

# Risk factors of bleeding after endoscopic submucosal dissection for early gastric cancer

Shorttitle: Risk factors of bleeding after ESD for EGC

Jiaxu Wang, Jie Xing, Xiujing Sun\*, Peng Li, Shutian Zhang

Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University; National Clinical Research Center for Digestive Diseases; Beijing Digestive Disease Center; Faculty of Gastroenterology of Capital Medical University; Beijing Key Laboratory for Precancerous Lesion of Digestive Diseases, Beijing, China (100050)

Corresponding author: Xiujing Sun, Department of Gastroenterology, Beijing Friendship Hospital, Capital Medical University; National Clinical Research Center for Digestive Diseases; Beijing Digestive Disease Center; Faculty of Gastroenterology of Capital Medical University; Beijing Key Laboratory for Precancerous Lesion of Digestive Diseases, 95Yong'an Road, Tianqiao street, Xicheng District, Beijing, China

Tel: +8613522653532

Fax: +86 010 63139351

Email: sunxiujing@ccmu.edu.cn

## **ABSTRACT**

Endoscopic submucosal dissection (ESD) is usually used to resect the lesion at the mucosa and submucosa plane. However, compared with endoscopic mucosal resection (EMR), ESD is more difficult and complex, which will increase the incidence of various complications, including bleeding, perforation and infection. The most common adverse event of gastric ESD is bleeding. Prevention and early detection of bleeding after ESD play a great role in the effectiveness and safety of the operation. Many studies have reported the risk factors of bleeding after ESD for early gastric cancer, but there are still some problems worth discussing. Therefore, we reviewed the risk factors of bleeding after ESD for early gastric cancer, hoping to help endoscopists fully evaluate the risk of bleeding after ESD, and pay more attention to patients at high risk of bleeding.

**Keywords:** Delayed bleeding, Early gastric cancer, Endoscopic submucosal dissection, Risk factors

## **BACKGROUND**

Gastric cancer is the fifth largest malignant tumor and the fourth largest cause of cancer death in the world. <sup>[1]</sup> In Asia, the incidence rate of men is two times that of women, <sup>[2]</sup> which is a serious burden on the world economy. The prognosis of gastric cancer largely depends on early diagnosis. With the development and wide application of endoscopic techniques, the diagnostic rate of early gastric cancer (EGC) is increasing. <sup>[3]</sup> EGC refers to lesions confined to the mucosa and submucosa with or without lymph node metastasis (LNM). <sup>[4]</sup>

In recent years, with the advancement of endoscopic technology, endoscopic submucosal dissection (ESD) has increasingly become the main choice for EGC on account of its lower incidence of adverse events, association with a shorter hospital

stay, lower cost and higher quality of life than surgery. <sup>[5-7]</sup> In case of unclear diagnosis, diagnostic ESD is feasible. <sup>[8]</sup> However, ESD requires high technology, and adverse events can follow. The most common adverse event of gastric ESD is bleeding. <sup>[9,10]</sup> Any delay in the detection of bleeding can lead to serious complications, such as hypovolemic shock or even death. This paper reviewed the risk factors of bleeding after ESD for EGC.

## **BLEEDING AFTER ESD FOR EARLY GASTRIC CANCER**

With the development of coagulation therapy and the use of proton pump inhibitor (PPI), the incidence of bleeding after ESD decreases gradually. But it is still one of the primary problems to be solved in ESD complications. Immediate intraoperative bleeding is easily identified during ESD period and can be treated by endoscopy in most cases. Nevertheless, delayed bleeding, characterized by hematemesis or melena, may occur a few days after ESD and occasionally even after discharge. Since there is no consensus on the definition of ESD delayed bleeding, the previously reported incidence of bleeding after gastric ESD ranges from 2.4% to 18.3%. <sup>[11-24]</sup> Hemorrhage after gastric ESD was defined when two of the four following parameters were satisfied after the ESD period; (i) hematemesis, melena or dizziness, (ii) hemoglobin loss >2 g/dl, (iii) blood pressure decrease >20 mmHg or pulse rate increase >20/min and (iv) Forrest I or IIa-IIb on follow-up endoscopy. <sup>[25]</sup> There are also some studies that divide bleeding into early bleeding (within 48 hours after ESD) and late bleeding (more than 48 hours after ESD) according to the time of bleeding. <sup>[26]</sup> Most delayed bleeding can be stopped by oral hemostatic or endoscopic hemostatic methods. However, if endoscopists cannot detect bleeding in time, some cases may progress to hemorrhagic shock or even death. Therefore, endoscopists should fully evaluate the risk of delayed bleeding and pay more attention to patients at high risk of bleeding.

## **RISK FACTORS OF BLEEDING AFTER ESD FOR EGC**

As shown in Table 1, we reviewed nearly 10 years of risk factors for bleeding after ESD for gastric lesions. [11-16, 18-24, 27-32] According to our summary, the risk factors are classified into three categories: patient-related, tumor-related and procedure-related factors.

**Table 1 Risk factors of delayed bleeding for gastric lesions**

Authors (publication year)	Noflesi ons	Delayed bleeding (%)	Definition	Risk factors
Yu Gong <i>et al</i> (2021) <sup>[29]</sup>	699	10.6	Delayed bleeding occurs within 24 hours to 30 days after ESD: (1) symptoms such as nausea, dizziness and black stool; (2) blood pressure drop > 20 mmHg or heart rate increase 20 beats/ min; (3) bleeding from operation wound confirmed by endoscopy; (4) hemoglobin decreased $\geq 2\text{g/dl}$	Maximum length of the lesion $\geq 3$ cm, superficial and flat lesion
Jing Li <i>et al</i> (2021) <sup>[31]</sup>	92	8.7	Any of the: (1) symptoms such as nausea, dizziness and black stool; (2) blood pressure drop >20 mmHg or heart rate increase 20 beats/ min; (3) bleeding from operation wound confirmed by endoscopy; (4) hemoglobin decreased $\geq 2\text{g/dl}$	Long-term use of anticoagulant drugs, operation time $\geq 90\text{min}$ , lesion location in the upper 1/3 of the stomach, lesion diameter >4cm
Xiaoyan Wang <i>et al</i> (2020) <sup>[32]</sup>	122	18.0	The following conditions occur within 24 hours to 30 days after	Cardia-gastric fundus lesions, early gastric cancer

Authors (publication year)	Noflesi ons	Delayed bleeding (%)	Definition	Risk factors
Chaohu Yang (2020) <sup>[28]</sup>	1177	5.9	ESD : hematemesis or black stool, hemoglobin decreased $\geq 2\text{g/dL}$ , need emergency endoscopic hemostasis	
			Bleeding occurred within 30 days after ESD, accompanied by two or more of the following conditions: (1) symptoms such as dizziness, hematemesis or black stool after ESD; (2) hemoglobin decreased $> 20\text{ g/L}$ ; (3) increase of heart rate $> 20 / \text{min}$ or decrease of blood pressure $> 20\text{mmHg}$ ; (4) ulcer bleeding at operation site by endoscopy	Previous use of plavix or talcom, the lesion in the lower third of the stomach, the resection size $\geq 40\text{mm}$ , ulcer or scar
Hideomi Tomida et al (2020) <sup>[27]</sup>	849	14.0-18.0	An event requiring emergency endoscopy with endoscopic hemostasis or transfusion for the management of hematemesis or melena, or a decrease $> 2\text{ g/dL}$ of hemoglobin levels after ESD	Age $\geq 65$ , receiving multiple antithrombotic agents, resection of multiple lesions, lesion size $\geq 20\text{ mm}$
Tian Jin (2019) <sup>[30]</sup>	275	5.1	Obvious hematemesis, hematochezia, black stool and hemoglobin decreased $\geq 2\text{g/dL}$	Size of lesions $\geq 3\text{cm}$ , combining with chronic liver disease

Authors (publication year)	Noflesi ons	Delayed bleeding (%)	Definition	Risk factors
			after ESD or need endoscopic hemostasis	
Nam <i>et al</i> (2019) <sup>[12]</sup>	1864	4.1	Clinical evidence of bleeding in the artificial ulcer lesions such as overt hematemesis, melena, spurting or oozing bleeding from the artificial ulcer bed, and the presence of fresh blood or clots in the stomach during endoscopic examination	Early PEB (within 24 hours post-ESD): age $\leq 65$ years, resection size $\geq 30$ mm, procedure time $\geq 20$ min, lower third of the stomach, erosion, clopidogrel use Late PEB (after 24 hours post-ESD): mid to upper third of the stomach, undifferentiated carcinoma, erosion, high risk of stigma during second-look endoscopy, history of early PEB, clopidogrel use
Sanomura <i>et al</i> (2018) <sup>[13]</sup>	1243	4.1	Bleeding manifested by a fall in the hemoglobin level of 20 g/L or more below the most recent preoperative level, observation of any bleeding source or massive melena	Dialysis, the use of anticoagulants, operation time $\geq 75$ min
Ke Zhang <i>et al</i> (2018) <sup>[33]</sup>	112	5.4	(1) symptoms such as dizziness, hematemesis or black stool after ESD; (2) hemoglobin decreased $> 20$ g/L; (3) increase	The lesion is located in the gastric antrum, the diameter of the lesion is $\geq 4$ cm, the pathology is early gastric

Authors (publication year)	Noflesi ons	Delayed bleeding (%)	Definition	Risk factors
			of heart rate > 20 / min or decrease of blood pressure > 20mmHg; (4) ulcer bleeding at operation site by endoscopy	cancer
Yano <i>et al</i> (2017) <sup>[34]</sup>	1767	8.5	Any of the following conditions: (a) blood transfusion or emergency endoscopy for hematemesis or melena developing after ESD; (b) bloody gastric juice confirmed on second-look endoscopy; (c) hematemesis for spurting bleeding from the ulcer floor after ESD; or (d) a sudden drop in the hemoglobin level by 20 g/L or more	Overall: lesions at the distalstomach, procedure time ≥90min, specimen size ≥4 cm,antithrombotic therapy; Acute PEB (within 5 d after ESD): lesions at the distal stomach,specimen size ≥4 cm,antithrombotic therapy,expanded indication and nonindicated lesions; Delayed PEB: lesions at theproximal stomach,antithrombotic therapy,hemodialysis
Zheng Huang <i>et al</i> (2017) <sup>[35]</sup>	206	9.2	(1) symptoms such as dizziness, hematemesis or black stool after ESD; (2) hemoglobin decreased > 20 g/L; (3) increase of heart rate > 20 / min or decrease of blood pressure >	Lesion diameter ≥3cm, submucosal invasion, gastric antrum lesion, intraoperative blood loss > 800ml

Authors (publication year)	Noflesi ons	Delayed bleeding (%)	Definition	Risk factors
			20mmHg; (4) ulcer bleeding at operation site by endoscopy	
Qichao Fu <i>et al</i> (2017) <sup>[17]</sup>	506	2.4	There was no bleeding at the end of the operation, and at least 2 of the following indexes were met 0-30 days after operation: (1) symptoms such as dizziness, hematemesis or black stool after ESD; (2) hemoglobin decreased > 20 g/L; (3) increase of heart rate > 20 / min or decrease of blood pressure > 20mmHg; (4) ulcer bleeding at operation site by endoscopy	tumor diameter $\geq 4$ cm
Shindo <i>et al</i> (2016) <sup>[14]</sup>	262	8.8	Hematemesis and/or melena after the procedure requiring endoscopic hemostasis, or a decrease of the hemoglobin level by more than 20 g/L	Heparin replacement
Takahashi <i>et al</i> (2014) <sup>[15]</sup>	459	5.0	Postoperative hematemesis or melena requiring endoscopic hemostasis	Overall: younger age, lesions in the L segment, large size of the resected specimen; Immediate PEB (within 24 h after ESD):



Authors (publication year)	Noflesi ons	Delayed bleeding (%)	Definition	Risk factors
				lesions in the L segment, large resected specimens, large tumor size; Delayed PEB: younger age, concomitant renal disease
Matsumura <i>et al</i> (2014) <sup>[16]</sup>	425	4.7	A decrease in the blood hemoglobin level of >20 g/L accompanied by hematemesis, melena, or a combination of unstable vital signs within 4 weeks of ESD	Overall: heparin replacement, CKD undergoing hemodialysis, specimen size $\geq 4$ cm; Early PEB (within 5 days of ESD): continuous use of LDA + heparin replacement, specimen size $\geq 4$ cm; Delayed PEB: heparin replacement, CKD undergoing hemodialysis
Ebi <i>et al</i> (2014) <sup>[18]</sup>	186	4.2	Clinical evidence of bleeding after ESD, manifesting as hematemesis or melena, which requires urgent endoscopic treatment	Hypertension, depressed-type (IIc) tumors
Kim <i>et al</i> (2014) <sup>[36]</sup>	441	4.1	Massive bleeding at 1–56 days after ESD and as requiring emergency endoscopic hemostasis for endoscopically	Tumor size >2 cm

Authors (publication year)	Noflesi ons	Delayed bleeding (%)	Definition	Risk factors
			evident bleeding sites on resected lesions because of hematemesis, melena, hematochezia	
Koh <i>et al</i> (2013) <sup>[19]</sup>	1192	5.3	Clinical evidence of bleeding in ESD-induced ulcer lesions, as shown by overt hematemesis or melena and a confirmed presence of blood or coagulants in the stomach or bleeding spots under endoscopy	Overall: specimen size >4 cm; Early PEB (within 5 d after ESD): history of cardiovascular disease; Delayed PEP: oral antithrombotic drugs, specimen size >4 cm
Nakamura <i>et al</i> (2012) <sup>[20]</sup>	544	7.0	Clinical evidence of bleeding after ESD as shown by a decrease in hemoglobin levels of >20 g/L and/or hematemesis or melena requiring emergency endoscopic treatment, and/or active bleeding under endoscopy	Low platelet count (<150 × 10 <sup>9</sup> /L), positive or indeterminate lateral margin
Mukai <i>et al</i> (2012) <sup>[21]</sup>	161	13.0	Active bleeding from a post-ESD ulcer diagnosed by an emergency endoscopy or a planned follow-up endoscopy	Ulcer findings
Toyokawa <i>et al</i> (2012) <sup>[22]</sup>	1123	5.0	Occurrence of postoperative hematemesis or melena	Aged ≥80 y, a long procedure time

Authors (publication year)	Noflesi ons	Delayed bleeding (%)	Definition	Risk factors
Miyahara <i>et al</i> (2012) <sup>[23]</sup>	1190	6.9	Clinical evidence of bleeding after ESD indicated by hematemesis or melena or by >20 g/L decrease in hemoglobin levels within a 24-h period, requiring endoscopic hemostasis with metal clipping, electrocoagulation, etc	Tumor location, resected tumor size, scarring in lesion
Tsuji <i>et al</i> (2010) <sup>[24]</sup>	398	5.8	Hemorrhage resulting in hematemesis or melena that required endoscopic treatment	Beginner coagulators, tumor at the lower third of the stomach, daily use of medicine potentially related to gastric injury/ bleeding

## PATIENT-RELATED FACTORS

### *Use of antithrombotic drugs*

With the wide application of antithrombotic drugs in the prevention and treatment of arterial and venous thrombosis, the proportion of gastric ESD patients taking antithrombotic drugs is also increasing. At present, there is a great controversy about whether to discontinue antithrombotic drugs before ESD. On the one hand, discontinuation of antithrombotic drugs increases the risk of thromboembolism. On the other hand, continued use of antithrombotic drugs may increase the risk of postoperative bleeding. Therefore, it is important to assess the relationship between bleeding risk and thromboembolism when using antithrombotic drugs. Several studies have reported that the application of antithrombotic drugs is a risk factor for bleeding

after ESD. <sup>[13, 19, 34, 37]</sup> Chinese experts agree that anticoagulants and antiplatelet drugs should be discontinued for 5 to 7 days prior to the procedure.<sup>[25]</sup> In contrast, Other studies have shown that antithrombotic drugs do not increase this risk.<sup>[20, 21]</sup> The controversy may be due to the different types and duration of antithrombotic drugs used in these studies. Antithrombotic drugs include antiplatelet drugs and anticoagulants. Different types of antithrombotic drugs may have different effects on the risk of delayed bleeding.

In terms of antiplatelet drugs, some studies have shown that continuous or discontinuation of aspirin does not increase the incidence of delayed bleeding. <sup>[38-40]</sup> Therefore, the Japan Gastroenterological Endoscopy Society (JGES) guidelines recommend that aspirin treatment should be continued in patients receiving aspirin alone or aspirin in combination with thienopyridine even if there is a high risk of bleeding from endoscopic gastroenterological procedures in order to reduce the incidence of thrombotic events. <sup>[41, 42]</sup> Other studies have shown that taking a single antiplatelet drug is not associated with delayed bleeding. <sup>[40, 43]</sup> However, for patients receiving dual antiplatelet therapy, the incidence of delayed bleeding increased significantly. <sup>[44]</sup> In addition, studies by Nam *et al* <sup>[12]</sup> have shown that clopidogrel significantly increases the risk of both early (with 24 hours after ESD) and delayed bleeding. The guidelines also recommend discontinuing clopidogrel or switching to aspirin during gastric ESD. <sup>[40]</sup> So far, there have been few studies on other antiplatelet drugs, and more data is needed to clarify the association between delayed bleeding and these drugs.

Anticoagulants are considered to be one of the important risk factors for delayed bleeding. Yosuke Toya *et al* <sup>[45]</sup> retrospectively studied 2355 patients with EGC and found that the incidence of delayed bleeding after ESD in the group with anticoagulant therapy was significantly higher than the control group. Takeuchi *et al* <sup>[46]</sup> and Chiko Sato *et al* <sup>[44]</sup> also reported that anticoagulants can increase the incidence of bleeding after ESD. These researches illustrate that anticoagulants, including warfarin and direct oral anticoagulants (DOAC), are risk factors for delayed bleeding after ESD for gastric lesions. Japanese guidelines for gastroenterological

endoscopy in patients undergoing antithrombotic treatment in 2012 recommended heparin instead of warfarin for patients at high risk of bleeding.<sup>[47]</sup> Subsequently, the American Society for Gastrointestinal Endoscopy (ASGE) guidelines,<sup>[48]</sup> British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines<sup>[49]</sup> similarly recommend discontinuation of warfarin and substitution to low-molecular-weight heparin for high risk endoscopic procedures in patients at high thrombotic risk. But subsequent studies showed that patients undergoing heparin replacement therapy had a higher incidence of delayed bleeding than those who continued to use warfarin.<sup>[14, 50-52]</sup> Therefore, in 2017 guidelines of Japan Gastroenterological Endoscopy Society<sup>[42]</sup> no longer recommend heparin replacement therapy for patients undergoing endoscopic surgery with anticoagulants. It has been stated that even endoscopic procedures with a high risk of bleeding can be carried out without discontinuation of warfarin under a condition of its therapeutic range.

### ***Chronic Kidney Disease (CKD) and Hemodialysis***

Several studies have shown that CKD and hemodialysis increase the incidence of bleeding after gastric ESD.<sup>[13, 15, 16, 37]</sup> Takahashi *et al*<sup>[15]</sup> reported that the risk of bleeding after ESD in CKD patients was significantly higher than that in non-CKD patients. Sanomura *et al*<sup>[13]</sup> found that hemodialysis increased the incidence of delayed bleeding in patients with gastric lesions. Mending of manufactured ulcer caused by ESD may be postponed in patients with CKD due to delicate tissue, low albumin levels, blood vessel disease increased acid excretion and gastrin substance, etc, hence driving to postponed histological recuperation of ulcers and delayed bleeding.

### ***Chronic Liver Disease and Cirrhosis***

Jin *et al*<sup>[30]</sup> showed that combining with chronic liver disease was a risk factor for delayed bleeding. Libânio *et al*<sup>[37]</sup> revealed that cirrhosis was significant clinical risk

factors for delayed bleeding. It may be due to the dysfunction of coagulation mechanism, deficiency of coagulation factor and low platelet in patients with chronic liver disease and liver cirrhosis.

### ***Other Factors***

Some studies have identified elevated prothrombin time international normalized ratio, low hemoglobin level on admission and hypertension as risk factors for post ESD bleeding. <sup>[14, 18]</sup> Age may be another risk factor for bleeding after ESD of gastric lesions. Many studies have pointed out that there is a significant increase in the incidence of bleeding after ESD in elderly patients with gastric lesions, <sup>[22]</sup> but there is still no consensus on the age boundary. Moreover, the meta-analysis failed to discover this connect between the patient's age and the bleeding rate. <sup>[53]</sup> More informations are required to assess this connection.

## **TUMOR-RELATED FACTORS**

### ***Tumor Location***

According to the Japanese classification of gastric carcinoma, <sup>[4]</sup> the stomach is anatomically divided into three portions, the upper (U), middle (M), and lower (L) parts, by the lines connecting the trisected points on the lesser and greater curvatures. There are many theories about the association between the tumor location and gastric delayed bleeding. Several studies have reported higher rates of bleeding after ESD for lesions located in the lower third of the stomach than that in the upper and middle portions. <sup>[12, 34, 54]</sup> On the contrary, the report from Jing Li *et al* <sup>[31]</sup> pointed out that the upper tumor was a risk factor for bleeding after ESD or EMR in patients with EGC. This may be due to different vascular systems in different portions of the stomach. The submucosal artery in the middle and upper part of the stomach is thicker than the lower part of the stomach, and the blood supply is more abundant than the lower part of the stomach, which is more likely to cause bleeding. Thus, during ESD procedure,

experienced endoscopists tend to take more careful and complete hemostatic measures for the middle and upper part of the stomach, while the tumors in the lower part of the stomach are not fully coagulated, leading to a higher possibility of delayed bleeding in the lower portion. In addition, other studies have reported that tumors located in the gastric antrum may increase the incidence of delayed bleeding. <sup>[24]</sup> This may be because active gastric antral peristalsis and bile reflux will delay the healing of artificial ulcer caused by ESD and then increase the risk of delayed bleeding. <sup>[21]</sup>

### ***Tumor and Resected Specimen Size***

Previous studies have shown that tumor size as well as resected specimen size are the main predictor of bleeding after ESD for EGC. <sup>[54, 55]</sup> A number of retrospective studies have reported that the size of excised specimens larger than 40 mm is a significant risk factor for increased risk of delayed bleeding. <sup>[19, 56-58]</sup> A Meta analysis of 74 articles indicated that tumor size >20 mm was an important factor for delayed bleeding. <sup>[37]</sup> Theoretically, the larger the tumor or resected specimen is, the higher the risk of delayed bleeding because large lesions will form large post-ESD ulcers, which require more time for mucosal regeneration and healing.

### ***Depth of Tumor Invasion***

Previous studies on the relationship between the depth of tumor invasion and delayed bleeding are relatively few. The depth of invasion to the submucosa was found to be a risk factor for delayed bleeding after ESD in patients with EGC. <sup>[35]</sup> Toya *et al* also concluded that there was a significant correlation between depth of deep portion of the submucosa (SM2) and bleeding after ESD. <sup>[45]</sup> This suggests that the deeper the invasion of the tumor, the more likely it is to occur delayed bleeding.

### ***Ulcer or Scar***

Ulcers or scars can increase the incidence of delayed bleeding after gastric ESD. Chaohu Yang <sup>[28]</sup> concluded that ulcers or scars were important risk factors for delayed bleeding. Other studies supported that ulcers may increase the risk of bleeding. <sup>[21, 37]</sup> Miyahara *et al* <sup>[23]</sup> also pointed out that the tumor with scars was significantly associated with the increased incidence of delayed bleeding. On the one hand, the vascular growth in the ulcer area is vibrant. On the other hand, healing of an ulcer or scar can lead to local fibrosis. Because of these two factors, endoscopists are unable to adequately stanch the submucosal vessels. It turns out that the risk of delayed bleeding increases.

### ***Gross Tumor Morphology and Histological Classification***

Superficial flat type and superficial depressed type were associated with delayed bleeding after ESD. <sup>[18, 59]</sup> Through retrospective analysis, Yu Gong *et al* found that the superficial flat lesions were more prone to delayed bleeding. <sup>[28]</sup> The reasons for the concern are as follows: (1) Compared with the mass type, the superficial lesion is closer to the muscular layer, inappropriate biopsy is easy to cause submucosal fibrosis, leading to the higher probability of bleeding. (2) The submucosal vessels of superficial lesions are more abundant than those of mass lesions, thus the risk of postoperative bleeding is higher. In addition, histopathology showed that the risk of delayed bleeding in cancer was higher than that in intraepithelial neoplasia <sup>[12, 33]</sup>. This may be because after local tissue canceration, neovascularization and tissue cell variation increase the risk of bleeding. <sup>[32]</sup>

## **PROCEDURE-RELATED FACTORS**

### ***Procedural Time***

Procedure duration was the only factor significantly associated with the incidence of bleeding in the study of Akasaka *et al*. <sup>[60]</sup> Some studies have reported that prolonged operation increases the incidence of bleeding after ESD. <sup>[22, 34, 58]</sup> But there is no



consensus on the specific duration standard. Toyokawa *et al* <sup>[22]</sup> have shown that a long procedure time (mean procedure time is 145 min) is associated with a significantly increased risk of delayed bleeding. Libânio *et al* <sup>[37]</sup> reported that the operation time of more than 60 minutes was related to the increased incidence of gastric bleeding after ESD. Another study demonstrated that operation time  $\geq 90$  min was a risk factor for bleeding after ESD in patients with EGC. <sup>[31]</sup> Goto *et al* proposed a formula for predicting the duration of gastric ESD according to the size, location and ulcer of the tumor. <sup>[61]</sup> A long procedure time related to the location or size of the tumor may delay the healing of manufactured ulcer caused by ESD and increase the risk of delayed bleeding.

### ***Immediate Bleeding Grade and Volume***

According to the bleeding volume and the mode of hemostasis, Jeon *et al* <sup>[62]</sup> proposed that immediate bleeding during the ESD procedure should be graded as follow: grade 0 (no visible bleeding during procedure), grade 1 (trivial bleeding which stops spontaneously or easily controlled by single session of hemocoagulation), grade 2 (minor bleeding which controlled by multiple sessions of hemocoagulation or easily controlled by hemoclips), and grade 3 (major bleeding which needs multiple hemoclips and hemocoagulation). Based on this grading system, Liang Ding *et al* have found that the incidence of delayed bleeding in grade 3 is higher than that in grade 0-2. <sup>[63]</sup> Zheng Huang *et al* <sup>[35]</sup> also suggest that intraoperative blood loss  $>800$ ml is a risk factor for delayed bleeding. However, there is no study to explain the relationship between immediate bleeding and delayed bleeding in detail, and more clinical trials are needed.

## **CONCLUSION**

Although ESD has become the main choice for EGC, we still need to pay attention to the prevention and treatment of bleeding after gastric ESD, especially in patients with

high risk of bleeding after ESD <sup>[64, 65]</sup>. Endoscopists should grasp the factors that may increase the risk of bleeding after ESD in order to pay enough attention to patients with a higher risk of delayed bleeding and take effective preventive measures before, during and after ESD procedure to prevent delayed bleeding.

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