Risk factors of major intraoperative bleeding and postoperative bleeding associated with endoscopic submucosal dissection for gastric neoplasms

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Abstract

Background: Endoscopic resection bleeding (ERB) classification was proposed by the authors' team to evaluate the severity of intraoperative bleeding (IB) during endoscopic submucosal dissection (ESD). This study aimed to evaluate the application of ERB classification and to analyze the risk factors of major IB (MIB) and postoperative bleeding (PB) associated with ESD for gastric neoplastic lesions.

Methods: We retrospectively enrolled a total of 1334 patients who underwent ESD between November 2006 and September 2019 at The First Medical Center of Chinese People's Liberation Army General Hospital. All patients were divided into the non-MIB group (including ERB-0, ERB-controlled 1 [ERB-c1], and ERB-c2) and the MIB group (including ERB-c3 and ERB-uncontrolled [ERB-unc]) according to the ERB classification. Risk factors of major MIB and risk factors of PB were analyzed using a logistic regression model.

Results: Among the 1334 patients, 773 (57.95%) had ERB-0, 477 (35.76%) had ERB-c1, 77 (5.77%) had ERB-c2, 7 (0.52%) had ERB-c3, and no patients had ERB-unc. The rate of PB in patients with IB classifications of ERB-0, ERB-c1, ERB-c2, and ERB-c3 were 2.20% (17/773), 3.35% (16/477), 9.09% (7/77), and 2/7, respectively. In multivariate analysis, proximal location (odds ratio [OR]: 1.488; 95% confidence interval [CI]: 1.045–3.645; $P = 0.047$) was the only significant risk factor of MIB. Chronic kidney disease (CKD) (OR: 7.844; 95% CI: 1.637–37.583; $P = 0.010$) and MIB (ERB-c3) (OR: 13.932; 95% CI: 2.585–74.794; $P = 0.002$) were independent risk factors of PB.

Conclusions: Proximal location of lesions was a significant risk factor of MIB. Additionally, CKD and MIB (ERB-c3) were independent risk factors of PB. More attention should be paid to these high-risk patients for MIB and PB.

Keywords: Endoscopic resection bleeding classification; Endoscopic submucosal dissection; Gastric neoplasms

Introduction

Endoscopic submucosal dissection (ESD) has been widely accepted as the standard treatment for gastric neoplastic lesions with no evidence of lymphovascular invasion, including intraepithelial neoplasia and early gastric cancer (EGC). Although ESD enables a higher *en bloc* resection rate, it demands higher technical skills and a longer procedure time (PT) compared with the traditional endoscopic mucosal resection. Accordingly, ESD is accompanied by a relatively high risk of procedure-related adverse events, such as bleeding.[1,2] According to the previous studies, rates of intraoperative bleeding (IB) can range from 2.9% to 45.1%.[3,4] However, the standards to evaluate the IB rate vary in different studies, causing major discrepancies and making the results incomparable. Although one study reported a grading method to define the degree of IB according to the amount of bleeding and hemostatic time,[5] it is much more difficult to accurately evaluate the amount of bleeding during endoscopic operations than during surgical operations, and the operator's experience makes a difference in controlling IB. To overcome these problems, Linghu[6] proposed a new classification of IB, termed the endoscopic resection bleeding (ERB) classification.

Previous studies have reported that the risk factors for IB are patient age, lesion location, the presence of gastric

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001840

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Chinese Medical Journal 2022;135(3)

Received: 04-03-2021; **Online:** 06-01-2022 **Edited by:** Yuanyuan Ji

malignancy, prolonged PT, and endoscopist's experience.[4,5,7,8] However, those studies only defined the risk factors for overall or subjectively classified IB. Therefore, this study divided patients into two groups: the non-major IB (NMIB) group (including ERB-0, ERB-controlled 1 [ERB-c1], and ERB-c2) and the major IB (MIB) group (including ERB-c3 and ERB-uncontrolled [ERB-unc]) according to ERB classification, then we analyzed the characteristics of different ERB classification, risk factors of MIB, and risk factors of postoperative bleeding (PB).

Methods

Patients and ethical approval

We retrospectively reviewed a total of 1707 patients who underwent gastric ESD between November 2006 and September 2019 at The First Medical Center of Chinese People's Liberation Army (PLA) General Hospital. In cases with multiple synchronous lesions, the lesions that showed deeper invasion or were larger in diameter if the invasion depths were the same, were included. The inclusion criteria were as follows: (1) the pathological results of biopsy or ESD were intraepithelial neoplasia or EGC; (2) medical records were complete and endoscopic pictures were clear; (3) all patients were treated by ESD. Ultimately, a total of 1334 patients with 1334 lesions were enrolled for analysis and were divided into four groups according to the ERB classification. The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of The First Medical Center of Chinese PLA General Hospital (No. S2017-010-02). Before ESD was performed, all patients signed informed consent.

ESD procedure and postoperative treatment

During the operation, the patient was placed in the left lateral position or supine position with the right shoulder elevated. The entire operation was performed under endotracheal intubation anesthesia, and the patient's respiratory rate, heart rate, and blood pressure were monitored. The specific steps of ESD included the following: (1) circumferential marking: after close observation and confirmation of the gastric lesion, a marking was made 3–5 mm away from the lesion boundary; (2) submucosal injection: a submucosal injection was performed around the lesion in the order of distal-to-proximal so that the mucosa was separated from the muscularis propria, and then the lesion was fully lifted; (3) circular incision: after the lesion was fully lifted, the lesion mucosa was cut approximately 3 mm outside the marked point; (4) submucosal dissection: during the dissection, submucosal injections were performed intermittently to ensure adequate submucosal lift; (5) wound treatment: electrocoagulation, hemostatic forceps, or argon plasma coagulation (APC) were used to treat the exposed blood vessels at the base of the ulcer, and if necessary, fibrin protein glue was sprayed to protect the wound.

After ESD, all patients remained fasting and were treated with a proton pump inhibitor (PPI) and other indicated treatments. Specifically, patients with large wounds or complications, such as perforation or aspiration pneumonia, were treated with antibiotics. In general, the patients were given fluid food 3 days later and the diet was gradually advanced if no obvious discomfort occurred, at this time patients began to take PPI orally instead of intravenous PPI for at least 4 weeks. The patient was discharged from the hospital when tolerating liquids or semi-liquids. Adverse events, such as PB, were closely observed after ESD. Patients were instructed to return to the hospital immediately if they noticed hematemesis or melena after discharge from the hospital.

ERB classification

ERB classification includes three grades and five sub-grades, as follows: ERB-0, no bleeding is seen during gastric ESD due to timely pretreatment.[6] ERB-c, bleeding that can be controlled under endoscopy, which is divided into three sub-grades (ERB-c1 [minor bleeding that can be easily stopped by endoscopy, does not influence the patient's vital signs, and does not require blood transfusion], ERB-c2 [the bleeding volume is between c1 and c3]; and ERB-c3 [major bleeding, although the bleeding can be controlled under endoscopy, control of bleeding is technically difficult and a blood transfusion is required during or after gastric ESD]); and ERB-unc refers to uncontrollable bleeding under endoscopy, which must be stopped by surgery or vessel embolotherapy [Figure 1]. Endoscopic hemostasis methods include APC, electrocoagulation, hemostatic forceps, and hemostatic clips. The ERB classification was evaluated by two endoscopists who reviewed endoscopic pictures, endoscopic reports, endoscopic videos, and medical records. If there was a disagreement between reviewers, the consensus was reached by a third experienced physician.

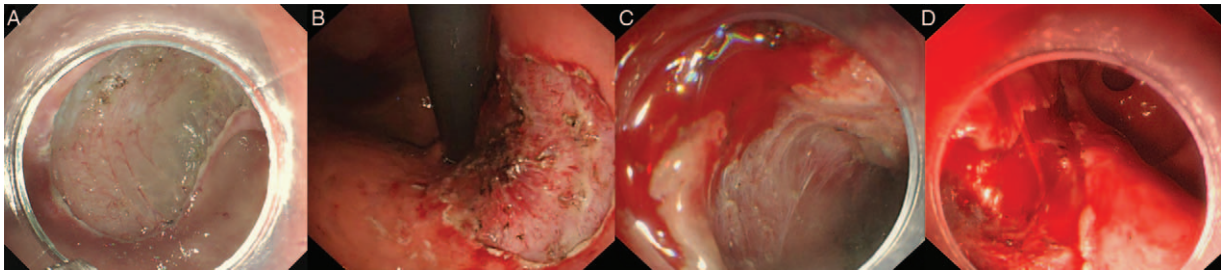

Figure 1: ERB classification: (A) ERB-0 means that no bleeding is seen during gastric ESD. (B) ERB-c1: minor bleeding. (C) ERB-c2: the bleeding volume is between c1 and c3. (D) ERB-c3: major bleeding. ERB: Endoscopic resection bleeding; ESD: Endoscopic submucosal dissection; ERB-c1: ERB-controlled1.

Table 1: Characteristics of patients undergoing gastric ESD among different ERB classifications.

Characteristics	NMIB group			MIB group	P value
	ERB-0 ($n=773$)	ERB-c1 ($n=477$)	ERB-c2 ($n=77$)	ERB-c3 ($n=7$)	
Age (years)	61.0 ± 10.3	60.5 ± 10.3	61.8 ± 10.4	57.6 ± 13.7	0.360
BMI (kg/m^2)	24.45 ± 3.31	24.31 ± 3.14	25.50 ± 3.44	22.78 ± 3.80	0.069
Male	565 (73.09)	402 (84.28)	70 (90.91)	7/7	<0.001
Smoking	291 (37.65)	207 (43.40)	36 (46.75)	1/7	0.059
Drinking	278 (35.96)	207 (43.40)	38 (49.35)	3/7	0.104
Comorbidities					
Hypertension	213 (27.55)	120 (25.16)	28 (36.36)	1/7	0.178
Diabetes mellitus	104 (13.45)	65 (13.63)	14 (18.18)	1/7	0.721
Liver diseases	38 (4.92)	21 (4.40)	4 (5.19)	0	0.906
Heart diseases	54 (6.99)	35 (7.34)	5 (6.49)	0	0.889
CKDs	10 (1.29)	2 (0.42)	1 (1.30)	0	0.477
Usage of anticoagulant and/or antiplatelet drugs					
Aspirin	50 (6.47)	24 (5.03)	5 (6.49)	1/7	0.664
Clopidogrel	6 (0.78)	12 (2.52)	0	0	0.147

Values were shown as mean ± standard deviation, *n* (%), or *n*. BMI: Body mass index; CKD: Chronic kidney disease; ESD: Endoscopic submucosal dissection; ERB: Endoscopic resection bleeding; ERB-c1: ERB-controlled1; IB: Intraoperative bleeding; MIB: Major intraoperative bleeding; NMIB: Non-major intraoperative bleeding.

Definition

In this study, NMIB means no bleeding during ESD or bleeding that can be controlled by endoscopy during ESD without affecting postoperative vital signs and with no need for extra treatments, such as blood transfusion; MIB refers to bleeding that requires additional treatment after ESD, such as blood transfusion or must be treated by surgery or vessel embolotherapy. PB was defined as one of the following: apparent hematemesis or melena, unstable vital signs, or a >2 g/dL decrease in hemoglobin concentration after ESD.[7] The long location of lesions was divided into three parts (upper, middle, and lower) and the short location of lesions was divided into lesser curvature, greater curvature, anterior wall, posterior wall, and others.[9] According to the Pairs endoscopic classification,[10] macroscopic type was classified into elevated (type I, IIa, and IIa+IIc), flat (type IIb), and depressed (type IIc, IIc +IIa, and III). The PT was defined as the time required from marking the lesion margin to completing the removal of the lesions. *En bloc* resection indicates that the lesion was removed under an endoscope and a single specimen was obtained. In the present study, the average and the median number of gastric ESD cases per endoscopist were 98 and 88, respectively, thus we defined junior endoscopists as those who had performed <100 ESD procedures; whereas experienced endoscopists were defined as those who had performed ≥100 cases.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) and analyzed using Student's *t* test or the Mann–Whitney test. Categorical variables are shown as numbers with percentages and were analyzed using a chi-squared test or Fisher exact test. The values with a P value < 0.10 in the univariate analysis were included in the multivariate logistic regression model. All statistical analyses were performed with SPSS v22.0 (IBM, Corp., Armonk, NY, USA). A P value < 0.05 was considered to be statistically significant.

Results

Patient-related characteristics in the NMIB and MIB groups

Of the 1334 patients, 773 (57.95%) had ERB-0, 477 (35.76%) had ERB-c1, 77 (5.77%) had ERB-c2, 7 (0.52%) had ERB-c3, and no patients had ERB-unc. The proportion of male patients who had ERB-0, ERB-c1, ERB-c2, and ERB-c3 was 73.09% (565/773), 84.28% (402/477), 90.91% (70/77), and 7/7, respectively ($\chi^2 = 37.471$, $P < 0.001$). No significant differences were found in age, history of smoking, and drinking, comorbidities, such as hypertension, diabetes mellitus, liver disease, heart disease, chronic kidney disease (CKD), and usage of aspirin or clopidogrel among different ERB classifications [Table 1].

Lesion-related characteristics in the NMIB and MIB groups

Lesion-related characteristics in the minor and MIB groups are shown in Table 2. With the increasing ERB classification, the rate of ulcer, submucosal adhesion, and EGC also gradually increased, as did the proportion of lesions located in the middle and upper part of the stomach. Macroscopic types were not significantly different among ERB-0, ERB-c1, ERB-c2, and ERB-c3 ($\chi^2 = 10.312$, $P = 0.112$). 5.69% (44/773), 11.53% (55/477), and 16.88% (13/77) of lesions in ERB-0, ERB-c1, and ERB-c2 group, respectively, involved the submucosa, whereas those in the ERB-c3 group were all limited to the mucosa layer ($\chi^2 = 21.295$, $P < 0.001$).

Procedure-related characteristics in the NMIB and MIB groups

Table 3 shows that from ERB-0 to ERB-c3, the PT was gradually prolonged ($t = 41.089$, $P < 0.001$) and the specimen size also gradually increased ($t = 89.601$, $P < 0.001$), the

Table 2: Lesion-related characteristics of patients undergoing gastric ESD among different ERB classifications.

Characteristics	NMIB group			MIB group	*P* value
	ERB-0 (*n* = 773)	ERB-c1 (*n* = 477)	ERB-c2 (*n* = 77)	ERB-c3 (*n* = 7)	
Lesion size (cm)	1.45 ± 1.08	1.59 ± 1.05	1.73 ± 1.04	1.16 ± 0.62	0.005
Ulcer					0.003
Absence	684 (88.49)	389 (81.55)	62 (80.52)	5/7	
Presence	89 (11.51)	88 (18.45)	15 (19.48)	2/7	
Adhesion					<0.001
No	724 (93.66)	398 (83.44)	60 (77.92)	4/7	
Yes	49 (6.34)	79 (16.56)	17 (22.08)	3/7	
Location					<0.001
Upper	180 (23.29)	216 (45.28)	45 (58.44)	4/7	
Middle	168 (21.73)	131 (27.46)	16 (20.78)	3/7	
Lower	425 (54.98)	130 (27.25)	16 (20.78)	0	
Macroscopic type					0.112
Elevated	572 (74.00)	329 (68.97)	51 (66.23)	4/7	
Flat	93 (12.03)	62 (13.00)	13 (16.88)	0	
Depressed	108 (13.97)	86 (18.03)	13 (16.88)	3/7	
Histological type					<0.001
EGC	297 (38.42)	247 (51.78)	34 (44.16)	4/7	
HGIN	315 (40.75)	164 (34.38)	33 (42.86)	2/7	
LGIN	161 (20.83)	66 (13.84)	10 (12.98)	1/7	
Invasion depth					<0.001
Mucosa	729 (94.31)	422 (88.47)	64 (83.12)	7/7	
SM	44 (5.69)	55 (11.53)	13 (16.88)	0	

Values were shown as mean ± standard deviation, *n* (%), or *n*. ERB: Endoscopic resection bleeding; EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection; ERB-c1: ERB-controlled1; HGIN: High-grade intraepithelial neoplasia; LGIN: Low-grade intraepithelial neoplasia; MIB: Major intraoperative bleeding; NMIB: Non-major intraoperative bleeding; PT: Procedure time; SM: Submucosa.

Table 3: Procedure-related characteristics of patients undergoing gastric ESD among different ERB classifications.

Characteristics	NMIB group			MIB group	*P* value
	ERB-0 (*n* = 773)	ERB-c1 (*n* = 477)	ERB-c2 (*n* = 77)	ERB-c3 (*n* = 7)	
PT (min)	36.11 ± 23.75	65.87 ± 53.57	97.56 ± 71.84	194.43 ± 153.07	<0.001
<120 min	766 (99.09)	414 (86.79)	53 (68.83)	2/7	<0.001
≥120 min	7 (0.91)	63 (13.21)	24 (31.17)	5/7	
Specimen size (cm)	3.53 ± 1.41	4.03 ± 1.62	4.32 ± 1.57	4.74 ± 1.72	<0.001
En bloc resection					<0.001
No	22 (2.85)	60 (12.58)	16 (20.78)	2/7	
Yes	751 (97.15)	417 (87.42)	61 (79.22)	5/7	
Endoscopists					0.238
Junior	237 (30.66)	145 (30.40)	19 (24.68)	0	
Experienced	536 (69.34)	332 (69.60)	58 (75.32)	7/7	
PB					<0.001
No	756 (97.80)	461 (96.65)	70 (90.91)	5/7	
Yes	17 (2.20)	16 (3.35)	7 (9.09)	2/7	

Values were shown as mean ± standard deviation, *n* (%), or *n*. ESD: Endoscopic submucosal dissection; ERB: Endoscopic resection bleeding; ERB-c1: ERB-controlled 1; MIB: Major intraoperative bleeding; NMIB: Non-major intraoperative bleeding; PT: Procedure time; PB: Postoperative bleeding.

rate of PT ≥ 120 min was also increased from ERB-0 to ERB-c3, whereas the *en bloc* resection rate was gradually decreased ($P < 0.001$). Additionally, the incidences of PB in patients with IB classifications of ERB-0, ERB-c1, ERB-c2, and ERB-c3 were 2.20% (17/773), 3.35% (16/477), 9.09% (7/77), and 2/7, respectively ($\chi^2 = 26.105$, $P < 0.001$). There was no significant difference in the endoscopic experience of endoscopists among cases of different ERB classifications ($\chi^2 = 4.229$, $P = 0.238$).

Univariate and multivariate analysis for predictors of major IB

In the univariate analysis, submucosal adhesion ($P = 0.033$), lesion location (long axis) ($\chi^2 = 3.898$, $P = 0.034$), and PT ≥ 120 min ($P < 0.001$) were significantly correlated with MIB. However, only proximal location (upper, odds ratio [OR]: 1.488; 95% confidence interval [CI]: 1.045–3.645; $P = 0.047$) and PT ≥ 120 min

Table 4: Univariate and multivariate analysis of major intraoperative bleeding among patients undergoing gastric ESD.

Variables	NMIB group ($n = 1327$)	MIB group ($n = 7$)	*P* value	Multivariate analysis OR (95% CI)	*P* value
Patient characteristics					
Age (years)	60.9 ± 10.3	57.6 ± 13.7	0.255		
Male	1037 (78.15)	7/7	0.358		
Usage of aspirin	79 (5.95)	1/7	0.352		
Usage of clopidogrel	18 (1.36)	0	1.000		
Hypertension	361 (27.20)	1/7	0.683		
Heart diseases	94 (7.08)	0	1.000		
Liver diseases	63 (4.75)	0	1.000		
Diabetes mellitus	183 (13.79)	1/7	1.000		
CKDs	13 (0.98)	0	1.000		
Lesion characteristics					
Ulcer	192 (14.47)	2/7	0.271		
Adhesion	145 (10.93)	3/7	0.033	0.477 (0.086–2.637)	0.397
Location (long axis), upper/middle/lower	441/315/571	4/3/0	0.034	1.488 (1.045–3.645)	0.047
Location (short axis), LC/AW/GC/PW/others	552/182/213/326/54	5/0/0/2/0	0.420		
Macroscopic type, elevated/flat/depressed	952/168/207	4/0/3	0.159		
Histology type, EGC/HGIN/LGIN	578/512/237	4/2/1	0.881		
Invasion depth, M/SM	1215/112	7/0	1.000		
Lesion size ≥3 cm	101 (7.61)	0	0.534	1.000	
Procedure characteristics					
PT ≥120 min	94 (7.08)	5/7	<0.001	19.033 (3.066–118.153)	0.002
En bloc resection	1129 (92.61)	5/7	0.091	0.913 (0.148–5.640)	0.922
Specimen size ≥4 cm	561 (42.28)	5/7	0.347		
Endoscopists, junior	401 (30.22)	0	0.110		
Multiple lesions	87 (6.56)	2/7	0.074	1.465 (0.670–4.325)	0.826

Values were shown as mean ± standard deviation, *n* (%), or *n*. AW: Anterior wall; CKD: Chronic kidney disease; CI: Confidence interval; EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection; GC: Greater curvature; HGIN: High-grade intraepithelial neoplasia; IB: Intraoperative bleeding; LC: Lesser curvature; LGIN: Low-grade intraepithelial neoplasia; M: Mucosa; MIB: Major intraoperative bleeding; NMIB: Non-major intraoperative bleeding; OR: Odds ratio; PW: Posterior wall; PT: Procedure time; SM: Submucosa.

(OR: 19.033; 95% CI: 3.066–118.153; $P = 0.002$) were significantly related with MIB in the multivariate analysis [Table 4].

Characteristics and predictors of PB patients

A total of 42 patients had PB. The median occurrence time of PB was 2 days (range, 1–30 days) after gastric ESD. Of the patients, 97.62% (41/42) of patients had PB within 2 weeks after gastric ESD. Only one patient had PB 30 days after gastric ESD. The most common symptoms of patients with PB are hematemesis and melena. Of the 42 patients with PB, 27 underwent endoscopic hemostasis, including epinephrine injection (4 patients), hemostatic clip/forceps (1 patient), and APC or electrocoagulation (22 patients). The remaining 15 patients achieved hemostasis through conservative treatment. All patients with PB successfully stopped bleeding.

In the univariate analysis, PT ≥ 120 min ($P = 0.031$) and MIB (ERB-c3; $P < 0.001$) were significantly correlated with PB. In addition, the rate of patients with CKD in the PB group was higher than the non-PB group ($P = 0.061$). Multivariate analysis also showed that CKD (OR: 7.844; 95% CI: 1.637–37.583; $P = 0.010$) and MIB (ERB-c3; OR: 13.932; 95% CI: 2.585–74.794; $P = 0.002$) were independent risk factors of PB (Table 5).

Discussion

In this study, we found that the incidence of MIB was 0.52% and the incidence of PB gradually increased from ERB-0 to ERB-c3 ($P < 0.001$). Multivariate analysis indicated that proximal location ($P = 0.047$) was the only significant risk factor of MIB, whereas CKD ($P = 0.010$) and MIB (ERB-c3) ($P = 0.002$) were independent risk factors of PB.

Previous studies have reported the risk factors of IB during ESD. Oda *et al*[11] analyzed the relationship between IB and lesion location, lesion size, and findings of ulceration, but found that only location (upper and middle third) and lesion size (≥31 mm) were significantly associated with IB. Jeon *et al*[5] found that younger age and more proximal lesion locations were significant predictors of IB. Toyonaga *et al*[12] and Horikawa *et al*[13] also found that IB usually develops with lesions in the proximal location of the stomach. Our results are consistent with the aforementioned studies. Possible reasons are as follows: first, the proximal stomach is a difficultly accessible site for

Table 5: Univariate and multivariate analysis of postoperative bleeding among patients undergoing gastric ESD.

Variables	NPB ($n = 1292$)	PB ($n = 42$)	*P* value	Multivariate analysis	
				OR (95% CI)	*P* value
Patient characteristics					
Age (years)	60.9 ± 10.3	58.8 ± 11.6	0.288		
Male	1008 (78.02)	36 (85.71)	0.234		
Usage of aspirin	78 (6.04)	2 (4.76)	0.510		
Usage of clopidogrel	17 (1.32)	1 (2.38)	0.440		
Hypertension	352 (27.24)	10 (23.81)	0.622		
Heart diseases	91 (7.04)	3 (7.14)	0.980		
Liver diseases	60 (4.64%)	3 (7.14)	0.452		
Diabetes mellitus	181 (14.01)	3 (7.14)	0.204		
CKDs	11 (0.85)	2 (4.76)	0.061	7.844 (1.637–37.583)	0.010
Lesion characteristics					
Lesion size ≥3 cm	99 (7.66)	2 (4.76)	0.594		
Location (long axis), upper/middle/lower	433/306/553	12/12/18	0.703		
Location (short axis), LC/AW/GC/PW/others	535/177/208/318/54	22/5/5/10/0	0.480		
Macroscopic type, elevated/flat/depressed	926/163/203	30/5/7	0.980		
Histology type, EGC/HGIN/LGIN	564/499/229	18/15/9	0.815		
Invasion depth, M/SM	1183/109	39/3	0.766		
Procedure characteristics					
PT ≥120 min	92 (7.12)	7 (16.67)	0.031	1.738 (0.625–4.833)	0.289
En bloc resection	1198 (92.72)	36 (85.71)	0.090	0.618 (0.229–1.668)	0.342
Specimen size ≥4 cm	542 (41.95)	24 (57.14)	0.115		
Endoscopists, junior	386 (29.87)	15 (35.71)	0.054	2.119 (0.920–4.881)	0.078
MIB (ERB-c3)	4 (0.31)	2 (4.76)	<0.001	13.932 (2.585–74.794)	0.002
Multiple lesions	86 (6.66)	3 (7.14)	0.756		

Values were shown as mean ± standard deviation, *n* (%), or *n*. AW: Anterior wall; CKD: Chronic kidney disease; CI: Confidence interval; EGC: Early gastric cancer; ERB: Endoscopic resection bleeding; ESD: Endoscopic submucosal dissection; GC: Greater curvature; HGIN: High-grade intraepithelial neoplasia; IB: Intraoperative bleeding; LC: Lesser curvature; LGIN: Low-grade intraepithelial neoplasia; M: Mucosa; MIB: Major intraoperative bleeding; NPB: No postoperative bleeding; OR: Odds ratio; PW: Posterior wall; PB: Postoperative delayed bleeding; PT: Procedure time; SM: Submucosa.

endoscopists, so lesions in this area are more difficult to treat; second, the diameter and number of the submucosal blood vessels in the proximal area are larger than in the other areas.[12]

In addition, we not only found that PT was significantly related to the incidence of MIB but also that it was related to the degree of bleeding during ESD. This result was consistent with the previous studies.[14-16] Larger lesions, difficult lesion locations, or a difficult dissection due to submucosal adhesion or ulcers may lead to prolonged PT. However, the more severe IB is, the more difficult it is to stop bleeding under endoscopy, and the longer the hemostasis time may also be. These findings may explain the gradually prolonged PT from ERB-0 to ERB-c3. Therefore, we believe that a longer PT may result from IB, not the reason for the IB.

In our analysis of the relationship between IB and PB, we found that PB increased with increased ERB classification. Moreover, IB classified as ERB-c3 (MIB) was an independent risk factor for PB (OR: 13.932; 95% CI: 2.585–74.794; $P = 0.002$). Okano *et al*[17] reported that the rate of PB was 8.13-fold higher in patients with IB compared with the patients without IB ($P < 0.001$). Park *et al*[4] divided the delayed bleeding into early delayed bleeding (EDB) and late delayed bleeding (LDB) and found the incidences of EDB and LDB in patients with IB were 3.14-fold ($P < 0.001$) and 1117.94-fold ($P < 0.001$) that of patients without IB. One possible reason is that the predilection sites for IB and PB are different. In this study, most IB (57.14%) occurred in the upper third of the stomach, whereas the majority of PB (42.86%) was found in the lower third. Tsuji *et al*[18] and Miyahara *et al*[16] reported that the lower part of the stomach is more prone to PB than the upper or middle part. So, the upper and middle parts of the stomach require more careful endoscopic hemostasis during gastric ESD, which may ultimately prevent PB.[11,16-19] Moreover, antral active peristalsis and bile reflux may contribute to the high incidence of PB in the lower part of the stomach.[18,19]

This present study also found that CKD is an independent risk factor of PB. Cheung *et al*[20] reported that the rate of bleeding in patients with CKD significantly increased. A propensity score-matched study conducted by Choi *et al*[21] found that stage 4 (OR: 5.79; 95% CI 1.52–22.0; $P = 0.010$) and stage 5 CKD patients (OR: 4.80; 95% CI 1.58–14.6; $P = 0.006$) had higher bleeding risks than non-CKD patients. Based on multivariate analysis, stage 4/5 CKD was a significant predictor for bleeding risk (OR: 4.99; 95% CI 1.32–18.8; $P = 0.018$). A meta-analysis also found that CKD was one of the independent risk factors of PB after ESD.[22] A possible reason for this conclusion is

that renal dysfunction or the drugs used in CKD treatment may affect coagulation.

Prevention of bleeding is very important. The methods to prevent bleeding are as follows: first, when vessels are encountered during the procedure, they should be cut after preventative coagulation techniques; second, the amount of fluid should be sufficient to ensure the full lifting of the mucosa; third, reaching the appropriate deep submucosal layer in the process of submucosal dissection is one way to prevent bleeding, because the deep submucosal layer contains larger but fewer penetrating vessels and fibrotic tissue.[23] When hemorrhage occurs during ESD, it's important to immediately identify the exact bleeding point. Endoscopic instruments with water jet function are beneficial to maintain a good view during the process of gastric ESD, and to find the bleeding point.[24] Minor hemorrhage (such as bleeding classified as ERB-c1 and ERB-c2) can also be easily controlled using the cutting device alone by coagulation. Major hemorrhage (such as bleeding classified as ERB-c3) may require endoscopists to use hemostatic forceps or clips to ensure complete hemostasis.[25] It has been reported that the use of hemostatic forceps for preventative coagulation is an effective method to prevent IB.[26]

The limitations of this study include the following. First, this is a retrospective and single-center study, which meant that some data, such as the types of scope or device and submucosal injection fluid during ESD could not be collected. In addition, an ERB classification of IB could not be evaluated in all patients by reviewing endoscopic videos. Prospective multicenter studies are warranted to validate our results. Second, in our study, the incidence of MIB was too small to evaluate the risk factors by multivariate logistic regression analysis, and there were no patients with IB classified as ERB-unc, so the results may have some bias.

In conclusion, ERB classification can be used to objectively assess the degree of IB during ESD for gastric neoplastic lesions and it is also related to PB. Our multivariate analysis showed that the proximal location of lesions was a predictor of MIB. In addition, CKD and IB classified as ERB-c3 were the independent risk factors of PB. More attention should be paid to these high-risk patients for MIB and PB.

Funding

The present study was supported by a grant from the National Key Research & Development Program of China (No. 2016YFC1303601).

Conflicts of interest

None.

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How to cite this article: Xu S, Chai N, Tang X, Linghu E, Wang S. Risk factors of major intraoperative bleeding and postoperative bleeding associated with endoscopic submucosal dissection for gastric neoplasms. Chin Med J 2022;135:309–316. doi: 10.1097/CM9.0000000000001840