delayed bleeding after ESD, but a larger lesion size was not significantly associated with delayed bleeding.

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