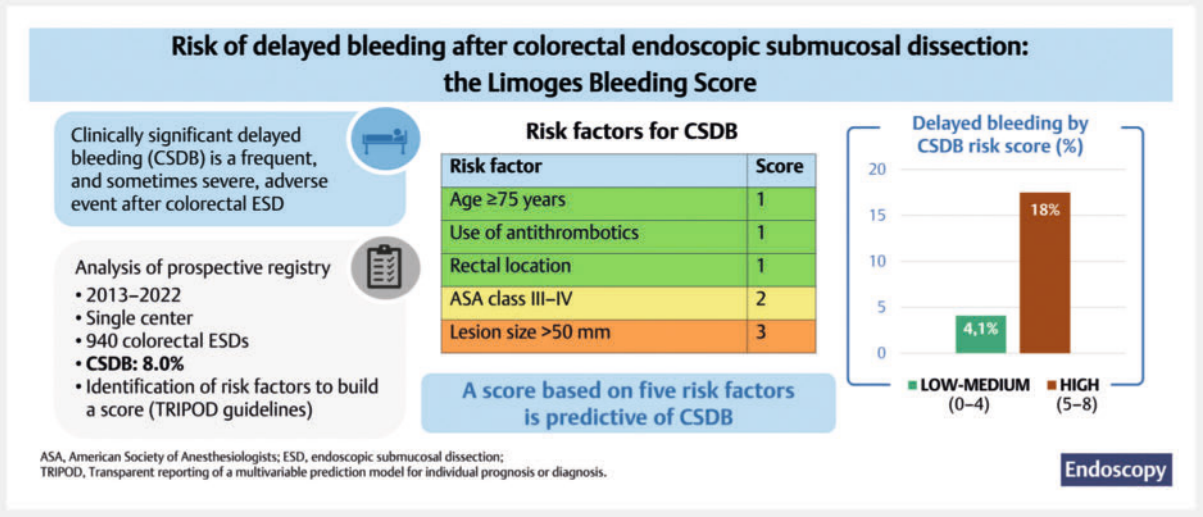
Thieme

Risk of delayed bleeding after colorectal endoscopic submucosal dissection: the Limoges Bleeding Score

GRAPHICAL ABSTRACT



Authors

Jérémie Albouys[1], Sheyla Montori Pina[2,3], Safia Boukechiche[4], Eduardo Albéniz[3,5], Guillaume Vidal[6], Romain Legros[6], Martin Dahan[6], Hugo Lepetit[6], Mathieu Pioche[7], Marion Schaefer[8], Sophie Geyl[6], Paul Carrier[6], Veronique Loustaud-Ratti[6], Virginie Valgueblasse[9], Clémentine Brule[6], Rebecca Rodrigues[6], Monica Enguita German[10,‡], Jérémie Jacques[6,‡]

Institutions

1 Hépato-gastro-entérology, Hopital Dupuytren, Limoges, France
2 Gastrointestinal Endoscopy Research Unit, Navarrabiomed, Hospital Universitario de Navarra (HUN), Universidad Pública de Navarra (UPNA), Pamplona, Spain
3 IdiSNA , Instituto de Investigación Sanitaria de Navarra, Pamplona, Spain
4 Hépato-gastro-entérology, Dupuytren Hospital, Limoges, France
5 Gastroenterology Department, Hospital Universitario de Navarra (HUN), Navarrabiomed, Universidad Pública de Navarra (UPNA), Pamplona, Spain
6 Hépato-gastro-entérologie, Hospital Dupuytren, Limoges, France
7 Endoscopy Unit, Edouard Herriot Hospital, Lyon, France
8 Hépato-gastro-entérology, Nancy University Hospital, Nancy, France
9 Hépato-gastro-entérology, Hospital Dupuytren, Limoges, France
10 Methodology Unit, Navarrabiomed, Hospital Universitario de Navarra (HUN), Universidad Pública de Navarra (UPNA), Pamplona, Spain

received 30.3.2023
accepted after revision 10.10.2023
accepted manuscript online 10.10.2023
published online 20.12.2023

Bibliography
Endoscopy 2024; 56: 110–118
DOI 10.1055/a-2189-0807
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Supplementary material
Supplementary material is available under https://doi.org/10.1055/a-2189-0807

Corresponding author
Jérémie Jacques, MD, PhD, Hospital Dupuytren, Hépato-gastro-entérologie, Avenue Martin Luther King 2, 87042 Limoges, France
jeremiejacques@gmail.com

‡ Contributed equally to the work.

ABSTRACT

Background Clinically significant delayed bleeding (CSDB) is a frequent, and sometimes severe, adverse event after colorectal endoscopic submucosal dissection (ESD). We evaluated risk factors of CSDB after colorectal ESD.

Methods We analyzed a prospective registry of 940 colorectal ESDs performed from 2013 to 2022. The incidence of bleeding was evaluated up to 30 days. Risk factors for delayed bleeding were evaluated by multivariate logistic regression. A Korean scoring model was tested, and a new risk-scoring model was developed and internally validated.

Results CSDB occurred in 75 patients (8.0%). The Korean score performed poorly in our cohort, with a receiver operating characteristic (ROC) curve of 0.567. In the multivariate analysis, risk factors were age ≥75 years (odds ratio [OR] 1.63; 95%CI 0.97–2.73; 1 point), use of antithrombotics (OR 1.72; 95%CI 1.01–2.94; 1 point), rectal location (OR 1.51; 95%CI 0.92–2.48; 1 point), size >50 mm (OR 3.67; 95%CI 2.02–7.14; 3 points), and American Society of Anesthesiologists (ASA) score of III or IV (OR 2.26; 95%CI 1.32–3.92; 2 points). The model showed fair calibration and good discrimination, with an area under the ROC curve of 0.751 (95%CI 0.690–0.812). The score was used to define two groups of patients, those with low–medium risk (0 to 4 points) and high risk (5 to 8 points) for CSDB (respective bleeding rates 4.1% and 17.5%).

Conclusion A score based on five simple and meaningful variables was predictive of CSDB.

Introduction

Endoscopic submucosal dissection (ESD) allows en bloc resection of large superficial colorectal lesions. ESD is the gold standard in Japan for this indication and is used increasingly frequently in the Western world because of its advantages in term of recurrence and oncological outcomes, compared with piecemeal endoscopic mucosal resection (EMR).

Clinically significant delayed bleeding (CSDB) is one of the most frequent complications after colorectal ESD (incidence 1%–9% [1,2,3,4]). Delayed bleeding increases the length of stay or induces new hospitalization, and can require blood transfusion or new hemostatic colonoscopy, thereby increasing costs. Few data are available on risk prediction and risk factors of post-ESD delayed bleeding; those that are available are from observational Asian studies. A large Korean study developed a risk prediction model based on three risk factors: use of antiplatelet agents, tumor size >30 mm, and location in the rectosigmoid area [5]. This enabled differentiation of a low risk group (1.9% bleeding rate) and a high risk group (4.9%). However, the study population did not reflect Western populations, with small lesions (median 28 mm), low rate of anticoagulant use (3%), and few comorbidities (9.2% American Society of Anesthesiologists [ASA] class III or IV) [5]. Moreover, planned hybrid ESD was performed in 27.7% of the cases.

We performed a large Western cohort study to identify risk factors of post-colorectal ESD bleeding, tested the Korean model in a Western population, and developed a new scoring system to accurately predict bleeding after colorectal ESD.

Methods

Study design

We performed a post hoc analysis of a single-center prospectively maintained consecutive database (Institutional Review Board approval #87RI20–0021_FECCo). The Ethics Committee of Limoges University Hospital approved the study, and a No Opposition to Data Use form (mandated by French legislation on RIPH3-type studies) was sent to all patients, who then provided written informed consent for the procedures.

The patients were contacted (face to face or by telephone) after 1 month for histopathological results and verification of complications (including post-ESD delayed bleeding). Details of the CSDB (date of bleeding, characteristics of the bleeding, clinical outcome of the bleeding) were collected retrospectively.

Definitions

Laterally spreading tumors (LSTs) were defined according to the Japanese definition as lesions larger than 10 mm with width greater than height and as granular or nongranular according to their morphology. Lesions that were larger than 10 mm (except sessile serrated lesions) with height greater than width were defined as protruding lesions.

CSDB was defined as a post-ESD bleeding event (hematochezia) needing a prolongation of hospitalization, readmission, new endoscopy (or surgery or angiography), or a blood transfusion, and occurring at least 6 hours after, and within 30 days after the procedure.

Periprocedural perforation was defined as exposure of the peritoneal space as a result of a muscular defect (Sidney classification IV–V [6]). R0 resection (histologically complete) was defined as neoplasia-free vertical and lateral resection margins on histology examination. Curative resection was defined according to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines [7] as R0 resection and the absence of high risk features on pathology (submucosal invasion >1000 µm, lymphovascular invasion, poor differentiation, significant budding [8]) and requiring secondary surgery.

Inclusion criteria

All epithelial colonic lesions treated by ESD were included prospectively and consecutively from January 2013 to March 2022. We stopped inclusion in March 2022 because our center was involved in a multicenter randomized trial of the efficacy of a self-assembling peptide in preventing post-colorectal ESD delayed

bleeding (NCT05031325). All adult patients (≥18 years)were included from the time at which ESD was initiated, irrespective of whether ESD was discontinued because of technical difficulty.

Exclusion criteria

Lesions exhibiting signs of deep submucosal carcinoma by optical examination (Japan Narrow-band imaging Expert Team [JNET] III, Sano IIIB, Kudo Vn, Colorectal Neoplasia Classification to Choose the Treatment [CONECCT] III) were excluded. Submucosal lesions, neuroendocrine tumors, and non-neoplastic lesions were also excluded. Patients with two lesions resected by ESD during the same colonoscopy were excluded because of the difficulty in identifying the lesion responsible for the delayed bleeding.

ESD procedure

In our unit we have performed ESD for all large (>25 mm) LSTs of the rectum since 2013 and for the colon since 2016.

ESD procedures were performed by five operators (J.J., R.L., M.D., J.A., and H.L.), all of whom had extensive experience of ESD in animal models prior to study commencement and who were trained in France.

Single-channel high-resolution endoscopes were used for ESD, with patients under general anesthesia. After detailed optical diagnosis confirming the resectability of the lesion, a complete or partial incision was performed using an endoscopic knife. The strategy for submucosal dissection was at the discretion of the operators, but our team has developed and frequently uses a double-clip traction strategy with clips and rubber bands.

VIO200 D and VIO 3 (since 2018) electrosurgical units (Erbe Elektromedizin, Tübingen, Germany) were used. EndoCUT I was used for mucosal incision, and swiftCOAG, preciseSECT, or endoCUT I was used for submucosal dissection. At the end of the procedure, visible vessels were systematically prophylactically coagulated using monopolar coagulation forceps. We did not include adrenalin in the injection solution and did not routinely close mucosal defects after ESD.

Owing to geographical constraints, many patients were hospitalized the day before the procedure. With the exception of patients with small lesions who lived less than 20 minutes from the hospital (outpatient treatment), all patients remained in hospital for 1 night after ESD. Only patients who experienced adverse events had prolonged hospitalization of more than 1 night after ESD.

Management of patients on anticoagulants or antiplatelets

Anticoagulants were managed according to the ESGE guidelines [9]. Warfarin was stopped 5 days before the procedure and restarted 1 day after the procedure. Heparin bridge therapy was performed only in cases at high risk of thromboembolic events. Direct oral anticoagulants were stopped 2 days before the procedure and restarted 2 days after the procedure. Regarding antiplatelet agents, aspirin was not stopped for the ESD procedures. All other antiplatelets were stopped 5 days before the procedure and replaced by aspirin monotherapy, which continued for 5 days after the procedure. On Day 6, aspirin was replaced with the previous antiplatelet agent.

Statistical analysis

The characteristics of patients were described using descriptive statistics, with frequency (percentage) for categorical variables, and mean (SD) or median (interquartile range) for continuous variables, depending on their distribution. The chi-squared test (or Fisher's exact test) was used for between-group comparisons, and a value of $P<0.05$ was taken to indicate statistical significance.

The incidence of CSDB was estimated using sample proportions with 95%CIs. We evaluated the performance of an Asian risk-scoring model for the prediction of delayed bleeding after colorectal ESD [5]. Model discrimination was described by the area under the receiver operating characteristic (ROC) curve (AUC) with 95%CIs. Univariate logistic regression models were used to analyze a set of variables considered to be related to delayed bleeding based on clinical criteria (sex, age, polyp size, ASA, polyp location, anticoagulant or antiplatelet use, en bloc resection, clip closure, chronic kidney disease, and high blood pressure); those variables with $P<0.2$ were included in a multivariate model and only those with $P<0.2$ in the multivariate model were retained to develop the CSDB risk model. The risk model odds ratios (ORs) and 95%CIs are presented.

We assessed model calibration using the Hosmer–Lemeshow goodness-of-fit test, together with calibration plots of predicted risk against actual risk for each decile. The model was validated internally using the resampling validation method for logistic models with 250 bootstrap re-samples, and the optimism-corrected ROC and discrimination slope (difference in mean of predictions between patients with or without CSDB) with their 95%CIs were estimated. Complementarily, leave-one-out cross-validation was performed to calculate the accuracy of the model (measured as the percentage of corrected classified patients) when the probability threshold was the observed incidence of CSDB. We developed a risk score by assigning a weight to each predictor based on the β parameter from the multivariate final model. These β coefficients were divided by the smallest β coefficient and rounded to the nearest integer as described previously [10, 11, 12, 13]. We divided the 9-point score into two risk categories for simple interpretation in a clinical setting using the Youden index or the incidence of CSDB (giving similar results). The weighted averaged probabilities of CSDB were estimated for each risk group. Finally, a decision curve was plotted relating the net benefit of using the score compared with the treat-all and treat-none approaches for a range of plausible risk thresholds.

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) v. 25.0 (IBM Corp., Armonk, New York, USA) and R v. 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria). This study complies with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis guidelines (see the online-only Supplementary material) [14].

Results

General characteristics of the patients and lesions

A total of 940 ESDs of large colorectal lesions were performed consecutively in 940 patients (▶ **Fig. 1, Table 1**). There were 514 male patients (54.7%), and the mean age of the cohort was 69 years (SD 10.1 years; range 63–75 years). The ASA score was III or IV in 340 patients (36.2%). A total of 267 patients (28.4%) had some form of anticoagulant/antiplatelet therapy prescribed. The mean lesion size was 60.6 (SD 25.4) mm (range 45–70 mm). Lesion location was the rectum in 369 patients (39.3%) and the proximal colon in 339 patients (36.1%).

ESD characteristics

The resection was en bloc in 899 patients (95.6%), R0 in 798 (84.9%), and curative in 755 (80.3%) (▶ **Table 2**). Lateral margins were free of adenoma for 820 lesions (87.2%) and deep margins were free of cancer in 899 lesions (95.6%). The mean duration of the procedure was 85.8 (SD 71.5) minutes (range 6–570 min). The mean speed of the procedure was 35.7 (SD 19) mm^2/min. After ESD, 111 defects (11.8%) were closed completely with clips.

Adverse events

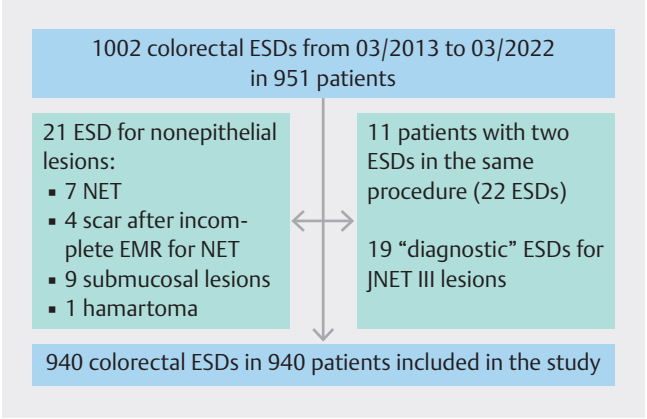
CSDB occurred in 75 patients (8.0%; 95%CI 6.36–9.95) and perforation in 95 patients (10.1%). A blood transfusion was necessary in 12 patients (1.3%). Significant bleeding led to prolonged hospitalization in 19 patients (2.0%) and new admission in 54 patients (5.7%). Overall, 40 patients (4.3%) required new endoscopic treatment for hemostasis, and 72 patients (7.7%) needed secondary surgery (4 [0.4%] for post-procedural perforation, 1 [0.1%] for appendicitis, 13 [1.4%] for ESD failure, and 54 [5.7%] for high risk noncurative adenocarcinoma) (▶ **Table 2**). One patient (0.1%) died 1 day post-procedure of a sudden unexplained cardiac arrest while returning home.

Performance of the Asian model

The scores of the independent variables according to the Asian predictive model are described in Seo et al. [5]. **Table 1s** shows a univariate comparison using the Asian model CSDB predictors in the current Limoges cohort. Two of the CSDB predictors of the Asian model (tumor size and antiplatelet agents) were not associated with CSDB in the Limoges cohort. When the Asian score model was applied to the Limoges cohort, an AUC of 0.567 (95%CI 0.508–0.626) was obtained, suggesting low discriminative ability (AUC <0.70).

Development and performance of our model

▶ **Table 3** shows univariate and multivariate analyses of factors independently predictive of CSDB after ESD. The factors found to be predictive in the final model (▶ **Table 4**) were age ≥75 years (OR 1.63; 95%CI 0.97–2.73; $P=0.06$), antithrombotic agent (anticoagulant or antiplatelet) use during ESD (OR 1.72; 95%CI 1.01–2.94; $P=0.046$), location in the rectum (OR 1.51; 95%CI 0.92–2.48; $P=0.10$), ASA class III or IV (OR 2.26; 95%CI 1.32–3.92; $P=0.003$), and lesion size >50 mm (OR 3.67; 95%CI 2.02–7.14; $P<0.001$).



▶ **Fig. 1** Flow chart of the study. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; JNET, Japan Narrow-band imaging Expert Team; NET, neuroendocrine tumor.

▶ **Table 1** Patient characteristics.

Characteristic	Total[1]	No CSDB[1]	CSDB[1]	*P* value[2]
Patients, n (%)	940	865 (92.0)	75 (8.0)	
Demographic characteristics				
Sex, n (%)				
▪ Male	514 (54.7)	474 (92.2)	40 (7.8)	0.81
▪ Female	426 (45.3)	391 (91.8)	35 (8.2)	
Age, mean (SD), years	69 (10)	69 (10)	73 (10)	<0.001
▪ <75 years, n (%)	668 (71.1)	630 (94.3)	38 (5.7)	<0.001
▪ ≥75 years, n (%)	272 (28.9)	235 (86.4)	37 (13.6)	
Clinical characteristics				
ASA classification, n (%)				
▪ I–II	600 (63.8)	572 (95.3)	28 (4.7)	<0.001
▪ III–IV	340 (36.2)	293 (86.2)	47 (13.8)	
Antiplatelet/anticoagulant therapy, n (%)				
▪ Any therapy	267 (28.4)	231 (86.5)	36 (13.5)	<0.001
▪ Anticoagulant	97 (10.3)	76 (78.4)	21 (21.6)	<0.001
▪ Antiplatelet	182 (19.4)	161 (88.5)	21 (11.5)	0.07
▪ Chronic kidney disease, n (%)	59 (6.3)	50 (84.7)	9 (15.3)	0.04[3]

▶ **Table 1** (Continuation)

Characteristic	Total[1]	No CSDB[1]	CSDB[1]	*P* value[2]
▪ High blood pressure, n (%)	458 (48.7)	411 (89.7)	47 (10.3)	0.02
Location, n (%)				
▪ Rectum	369 (39.3)	331 (89.7)	38 (10.3)	0.07
▪ Distal	165 (17.6)	153 (92.7)	12 (7.3)	
▪ Transverse	67 (7.1)	66 (98.5)	1 (1.5)	
▪ Proximal	339 (36.1)	315 (92.9)	24 (7.1)	
Lesion size, mean (SD), mm	61 (25)	59 (23)	82 (37)	<0.001
▪ ≤50 mm, n (%)	412 (43.8)	399 (96.8)	13 (3.2)	<0.001
▪ >50 mm, n (%)	528 (56.2)	466 (88.3)	62 (11.7)	
Type of lesion, n (%)				
▪ Protruding lesion	138 (14.7)	130 (94.2)	8 (5.8)	0.02
▪ Granular LST	613 (65.2)	552 (90.0)	61 (10.0)	
▪ Nongranular LST	167 (17.8)	161 (96.4)	6 (3.6)	
▪ Others	22 (2.3)	22 (100)	0 (0)	
Pathological analysis, n (%)				
▪ Traditional serrated adenoma	1 (0.1)	1 (100)	0 (0)	0.87
▪ LGD	409 (43.5)	382 (93.4)	27 (6.6)	
▪ HGD	225 (23.9)	202 (89.8)	23 (10.2)	
▪ Intramucosal cancer	187 (19.9)	171 (91.4)	16 (8.6)	
▪ Superficial sm cancer	42 (4.5)	38 (90.5)	4 (9.5)	
▪ Deep sm cancer	43 (4.6)	40 (93.0)	3 (7.0)	
▪ T2	13 (1.4)	12 (92.3)	1 (7.7)	
▪ Sessile serrated adenoma	20 (2.1)	19 (95.0)	1 (5.0)	

CSDB, clinically significant delayed bleeding; ASA, American Society of Anesthesiologists; LST, laterally spreading tumor; LGD, low grade dysplasia; HGD, high grade dysplasia;
[1]Information in the column "Total" is presented as frequencies (%) by column whereas, information in "No CSDB" and "CSDB" columns is presented as frequencies (%) by row. [2]*P* <0.05 was considered significant. [3]Fisher's exact test.

▶ **Table 2** Procedure characteristics.

Characteristic	Total[1]	No CSDB[1]	CSDB[1]	*P* value[2]
ESD characteristics				
Resection, n (%)				
▪ En bloc	899 (95.6)	828 (92.1)	71 (7.9)	0.56[3]
▪ R0	798 (84.9)	737 (92.4)	61 (7.6)	0.47
▪ Curative	755 (80.3)	698 (92.5)	57 (7.5)	0.41
▪ Procedure duration, mean (SD), minutes[4]	86 (71)	82 (66)	133 (109)	<0.001
▪ Complete closure, n (%)	111 (11.8)	105 (94.6)	6 (5.4)	0.38
Adverse events, n (%)				
Perforation				
▪ No	845 (89.9)	781 (92.4)	64 (7.6)	0.24
▪ Yes	95 (10.1)	84 (88.4)	11 (11.6)	
▪ Transfusion	12 (1.3)	1 (8.3)	11 (91.7)	<0.001[3]
▪ New endoscopy for bleeding	40 (4.3)	0 (0)	40 (100)	<0.001[3]
▪ Increased length of stay due to bleeding	19 (2.0)	0 (0)	19 (100)	<0.001[3]
Secondary surgery and reason	72 (7.7)	68 (94.4)	4 (5.6)	0.57
▪ Pathological analysis	54 (5.7)	50 (92.6)	4 (7.4)	0.80
▪ ESD failure	13 (1.4)	13 (100)	0 (0)	
▪ Postprocedural perforation	4 (0.4)	4 (100)	0 (0)	
▪ Postprocedural appendicitis	1 (0.1)	1 (100)	0 (0)	

CSDB, clinically significant delayed bleeding; ESD, endoscopic submucosal dissection.
[1]Information in the column "Total" is presented as frequencies (%) by column whereas, information in "No CSDB" and "CSDB" columns is presented as frequencies (%) by row.
[2]*P* <0.05 was considered significant.
[3]Fisher's exact test.
[4]Data available for 916 patients (97.4%).

▶ **Table 3** Univariate and multivariate analyses of factors independently predictive of clinically significant delayed bleeding after endoscopic submucosal dissection (N = 940).

Characteristic	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Female sex	1.06 (0.66–1.70)	0.81		
Age ≥75 years	2.61 (1.62–4.21)	<0.001	1.60 (0.94–2.69)	0.08
Size >50 mm	4.08 (2.29–7.86)	<0.001	3.67 (2.03–7.15)	<0.001
ASA III–IV (vs. ASA I–II)	3.28 (2.02–5.40)	<0.001	2.20 (1.27–3.86)	0.01
Rectal location	1.66 (1.03–2.66)	0.04	1.52 (0.93–2.50)	0.10
Proximal location	0.82 (0.49–1.35)	0.44		
Anticoagulant/antiplatelet use	2.53 (1.57–4.09)	<0.001	1.67 (0.96–2.89)	0.07
Chronic kidney disease	2.22 (0.99–4.52)	0.05	1.09 (0.46–2.37)	0.83
High blood pressure	1.85 (1.15–3.05)	0.01	1.12 (0.65–1.95)	0.69
Not en bloc resection	1.26 (0.37–3.26)	0.68		
Not complete closure	1.59 (0.73–4.18)	0.26		

OR, odds ratio; ASA, American Society of Anesthesiologists.

▶ **Table 4** Final clinically significant delayed bleeding score after endoscopic submucosal dissection

Predictors	Delayed bleeding (final model)		Score
	OR (95%CI)	*P* value[1]	
(Intercept)	0.01 (0.01–0.03)	<0.001	
Age ≥75 years	1.63 (0.97–2.73)	0.06	1
Size >50 mm	3.67 (2.02–7.14)	<0.001	3
ASA III–IV	2.26 (1.32–3.92)	0.003	2
Location in rectum	1.51 (0.92–2.48)	0.10	1
Anticoagulants/ antiplatelet	1.72 (1.01–2.94)	0.046	1

OR, odds ratio.
[1] *P* <0.05 was considered significant.

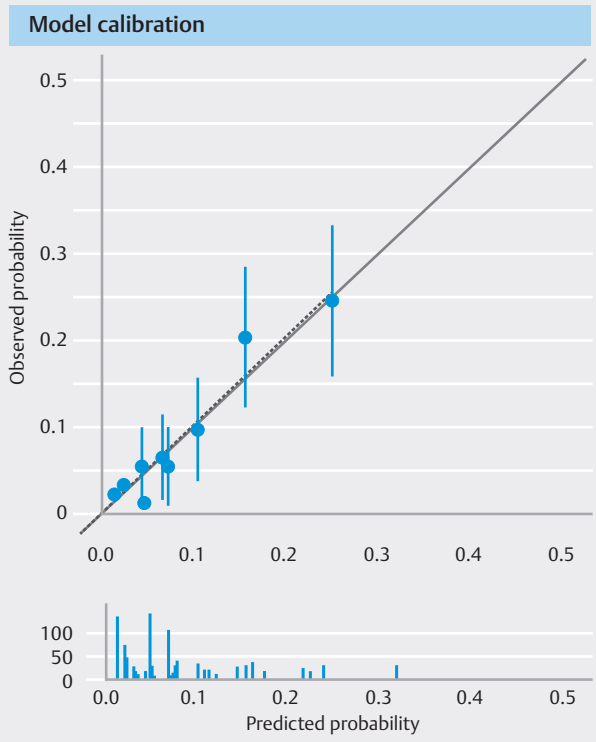
The multivariate model had an AUC of 0.751 (95%CI 0.690–0.812), showing good discrimination (**Fig. 1s**). The bias-corrected index after internal bootstrap validation was 0.739 (95%CI 0.671–0.805). Calibration of the model was fair according to calibration curves (▶ **Fig. 2**) and to the Hosmer–Lemeshow test results (chi-squared 7.652; *P* = 0.47). The discrimination slope (difference in average predictions for those with and without the outcome) was 0.07 (95%CI 0.04–0.13). Additionally, leave-one-out cross-validation was performed to calculate the accuracy of the model (measured as the percentage of corrected classified patients), obtaining an accuracy equal to 74.2%.

The constructed CSDB score ranged from 0 (lowest risk) to 8 (highest risk) (**Table 2s**). The formula and illustration of the CSDB score and risk calculator are shown in **Table 3s**. The probability of CSDB according to the score is shown in ▶ **Table 5**. The Youden index and the observed incidence of CSDB were used to categorize the score into two risk groups (similar for both approaches), those with low–medium CSDB risk (0 to 4 points), and those with high CSDB risk (5 to 8 points), with respective bleeding rates of 4.1% and 17.5%. Applied to our population, 269 patients (28.6%) were in the high risk category (**Table 4s**). The decision curve showed the net benefit, across a range of cutoffs, of using the score compared with the treat-all and treat-none approaches (**Fig. 2s**). The net benefit for the 9% delayed bleeding risk threshold calculated using the Youden index (corresponding to a 1:10 harm:benefit ratio) was 0.393. When a 14% risk threshold was used (corresponding to a 1:6 harm:benefit ratio), the net benefit was equal to 0.252. In this more restrictive situation, the high risk group would include only patients with 7–8 points in the score (corresponding to 20% of the sample and a weighted average risk of delayed bleeding equal to 20.3%).

Discussion

CSDB occurred in 8% of patients in this large series of colorectal ESD cases. Rectal location, size >50 mm, ASA score III/IV, treatment with antithrombotic agents, and age >75 years were significant risk factors in a multivariate analysis, and these factors were used to develop a score to predict CSDB. The score was based on pre-procedural data, and the scoring system is easy to use. The risk of CSDB increased as the risk score increased, with a 50% increase in risk for each 1-point increase in score.

A CSDB prediction model has been developed previously in Korea [5]. This score was not predictive of CSDB in our cohort (AUC 0.567, compared with AUC 0.751 for our score). Differences in the lesions and patients included in the Asian study are



▶ **Fig. 2** Calibration curve for the multivariate regression.

▶ **Table 5** Probability of clinically significant delayed bleeding according to score.

Score	Delayed bleeding risk, % (95%CI)	Delayed bleeding risk category, %
0	1.3 (0.7–2.5)	Low–medium risk: 4.1
1	2.0 (1.2–3.5)	
2	3.1 (2.0–4.8)	
3	4.7 (3.4–6.6)	
4	7.2 (5.6–9.3)	
5	10.7 (8.6–13.3)	High risk: 17.5
6	15.8 (12.5–19.8)	
7	22.7 (17.2–29.3)	
8	31.3 (22.6–41.6)	

likely to explain the ineffectiveness of this model in our population. Indeed, the median lesion size was 28 mm (60 mm in our cohort), only 2.3% of polyps were <30 mm (none of which bled), only 3% of the population were on anticoagulants (10% in our cohort), and patients had fewer comorbidities (9.2% ASA III/IV vs. 36.2% ASA III/IV in our cohort). Moreover, 27.7% of the lesions were resected in a planned hybrid ESD procedure using a snare, which is more like an EMR than an ESD. This is important because our findings confirm a difference in bleeding risk factors between these two resection strategies – rectal location for ESD and right colon location for EMR [11, 15]. This difference of included lesions also explains the higher CSDB rate (8%) in the current study, which is similar to that in our recent prospective randomized trial of ESD and piecemeal EMR for large LSTs of the colon [16]. By contrast to observational retrospective studies, Asian randomized studies have reported a higher CSDB rate, similar to that found in the current study [17].

In our cohort, patients with CSDB were significantly older, with more comorbidity, and larger lesions more frequently located in the rectum, and were more frequently treated with antithrombotic agents compared with patients without CSDB. However, no difference was identified according to the closure rate between patients with and without CSDB.

Rectal location has previously been described as a risk factor in several Asian studies [1, 5, 18, 19, 20]. Right colon location is an important risk factor for post-EMR bleeding [11, 15, 21]. This discrepancy between the two techniques is difficult to explain but suggests a different pathophysiology of post-resection bleeding between EMR and ESD. This is important and precludes extrapolation of the post-EMR bleeding risk factors to colorectal ESD procedures.

Lesion size was the most important risk factor, and size is a risk factor for CSDB after both ESD and EMR [1, 5, 11, 15, 18, 21], which is likely to be because a larger lesion will leave a larger scar, meaning a greater number of injured submucosal vessels.

Other post-ESD CSDB risk factors include comorbidities (ASA III/IV), anticoagulants, and age. Further larger studies should focus on CSDB risk according to type of anticoagulant (vitamin K antagonist, direct oral anticoagulants) or type of antiplatelet. We were unable to perform such an analysis because separating patients according to anticoagulant or antiplatelet would have weakened the statistical power of the analysis.

The strengths of this study are the use of a prospective database with very few missing data, and in-person or telephone contact to evaluate delayed bleeding. Additionally, the nonuse of new preventive hemostatic strategies (gels or powders) prevented important bias of contamination of our results.

The main limitations of the study are the single-center design, the limited number of cases in the sample (75 CSDB cases), and the absence of external validation of the model. This means that the results need to be independently validated in Western and Asian populations. Moreover, the study was conducted over a long period (10 years); nevertheless, bleeding prevention, risk factors, and incidence have not changed much during this period. Stopping enrollment at the outset of a randomized study evaluating a new hemostatic agent prevented the introduction of bias into the results. Additionally, we did not analyze the importance of periprocedural bleeding as a potential risk factor of CSDB. We also did not analyze the number of times the coagulation forceps were used as a risk factor for bleeding; however, as the aim was to assess the risk of bleeding prior to the procedure, we focused on pre-procedure risk factors. Ideally, a greater number of events would have increased the power of our analysis and the precision of our estimates;

nevertheless, with 75 events, this study is the study with the largest number of events on this topic to date and the first from Western countries.

The 12% clip closure rate could be considered a limitation. However, there was no difference in CSDB rate between the clip closure and nonclosure groups. Clip closure reduced the rate of right colon bleeding after large EMRs in three high-level randomized controlled trials [22, 23, 24]. Clip closure after right colon EMR was effective only if the defect was completely closed. However, data on the effectiveness of clip closure after colorectal ESD to prevent CSDB are scarce, retrospective, and of low quality. The different risk factors for CSDB after ESD and EMR (i. e. rectum [5] and right colon locations, respectively) indicate that the two procedures must be considered distinct in terms of post-procedural CSDB. Therefore, the results for EMRs may not be directly applicable to ESDs. The complete clip closure rate was only 70% in a recent randomized trial of clip closure to prevent CSDB after EMR of lesions with mean size 30 mm [23]. In the current study, because more than 50% of the lesions were larger than 50 mm, systematic clip closure would have been impossible. However, new suturing systems are becoming increasingly available [25, 26], and our data will enable the selection of patients at high risk of CSDB, which could be prevented by closing the scar.

What is the potential impact of such a prediction model?

First, because the model was based on pre-procedural data, it could provide individualized information on the risk of CSDB and optimize the care of patients undergoing colorectal ESD. The score enabled identification of lesions at low–medium risk (CSDB score 0–4; 4.1% risk of bleeding) and high risk (CSDB score 5–8; 17.5% risk of bleeding) of delayed bleeding. This categorization is important from a clinical point of view as patients in the high-risk group might need close monitoring and use of prevention strategies. Ingestion of antithrombotic agents could be influenced by delaying their resumption in high risk patients. In this sense, the decision curve showed a higher net benefit of using the score compared with a treat-all or treat-none approach across a range of plausible cutoff thresholds, suggesting potential clinical usefulness.

The effect on CSDB of new topical agents and closing systems is not supported by a high level of evidence [25, 26, 27, 28]. Our results will help the design of a randomized trial investigating the efficacy of these new devices, one that enrolls patients at high risk of CSDB. Concerning the low–medium risk population, specific data on this population including cost-effectiveness analysis is mandatory to identify the best strategy in this subgroup of patients.

Moreover, after being independently validated, our prediction model should be used in further studies of CSDB risk, to enable comparison of post-ESD CSDB rates.

Finally, we created an excel calculator allowing individual estimation of the CSDB before the procedure to provide individual information and optimal management organization. (The calculator is available from the author on request.)

In conclusion, lesion size >50 mm, antithrombotic use, age >75 years, ASA score III/IV, and rectal location were independent risk factors for CSDB after ESD. Our easy-to-use risk score based on these factors enabled prediction of the risk of CSDB after colorectal ESD. After being independently validated, the CSDB score will allow provision of pre-procedural individualized information to patients, optimization of their care, and identification of patients who will benefit from new post-ESD CSDB prevention strategies.

Conflict of Interest

J. Jacques has received consulting and training fees from Boston scientific, Olympus, Fujifilm, Pentax., Cook, Janssen and Abbvie He has received Invitation to congresses from Janssen, Abbvie, alphasigma, Norgine and Amgen.

Clinical trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT04592003 | Type of study: Prospective cohort study

References

[1] Saito H, Igarashi K, Hirasawa D et al. The risks and characteristics of the delayed bleeding after endoscopic submucosal dissection for early gastric carcinoma in cases with anticoagulants. Scand J Gastroenterol 2020; 55: 1253–1260

[2] Boda K, Oka S, Tanaka S et al. Clinical outcomes of endoscopic submucosal dissection for colorectal tumors: a large multicenter retrospective study from the Hiroshima GI Endoscopy Research Group. Gastrointest Endosc 2018; 87: 714–722

[3] Bordillon P, Pioche M, Wallenhorst T et al. Double-clip traction for colonic endoscopic submucosal dissection: a multicenter study of 599 consecutive cases (with video). Gastrointest Endosc 2021; 94: 333–343

[4] Probst A, Ebigbo A, Märkl B et al. Endoscopic submucosal dissection for early rectal neoplasia: experience from a European center. Endoscopy 2017; 49: 222–232

[5] Seo M, Song EM, Cho JW et al. A risk-scoring model for the prediction of delayed bleeding after colorectal endoscopic submucosal dissection. Gastrointest Endosc 2019; 89: 990–998.e2

[6] Burgess NG, Bassan MS, McLeod D et al. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. Gut 2017; 66: 1779–1789 doi:10.1136/gutjnl-2015-309848

[7] Pimentel-Nunes P, Libânio D, Bastiaansen BAJ et al. Endoscopic submucosal dissection for superficial gastrointestinal lesions: European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2022. Endoscopy 2022; 54: 591–622 doi:10.1055/a-1811-7025

[8] Lugli A, Kirsch R, Ajioka Y et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol 2017; 30: 1299–1311 doi:10.1038/modpathol.2017.46

[9] Veitch AM, Radaelli F, Alikhan R et al. Endoscopy in patients on antiplatelet or anticoagulant therapy: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guideline update. Endoscopy 2021; 53: 947–969 doi:10.1136/gutjnl-2021-325184

[10] Steyerberg EW. Statistical models for prediction. In: Steyerberg EW (eds.) Clinical prediction models: a practical approach to development, validation, and updating. New York, NY: Springer; 2009: 53–82

[11] Albéniz E, Fraile M, Ibáñez B et al. A scoring system to determine risk of delayed bleeding after endoscopic mucosal resection of large colorectal lesions. Clin Gastroenterol Hepatol 2016; 14: 1140–1147 doi:10.1016/j.cgh.2016.03.021

[12] Conti Bellocchi MC, Crinò SF, Fioravante M et al. Development and validation of a risk score for prediction of clinical success after duodenal stenting for malignant gastric outlet obstruction. Expert Rev Gastroenterol Hepatol 2022; 16: 393–399

[13] Moons KGM, Harrell FE, Steyerberg EW. Should scoring rules be based on odds ratios or regression coefficients? J Clin Epidemiol 2002; 55: 1054–1055 doi:10.1016/s0895-4356(02)00453-5

[14] Collins GS, Reitsma JB, Altman DG et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015; 350: g7594 doi:10.1136/bmj.g7594

[15] Burgess NG, Metz AJ, Williams SJ et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. Clin Gastroenterol Hepatol 2014; 12: 651–661.e1–3

[16] Jacques J, Wallenhorst T, Chevaux J-B et al. Endoscopic submucosal dissection (ESD) versus piece-meal endoscopic mucosal resection (PM-EMR) for large laterally spreading lesions: French randomized controlled trial Resect-Colon. Gastrointestinal Endoscopy 2022; 95: AB138

[17] Kobara H, Tada N, Fujihara S et al. Clinical and technical outcomes of endoscopic closure of postendoscopic submucosal dissection defects: literature review over one decade. Dig Endosc 2023; 35: 216–231 doi:10.1111/den.14397

[18] Ogasawara N, Yoshimine T, Noda H et al. Clinical risk factors for delayed bleeding after endoscopic submucosal dissection for colorectal tumors in Japanese patients. Eur J Gastroenterol Hepatol 2016; 28: 1407–1414 doi:10.1097/MEG.0000000000000723

[19] Suzuki S, Chino A, Kishihara T et al. Risk factors for bleeding after endoscopic submucosal dissection of colorectal neoplasms. World J Gastroenterol 2014; 20: 1839–1845 doi:10.3748/wjg.v20.i7.1839

[20] Terasaki M, Tanaka S, Shigita K et al. Risk factors for delayed bleeding after endoscopic submucosal dissection for colorectal neoplasms. Int J Colorectal Dis 2014; 29: 877–882 doi:10.1007/s00384-014-1901-3

[21] Albéniz E, Gimeno-García AZ, Fraile M et al. Clinical validation of risk scoring systems to predict risk of delayed bleeding after EMR of large colorectal lesions. Gastrointest Endosc 2020; 91: 868–878.e3

[22] Gupta S, Sidhu M, Shahidi N et al. Effect of prophylactic endoscopic clip placement on clinically significant post-endoscopic mucosal resection bleeding in the right colon: a single-centre, randomised controlled trial. Lancet Gastroenterol Hepatol 2022; 7: 152–160 doi:10.1016/S2468-1253(21)00384-8

[23] Pohl H, Grimm IS, Moyer MT et al. Clip closure prevents bleeding after endoscopic resection of large colon polyps in a randomized trial. Gastroenterology 2019; 157: 977–984.e3

[24] Albéniz E, Álvarez MA, Espinós JC et al. Clip closure after resection of large colorectal lesions with substantial risk of bleeding. Gastroenterology 2019; 157: 1213–1221.e4

[25] Bi D, Zhang LY, Alqaisieh M et al. Novel through-the-scope suture closure of colonic endoscopic mucosal resection defects. Gastrointest Endosc 2023: doi:10.1016/j.gie.2023.02.031

[26] Abe S, Saito Y, Tanaka Y et al. A novel endoscopic hand-suturing technique for defect closure after colorectal endoscopic submucosal dissection: a pilot study. Endoscopy 2020; 52: 780–785 doi:10.1055/a-1120-8533

[27] Farha J, Ramberan H, Aihara H et al. A novel through-the-scope helix tack-and-suture device for mucosal defect closure following colorectal endoscopic submucosal dissection: a multicenter study. Endoscopy 2023: doi:10.1055/a-1970-5528

[28] Jung DH, Moon HS, Park CH et al. Polysaccharide hemostatic powder to prevent bleeding after endoscopic submucosal dissection in high risk patients: a randomized controlled trial. Endoscopy 2021; 53: 994–1002 doi:10.1055/a-1312-9420