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Low incidence of deep vein thrombosis after double-balloon endoscopy and colorectal submucosal dissection: Multicenter, prospective study

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ABSTRACT

Background and study aims Although deep vein thrombosis (DVT) and pulmonary embolism (PE) are major postoperative complications, risk of DVT/PE after endoscopic procedures remains unknown. This study aimed to identify risks of DVT/PE after colorectal endoscopic submucosal dissection (ESD) and double-balloon endoscopy (DBE).

Patients and methods Patients who were scheduled to undergo DBE and colorectal ESD were prospectively enrolled in this study. Before enrollment, all patients were confirmed to have no DVT on whole-leg ultrasonography (US) or contrast-enhanced computed tomography (CECT). All patients routinely underwent whole-leg US after ESD or DBE. The primary endpoint was incidence of DVT after colorectal ESD and DBE. The preplanned sample size was 170 patients in the colorectal ESD group and 75 in the DBE group.

Results Between September 2020 and June 2022, 170 patients who had colorectal ESD and 75 who had DBE were recruited for this study; however, 238 patients (ESD, n = 167; DBE, n = 71) were analyzed. Of these 238 patients, DVT occurred in only one patient after colorectal ESD and incidence of DVT was 0.4% (95% confidence interval [CI] 0–1.2) in total, including 0.6% (95% CI 0–1.8) after colorectal ESD and 0% after DBE. Conversely, no PE occurred in the entire cohort.

Conclusions This prospective study demonstrated that risk of DVT/PE following highly invasive endoscopic procedures including colorectal ESD and DBE is very low.

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Introduction

Deep vein thrombosis (DVT) is one of the major complications in patients who have undergone surgery and in immobile patients hospitalized for a medical illness [1]. Untreated DVT can cause pulmonary thromboembolism (PE), which has a potentially fatal outcome [2]. Therefore, early diagnosis and prevention of DVT are important issues to reduce risk of thrombosis-related complications.

Orthopedic surgery is associated with a high risk of DVT and PE [3]. Abdominopelvic surgery is also a potential risk for DVT and PE [4]. Therefore, perioperative patients must be treated with appropriate DVT prophylaxis, such as using graduated compression stockings (GCS), intermittent pneumatic compression, low-dose unfractionated heparin, and low-molecular-weight heparin, based on the results of preoperative risk evaluation [4, 5]. To stratify risk of DVT/PE, the Caprini and Padua risk assessment models have been used in patients undergoing surgery and patients hospitalized in Internal Medicine [4, 6, 7, 8]. However, how to perform risk assessment of DVT before endoscopy and whether DVT prophylaxis is required for patients undergoing endoscopic treatment remain unclear.

Advances in medical devices for endoscopy have made it possible to diagnose and treat small intestinal diseases and to resect large colorectal tumors en bloc [9, 10, 11, 12]. Double-balloon endoscopy (DBE) is a useful procedure that enables definitive diagnosis and endoscopic treatment for small intestinal diseases [9, 12, 13]. However, DBE requires a high degree of skill technique and takes longer than esophagogastroduodenoscopy and total colonoscopy. Previous studies have reported that the median insertion time required for panenteroscopy was over 120 minutes [9, 12], which may be a potential risk for DVT after DBE. In addition, DBE is frequently employed for diagnosis of patients with inflammatory bowel disease (IBD), who have a higher incidence of DVT/PE than those with other digestive diseases [14, 15].

Compared with endoscopic mucosal resection, colorectal endoscopic submucosal dissection (ESD) allows en bloc resection of large colorectal tumors, which leads to accurate pathological diagnosis and lower rates of recurrence [16, 17]. However, colorectal ESD also requires a more advanced technique than esophageal and gastric ESD. Furthermore, colorectal ESD requires a long operative time similar to DBE. In lesions measuring > 40 mm, median operative time for colorectal ESD was > 2 hours [16, 18].

DBE and colorectal ESD require that patients to remain in the same position for a long time and that air insufflation to the small and large intestines is continuous, resulting in increased abdominal pressure and venous insufficiency. Thus, DBE and colorectal ESD are the most invasive endoscopic procedures, and they and other surgical procedures may place patients at risk for DVT and PE. However, no prospective studies have examined incidence of DVT after DBE and colorectal ESD. Incidence of DVT after invasive endoscopy including DBE and colorectal ESD remains unknown. Thus, this multicenter, prospective, cohort study (De-ViT study) aimed to clarify risk of DVT and PE after highly invasive endoscopic procedures such as DBE and colorectal ESD.

Patients and methods

Patients and ethics

Patients who met all the inclusion criteria except for no DVT received screening whole-leg ultrasonography (US) or contrast-enhanced computed tomography (CECT), and patients who met all the inclusion criteria were prospectively enrolled from September 2020 to June 2022. Inclusion criteria were as follows: (1) patients who were scheduled to undergo colorectal ESD for superficial colorectal neoplasms or DBE for suspected small intestinal disease; (2) no DVT on whole-leg US or CECT before DBE or ESD; (3) age ≥ 20 and ≤ 89 years; and (4) agreement with signed informed consent. Exclusion criteria were as follows: (1) previous history of DVT/PE; (2) central venous access; (3) history of cerebral stroke within 3 months; (4) history of bone fracture within 3 months; (5) history of major surgery under general anesthesia within 3 months; (6) history of acute infection within 3 months; (7) history of an acute coronary syndrome within 6 months; (8) hematologic diseases including congenital or acquired coagulation abnormalities; (9) severe heart, lung, liver, and kidney dysfunction and severe diabetes; (10) arteriosclerosis obliterans or varicose veins; (11) lower extremity dermatitis or skin ulcers; (12) peripheral neuropathy; (13) poor status (Eastern Cooperative Oncology Group performance status ≥ 3); (14) pregnancy; (15) mental disorders and dementia such that there was inability to understand the study contents; and (16) unfit by physician's judgment.

Seven Japanese institutions participated in the De-ViT study. The study protocol was approved by each institution's ethics committee. The trial was performed according to the ethical guidelines of the 1975 Declaration of Helsinki (7th revision, 2013). Written informed consent was obtained from all participants before study enrollment. Before the trial commenced, it was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, UMIN000041789). The De-ViT study complied with the STROBE statement [19]. All authors had access to the study data and reviewed and approved the final manuscript.

Study design and procedures

The De-ViT study was a multicenter, prospective, cohort study that assessed incidence of DVT/PE following colorectal ESD or DBE. Patients undergoing colorectal ESD for superficial colorectal neoplasms or DBE for suspected intestinal diseases were prospectively enrolled. All enrolled patients were confirmed to have no DVT on whole-leg US or CECT within 21 days before ESD or DBE, and each investigator registered the patient in the central data center.

Risk assessment for DVT was performed using the Caprini score [4] and the Padua score [6] before ESD/DBE. All patients routinely underwent whole-leg US and blood examination including D-dimer between Days 1 and 7 after ESD or DBE. Before post-ESD/DBE whole-leg US, all patients were assessed for the possibility of DVT using the Wells score. Whenever patients

were diagnosed with DVT by whole-leg US or suspected of having DVT/PE, they had to undergo a chest CECT. In accordance with the preplanned protocol, patients who underwent emergent surgery or interventional radiology between enrollment and post-ESD/DBE whole-leg US were excluded from the analysis.

Colorectal ESD was performed using a single-channel endoscope (PCF-H290TI; Olympus Co., Tokyo, Japan). DBE (EI-580BT, EN-580T; Fujifilm Co., Tokyo, Japan), which has two inflatable balloons. The insertion route was selected depending on the target lesion inferred from other examinations before DBE, such as peroral insertion and transanal insertion for a suspected jejunal and ileal lesion, respectively. Carbon dioxide insufflation was used during colorectal ESD and DBE. Use of GCS for periprocedural DVT prophylaxis was determined beforehand, depending on the institution. No institutions used GCS for DBE. Regarding colorectal ESD, three institutions used GCS for all participants, but four institutions never used GCS.

Sample size and statistical analysis

The primary endpoint of this study was incidence of DVT within 30 days after colorectal ESD and DBE. Secondary endpoints were incidence of PE after ESD/DBE, adverse events, risk factors for DVT after ESD/DBE, conventional risk scores (Caprini, Padua, and Wells scores), and establishment of a novel risk stratification of post-ESD/DBE DVT. Incidence of DVT before ESD/DBE was also analyzed to predict risk of pre-ESD/DBE DVT.

This study was a novel prospective study, given the scarcity of available data on DVT post-endoscopic procedure. Only one study investigated post-endoscopic DVT, in which incidence of DVT after gastric ESD was 10% [20]. When incidence of DVT is 10%, the sample size estimated with ± 5% of 95% confidence interval (CI) was 162 for colorectal ESD and the sample size estimated with ± 8% of 95% CI was 69 cases for DBE. The final preplanned sample size was 170 patients for colorectal ESD and 75 for DBE, allowing for a dropout rate of approximately 10% because of withdrawal of consent or other reasons.

Results

Patient characteristics

Between September 2020 and June 2022, 271 patients who were scheduled to undergo colorectal ESD or DBE fulfilled the inclusion criteria and underwent screening whole-leg US or CT before study enrollment. Among the 271 patients who fulfilled the inclusion criteria, 25 with colorectal ESD and one with DBE were not enrolled, and a total of 245 patients (colorectal ESD cohort, n = 170; DBE cohort, n = 75) were enrolled in this study (▶ **Fig. 1**) [21]. After study enrollment, one patient was excluded because colorectal ESD was not performed and three patients in the DBE cohort were excluded because of enrollment error: one patient had DVT on screening US, one had a duplicated enrollment, and another patient did not undergo screening whole-leg US or CT before enrollment. Two patients with emergency surgery post-ESD/DBE were excluded, and finally, 238 patients (colorectal ESD cohort, n = 167; DBE cohort, n = 71) were analyzed in this study.

Baseline characteristics are shown in ▶ **Table 1**. None of the patients had DVT before enrollment. Median age was 67 years. Primary diseases necessitating colorectal ESD and DBE are also shown in ▶ **Table 1**. Median endoscopic procedure times were 110 and 64 minutes in the colorectal ESD and DBE cohorts, respectively. Median Caprini scores were both 3 points in the colorectal ESD and DBE cohorts. Median Padua scores were 1 and 0 points in the colorectal ESD and DBE cohorts, respectively. All median values before colorectal ESD and DBE were within reference ranges (**Supplementary Table S1**).

Clinical outcomes after ESD and DBE

Clinical outcomes following colorectal ESD and DBE are shown in ▶ **Table 2**. Of the 238 patients, DVT occurred in only one patient following colorectal ESD. Incidence of DVT was 0.4% (95% CI 0–1.2) in total, including 0.6% (95% CI 0–1.8) after colorectal ESD and 0% after DBE. Baseline characteristics and preprocedure values of the patient with DVT following ESD are shown in **Supplementary Table S2**. The patient was an 81-year-old woman with hypertension as a comorbidity. No specific abnormalities were found, and the Caprini and Padua scores before colorectal ESD were 4 and 1, respectively. She completed colorectal ESD without any complications in 148 minutes; however, an asymptomatic DVT was found on whole-leg US on post-ESD Day 4. Follow-up without specific medication was selected, and the DVT naturally disappeared on whole-leg US 1 month after colorectal ESD. In contrast, no PE was observed in the entire cohort. One patient died within 30 days following DBE because of hypoxic encephalopathy, and the mortality rate within 30 days after ESD/DBE was 0.4% (95% CI 0–1.2).

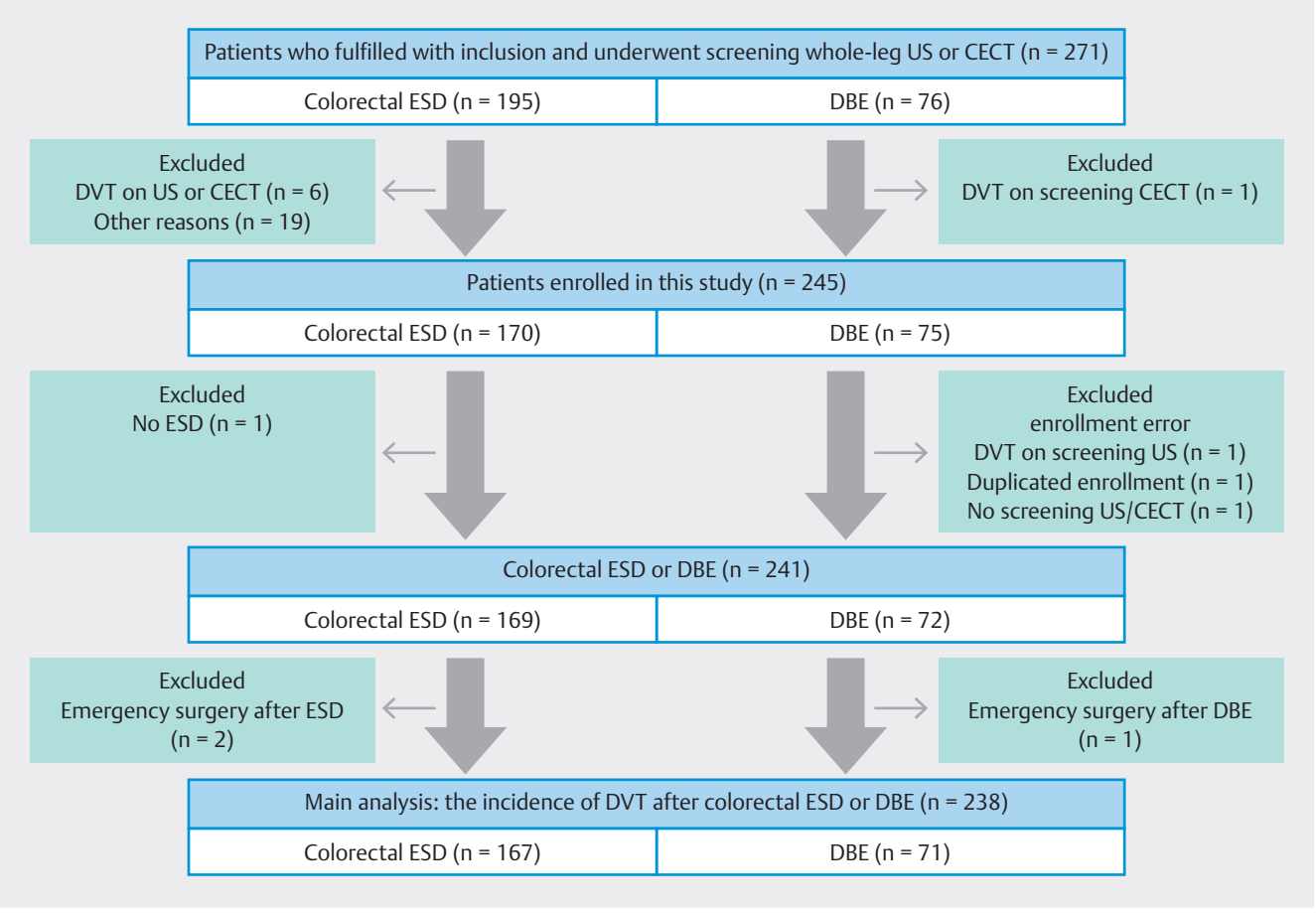
Incidence of DVT with or without GCS after colorectal ESD and DBE is shown in **Supplementary Table S3**. A patient with DVT following colorectal ESD used prophylactic GCS. No significant differences were found in incidence of DVT between patients using or not using GCS.

Risk factors for DVT before colorectal ESD or DBE

Risk factors of DVT before colorectal ESD or DBE were analyzed (▶ **Table 3**). Of the 271 patients who had undergone screening, 269 who received screening with whole-leg US or CECT were analyzed in this subset analysis. Among them, DVT was found in eight patients (3.0%) (pre-ESD, n = 6; pre-DBE, n = 2) (**Supplementary Fig. S1**). The proportion of female patients was significantly higher in the DVT group than in the non-DVT group ($P < 0.001$). Frequency of mental disorder was also significantly higher in the DVT group than in the non-DVT group ($P < 0.001$). No significant difference was found in Caprini score between the two groups, whereas the Padua score before ESD/DBE were significantly higher in the DVT group than in the non-DVT group ($P = 0.004$). All patients with DVT were observed without any specific medication therapy.

Discussion

To the best of our knowledge, this is the first multicenter, prospective study to determine incidence of DVT and PE following invasive endoscopic procedures including colorectal ESD and



▶ **Fig. 1** Consort diagram in the main analysis [21]. CECT, contrast-enhanced computed tomography; DBE, double-balloon endoscopy; DVT, deep vein thrombosis; ESD, endoscopic submucosal dissection; US, ultrasound.

DBE. Our findings demonstrated the low risk of DVT and PE even after highly invasive endoscopic procedures. Furthermore, screening with whole-leg US or CECT before colorectal ESD and DBE may be useful for detecting asymptomatic DVT. In addition, being female and presence of a mental disorder were significant risk factors for detection of DVT before colorectal ESD and DBE.

Several studies have reported a high incidence of DVT (10%-40%) after abdominal surgery [22, 23]. However, a few studies have focused on incidence of and risk factors for gastrointestinal endoscopy-related DVT or PE. Regarding ESD, only one study reported incidence of DVT, i. e., 10.0% after gastric ESD [20]. Although this was a prospective study, it analyzed a small number of cases (n = 60) at a single center, and background characteristics of the enrolled patients were unclear. A previous retrospective case-control study showed that patients with DVT or PE were more frequently subjected to gastrointestinal endoscopy within 3 months before disease onset than patients without DVT or PE (10.3% vs. 3.2%), suggesting that gastrointestinal endoscopy may enhance risk of DVT [24]. However, whether gastrointestinal endoscopy is a risk factor for DVT is still inconclusive because this study did not describe in detail baseline characteristics or presence or absence of other procedures.

In the present study, of the 238 patients who underwent colorectal ESD or DBE, only one had DVT after colorectal ESD. Thus, incidence of DVT was 0.4% in total, including 0.6% after colorectal ESD and 0% after DBE. These results suggest the extremely low risk of DVT after colorectal ESD and DBE when appropriate risk assessment is conducted before procedures. Furthermore, no significant difference was found in incidence of DVT between use and non-use of GCS to prevent DVT. This suggests that DVT prophylaxis such as GCS during invasive endoscopy might not be necessary for patients who are determined to be at low risk for DVT based on risk assessment before colorectal ESD or DBE.

Given that DVT/PE development following surgery can lead to fatal outcomes, preoperative assessment stratifying risk of DVT/PE is important. However, the significance of preoperative DVT screening using whole-leg US or CECT remains unclear for asymptomatic patients who undergo surgery. In addition, no study has reported risk factors for asymptomatic DVT before invasive endoscopy. In patients with gastric cancer, preoperative incidence of DVT with screening whole-leg US was 4.4% (7/160) [25]. Moreover, Tanizawa et al. showed that of 1140 patients with gastric cancer, 86 (7.5%) had DVT preoperatively [26]. In the present study, among 269 patients who underwent screening with whole-leg US or CECT before colorectal ESD and

▶ **Table 1** Background characteristics of patients.

	Colorectal ESD (n = 167)	DBE (n = 71)	Total (n = 238)
Median age (years) [range]	70 [34–89]	51 [20–88]	67 [20–89]
Sex (male/female)	101/66	52/19	153/85
Median BMI (kg/m2) [range]	22.8 [15.1–38.8]	22.2 [14.5–34]	22.6 [14.5–38.8]
The Methods of screening for DVT (US/CECT)	136/31	32/39	168/70
Comorbidity			
▪ Hypertension	58 (34.7%)	9 (12.6%)	67 (28.2%)
▪ Hyperlipidemia	27 (16.2%)	6 (8.4%)	33 (13.9%)
▪ Diabetes mellitus	28 (16.8%)	5 (7%)	33 (13.9%)
Medical history			
▪ Malignant tumor	8 (4.8%)	6 (8.4%)	14 (5.9%)
▪ Chronic lung disease*	5 (3%)	1 (1.4%)	6 (2.5%)
▪ Inflammatory bowel disease	3 (1.8%)	41(57.7%)	44 (18.5%)
▪ Collagen disease	3 (1.8%)	2 (2.8%)	5 (2.1%)
Family history of DVT or PE	1 (0.6%)	0	1 (0.4%)
Medication			
▪ Antiplatelet	10 (6%)	3 (4.2%)	13 (5.5%)
▪ Anticoagulant	6 (3.6%)	1 (1.4%)	7 (2.9%)
▪ Steroid	3 (1.8%)	2 (2.8%)	5 (2.1%)
▪ Oral contraceptives	1 (0.6%)	1 (1.4%)	2 (0.8%)
Primary disease			
▪ Colorectal cancer	104 (62.3%)	0	104 (43.7%)
– Tis	56 (33.5%)	0	56 (23.6%)
– T1	42 (25.1%)	0	42 (17.6%)
– T2	4 (2.4%)	0	4 (1.7%)
– Depth unknown	2 (1.2%)	0	2 (0.8%)
▪ Colorectal adenoma	53 (31.7%)	0	53 (22.3%)
▪ Sessile serrated lesion	2 (1.2%)	0	2 (0.8%)
▪ Neuroendocrine tumor	6 (3.6%)	0	6 (2.5%)
▪ Crohn disease	0	41 (57.7%)	41 (17.2%)
▪ Small intestine bleeding	0	4 (5.6%)	4 (1.7%)
▪ Small intestine tumor	0	12 (16.9%)	12 (5%)
▪ Others	2 (1.2%)	14 (19.7%)	16 (6.7%)
Endoscopy procedure time (min) [range]	110 [15–1020]	64 [6–130]	89 [6–1020]
Median Caprini score [range]	3 [0–6]	3 [0–6]	3 [0–6]
Median Padua score [range]	1 [0–3]	0 [0–4]	0 [0–4]

BMI, body mass index; CECT, contrast-enhanced computed tomography; DBE, double-balloon endoscopy; DVT, deep vein thrombosis; ESD, endoscopic submucosal dissection; PE, pulmonary embolism; PE, pulmonary embolism US, ultrasound.
*Not including asthma.

DBE, DVT was found in eight patients (3.0%) (pre-ESD, n = 6; pre-DBE, n = 2). Our findings revealed that DVT can be identified in not only patients with gastrointestinal cancer or IBD, who have been reported as at risk for DVT, but also patients categorized as having a low risk for DVT through preprocedure screening. Notably, being female and having a mental disorder were significant risk factors for DVT detection before colorectal ESD or DBE. Antipsychotic agent use was reported as a risk factor for DVT/PE [27], which is consistent with our results. Based on these findings, to prevent postoperative DVT, preoperative whole-leg US or CECT screening may be useful for identifying asymptomatic DVT, particularly in patients with these risk factors.

The Caprini and Padua scores have been used as models for DVT/PE risk assessment in patients undergoing surgery and patients hospitalized in Internal Medicine, respectively [4, 6, 7, 8]. However, no study has reported on how to assess risk for DVT before an invasive endoscopy. In the present study, the Padua score before ESD/DBE was significantly higher in the DVT group than in the non-DVT group (P = 0.004). In contrast, previous studies have reported that the Caprini score was more effective than the Padua score in identifying inpatients at risk for DVT/PE [28, 29]. Results of the present study and previous studies are

▶ **Table 2** Adverse events After ESD and DBE.

	Colorectal ESD (n = 167)	DBE (n = 71)	Total (n = 238)
DVT (n) (% [95%CI])	1 (0.6 [0–1.8])	0 (0% [0–0])	1 (0.4% [0–1.2])
PE (n) (% [95%CI])	0 (0% [0–0])	0 (0% [0–0])	0 (0% [0–0])
Mortality (% [95%CI])	0 (0% [0–0])	1 (1.4% [0–4.2])	1 (0.4% [0–1.2])
Other adverse events (% [95%CI])	14 (8.4% [4.2–12.6])	2 (2.8% [0–6.7])	16 (6.7% [3.5–9.9])
Delayed bleeding	3 (1.8% [0–3.8])	0 (0% [0–0])	3 (1.2% [0–2.7])
PECS	9 (5.4% [2.0–8.8])	0 (0% [0–0])	9 (3.8% [1.4–6.2])
Delayed perforation	2 (1.2% [0–2.8])	0 (0% [0–0])	2 (0.8% [0–2.0])
Pneumonia	0 (0% [0–0])	1 (1.4% [0–4.2])	1 (0.4% [0–1.2])
Others	0 (0% [0–0])	1 (1.4% [0–4.2])	1 (0.4% [0–1.2])
D-dimer (μg/mL) [range]	0.6 [0.03–5.76]	0.5 [0.1–8.2]	0.6 [0.03–8.2]
Wells score [range]	0 [–2–1]	0 [0–1]	0 [–2–1]

Rates of DVT, PE, mortality, and adverse event represent are 30 days after ESD or DBE. CI, confidence interval; DBE, double-balloon endoscopy; DVT, deep vein thrombosis; ESD, endoscopic submucosal dissection; PE, pulmonary embolism; PECS, post endoscopic submucosal dissection electrocoagulation syndrome.

▶ **Table 3** Characteristics of patients with DVT before colorectal ESD or DBE.

	Non-DVT (n = 261)	DVT (n = 8)	*P* value
Median age (years) [range]	67 [20–89]	73.5 [48–84]	0.069*
Sex (male/female)	169/92	0/8	< 0.001†
Methods of screening for DVT (US/CECT)	190/71	5/3	0.520†
ESD/DBE	189/72	6/2	> 0.999†
Primary disease			
Colorectal neoplasms	187 (71.6%)	6 (75%)	0.835†
Inflammatory bowel disease	42 (16.1%)	0	0.216†
▪ Small intestinal bleeding	4 (1.5%)	1 (12.5%)	0.141†
▪ Small intestinal tumor	12 (4.6%)	1 (12.5%)	0.330†
▪ Others	16 (6.2%)	0	> 0.999†
Family history of DVT or PE	1 (0.4%)	0	> 0.999†
Mental disorder	0	2 (25%)	< 0.001†
Oral contraceptives or hormone therapy	5 (1.9%)	1 (12.5%)	0.167†
Chemotherapy within 1 month	1 (0.4%)	1(12.5%)	0.058†
Median Caprini score [range]	3 [0–6]	3 [2–4]	0.838*
Median Padua score [range]	0 [0–4]	1 [1–1]	0.004*

CECT, contrast-enhanced computed tomography; DBE, double-balloon endoscopy; DVT, deep vein thrombosis; ESD, endoscopic submucosal dissection; PE, pulmonary embolism; US, ultrasound. *Mann-Whitney U test.
†Fisher's exact probability test.

different because of the differences in backgrounds of patients recruited in each study. Despite the significant difference in the Padua score between the non-DVT and DVT groups, the median score was 0 in the non-DVT group and 1 in the DVT group, and a tiny difference might be clinically meaningless. Moreover, the reported cutoff value of the Padua score was 4 for risk of venous thromboembolism in patients hospitalized in the Internal Medicine department [6]. Further research is needed to determine whether the Padua score is useful for screening pre-endoscopic DVT.

This study has some limitations. First, because incidence of DVT/ PE in the current study was much lower than expected,

the sample size may be low for finding the true incidence of DVT/PE after colorectal ESD and DBE. However, the most important and novel finding of this study is that incidence of DVT/PE after colorectal ESD and DBE is very low. Second, patients at high risk of DVT were excluded from this study because not employing prophylactic procedures for high-risk patients could present an ethical concern. Therefore, incidence of DVT and PE after invasive endoscopy in high-risk patients could not be evaluated. Because patients at high risk for DVT might have a higher risk for DVT and PE after invasive endoscopy than regular patients, screening with whole-leg US or CECT before endoscopy might be useful for early detection of DVT in the high-risk population.

Conclusions

In conclusion, risk of DVT and PE following highly invasive endoscopic procedures including colorectal ESD and DBE is extremely low, and patients without high-risk factors would not require DVT prophylaxis such as GCS. In contrast, screening with whole-leg US or CECT before colorectal ESD and DBE may be useful to identify DVT even in patients who are at low risk for DVT.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Clinical trial

UMIN Japan (http://www.umin.ac.jp/english/)
Registration number (trial ID): UMIN000041789
Type of Study: Multicenter, prospective cohort study

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