

Original Article



Bleeding After Gastric Endoscopic Submucosal Dissection Focused on Management of Xa Inhibitors

Shoko Ono ¹, Masahiro Ieko ², Ikko Tanaka ³, Yoshihiko Shimoda ³,
Masayoshi Ono ³, Keiko Yamamoto ³, Naoya Sakamoto ³

¹Division of Endoscopy, Hokkaido University Hospital, Sapporo, Japan

²Department of Clinical Laboratory, Iwate Prefectural Chubu Hospital, Kitakami, Japan

³Department of Gastroenterology and Hepatology, Graduate School of Medicine and Faculty of Medicine Hokkaido University, Sapporo, Japan

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Correspondence to

Shoko Ono

Division of Endoscopy, Hokkaido University Hospital, Sapporo, Japan Nishi-7, Kita-15, Kita-ku, Sapporo 060-8638, Japan.

Email: onosho@med.hokudai.ac.jp


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ORCID iDs

Shoko Ono 


<https://orcid.org/0000-0002-4485-6367>

Masahiro Ieko 


<https://orcid.org/0000-0003-1854-4543>

Ikko Tanaka 

<https://orcid.org/0000-0003-0171-5879>

Yoshihiko Shimoda 

<https://orcid.org/0000-0001-7532-7903>

Masayoshi Ono 

<https://orcid.org/0000-0002-3116-1638>

Keiko Yamamoto 

<https://orcid.org/0000-0003-2343-2984>

Naoya Sakamoto 

<https://orcid.org/0000-0003-0061-059X>

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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ABSTRACT

Purpose: The use of direct oral Xa inhibitors (DXaIs) to prevent venothrombotic events is increasing. However, gastrointestinal bleeding, including that related to endoscopic resection, is a concern. In this study, we evaluated bleeding and coagulation times during the perioperative period of gastric endoscopic submucosal dissection (ESD).

Materials and Methods: Patients who consecutively underwent gastric ESD from August 2016 to December 2018 were analyzed. Bleeding rates were compared among the 3 groups (antiplatelet, DXaIs, and control). DXaI administration was discontinued on the day of the procedure. Prothrombin time (PT), activated partial thromboplastin time, and the ratio of inhibited thrombin generation (RITG), which was based on dilute PT, were determined before and after ESD.

Results: During the study period, 265 gastric ESDs were performed in 239 patients, where 23 and 50 patients received DXaIs and antiplatelets, respectively. Delayed bleeding occurred in 17 patients (7.4%) and 21 lesions (7.1%). The bleeding rate in the DXaI group was significantly higher than that in the other groups (30.4%, $P < 0.01$), and the adjusted odds ratio of bleeding was 5.7 (95% confidence interval, 1.4–23.7; $P = 0.016$). In patients using DXaIs, there was a significant ($P = 0.046$) difference in the median RITG between bleeding cases (18.6%) and non-bleeding cases (3.8%).

Conclusions: A one-day cessation of DXaIs was related to a high incidence of bleeding after gastric ESD, and monitoring of residual coagulation activity at trough levels might enable the predicted risk of delayed bleeding in patients using DXaIs.

Keywords: Gastric cancer; Endoscopic submucosal dissection; Factor Xa inhibitor; Hemorrhage

INTRODUCTION

Gastric endoscopic submucosal dissection (ESD) is an acceptable method for endoscopic resection and exhibits minimal invasiveness for gastric neoplasms exhibiting little metastatic potential [1,2]. Technical developments have made it possible to remove large lesions during en bloc resection; however, one of the clinical issues associated with the procedure is delayed bleeding, especially in patients using antithrombotic agents [3,4]. It has been reported that anticoagulants have a stronger relationship with bleeding during endoscopic resection than antiplatelet agents [5,6].

Author Contributions

Conceptualization: O.S., I.M.; Data curation: T.I., S.Y., O.M., Y.K.; Formal analysis: O.S., I.M.; Investigation: T.I., S.Y., O.M., Y.K.; Methodology: O.S., I.M.; Project administration: O.S.; Supervision: I.M., S.N.; Validation: name; Visualization: O.S.; Writing - original draft: O.S.; Writing - review & editing: O.S., I.M., S.N.

Direct oral anticoagulants (DOACs), including direct oral Xa inhibitors (DXaIs) and thrombin inhibitors, have been used in place of vitamin K antagonists for the treatment of patients with nonvalvular arterial fibrillation and venous thromboembolism. When temporary interruption of anticoagulant administration is required to perform surgery or other invasive procedures, the pharmacokinetic characteristics of DOACs, including rapid onset/offset and short half-life, could be advantageous for perioperative management [7]. Although there are some guidelines for perioperative management of endoscopic procedures, the recommendations for interrupting the administration of antithrombotic agents are based on the pharmacokinetics and expert opinions [8-10]. Furthermore, there have been few reports showing clinical evidence supporting these recommendations.

Recently, there have been studies regarding the high bleeding risk in endoscopic resection for patients using DOACs [11,12]. However, there have been no reports on the recommendation of monitoring molecular markers related to bleeding during the perioperative period. In this study, we investigated delayed bleeding after gastric ESD and measured the molecular markers that predicted bleeding in patients using DXaIs.

MATERIALS AND METHODS

Patients

We retrospectively analyzed patients who underwent gastric ESD between August 2016 and December 2018. Patients were classified into 2 groups according to the antithrombotic agent used; that is, one group only used antiplatelets (antiplatelet group) and the other group used DXaIs with or without antiplatelet agents (DXaI group). Patients who did not use either anticoagulants or antiplatelets were used as controls. Lastly, patients administered warfarin and dabigatran were excluded from the study.

The study protocol was approved by the Hokkaido University Hospital Review Board (018-0308) and opt-out consent was obtained from all patients.

ESD

The indications for ESD were based on Japanese guidelines [13]. ESD procedures followed standard methods using IT knife2™ (KD-611L; Olympus Corp, Tokyo, Japan). A solution of 0.4% sodium hyaluronate (MucoUp; Johnson and Johnson, Tokyo, Japan) was used as the submucosal injection solution, and iatrogenic ulcers after resection were not sutured. A high-frequency electrosurgical generator VIO300D (Erbe, Tübingen, Germany) was used, and complete hemostasis was confirmed after ESD.

Our schedule after ESD was as follows: on postoperative day 1 (POD 1), blood laboratory tests were routinely performed and water intake was allowed. Meals were provided from POD 2 and second-look endoscopy was generally performed on POD 6. The hospitalization period was 7 days. In addition, patients visited the hospital for endoscopy and histological examination on POD 30.

Perioperative management of antithrombotic agents

DXaIs (apixaban, edoxaban, and rivaroxaban) were not administered on the morning of the day of the procedure and the last administration of drugs took place on the evening of the day before the procedure. Administration of DOACs was restarted on the morning of POD 1.

DOACs were generally withdrawn for approximately 36 hours during the perioperative period (from the last administration to resumption of administration). For patients who were judged by the prescribing doctors to have a high risk for thromboembolism and patients with high levels of soluble fibrin (SF) ($>7 \mu\text{g/mL}$, IATRO-SF, LSI Medience Corporation, Tokyo, Japan), heparin was continuously injected immediately after completion of ESD until 4 hours before resumption of DXaI administration on POD 1.

Generally, the period for withdrawal of antiplatelet agents was in accordance with the Japan Gastroenterological Endoscopy Society (JGES) guidelines published in 2012 [14]. For patients with low thrombotic risk, aspirin and thienopyridine were discontinued for 3 and 5 days, respectively. For patients with a high thrombotic risk, aspirin or cilostazole administration was continued during the perioperative period. Administration of other agents was stopped 1 day before the procedure. The last date of antithrombotic drug administration was checked and recorded immediately prior to the procedure.

Measurement of coagulation time

Prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured using Thromborel S (Siemens Healthcare Diagnostics, Marburg, Germany) and Thrombocheck aPTT-SLA (Sysmex, Kobe, Japan), respectively.

For patients who were administered DXaIs, the ratio of inhibited thrombin generation (RITG) and blood concentrations of each DXaI were determined. RITG based on dilute PT (dPT) was determined as the residual coagulation activity according to a previously reported method [15]. RITG was calculated using the following formula: $\text{RITG} = (\text{patient dPT} - \text{control dPT}) / \text{control dPT} \times 100$. RITG ranged from -18.2 to 13.7 (mean \pm SD). Plasma concentrations of DXaIs were also measured using an anti-Xa assay with heparin (Sekisui Medical Co., Ltd. Tokyo, Japan) [15]. Blood sampling was performed at 13:00 hour on the day of ESD (trough) and at 9:00 hour on POD 1 (peak was observed 2 hours after restarting the administration of DXaIs).

Outcomes

Delayed bleeding was defined as follows: active bleeding or adhesion of blood clots on the iatrogenic ulcer revealed by emergent endoscopy more than 24 hours after ESD, or as a decrease in hemoglobin level ($>2 \text{ g/dL}$) or need for transfusion within 30 days after ESD [16,17]. Patient factors, including age, sex, laboratory data, and procedural factors, such as lesion characteristics, were also analyzed. The incidence of thromboembolic events was confirmed through patient interviews on POD 30. These events included both arterial (such as ischemic stroke and ischemic heart disease) and venous events (such as deep vein thrombosis and pulmonary embolism).

Statistical analysis

JMP® Pro 14 (SAS Institute Inc., Cary, NC, USA) was used for data analysis. Summarized numerical data are expressed as medians with an interquartile range. Categorical data were compared using the χ^2 test and numerical data were compared using the Mann-Whitney U test or Kruskal-Wallis test. Multivariate logistic regression analysis was performed to calculate adjusted odds ratios (ORs). Correlations between RITG and PT or DXaI concentrations were determined using Spearman's correlation coefficients. A P-value of <0.05 was considered statistically significant.

RESULTS

During the study period, 265 gastric ESDs were performed on 239 patients. Nine patients who used warfarin and one who used dabigatran were excluded from analysis. A total of 253 ESDs were analyzed in 229 patients. Fifty patients used only antithrombotic agents and 7 who used only antiplatelets took multiple agents (2 agents, n=6; 4 agents, n=1). Twenty-three patients used DXaIs (rivaroxaban, n=8; apixaban, n=10; edoxaban, n=5) (**Fig. 1**). All patients had follow ups for 30 days after ESD. Patient characteristics and gastric lesions are presented in **Tables 1** and **2**, respectively. There were significant differences in eGFR, PT, and APTT.

Delayed bleeding after gastric ESD

Bleeding occurred in 17 patients (7.4%) and 21 lesions (7.1%). In patients with bleeding, the use of DXaIs, PT, and APTT was significantly higher than that in the non-bleeding cases (**Supplementary Table 1**). Logistic regression analysis showed that the use of DXaIs was an independent risk factor (adjusted OR, 4.40; 95% confidence interval [CI], 1.18–16.3; P=0.027).

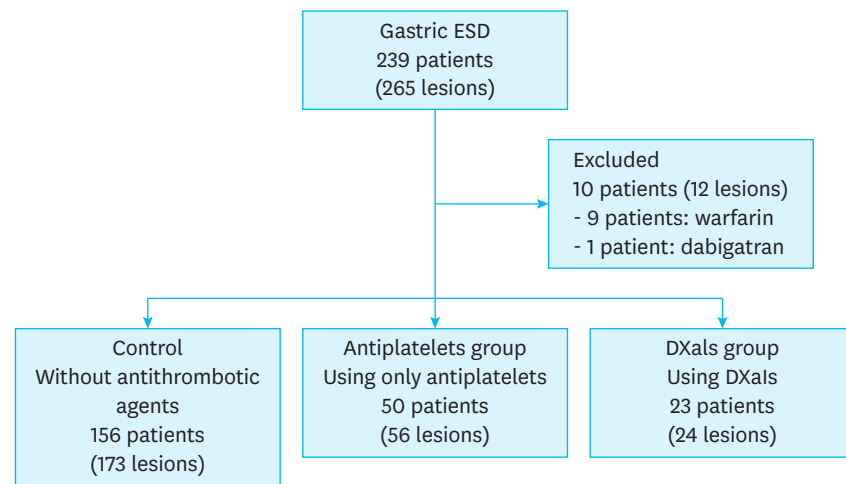


Fig. 1. Patient flow diagram.

A total of 239 patients were included in this study. Fifty patients used only antithrombotic agents, and 23 used DXals with or without antithrombotic agents.

ESD = endoscopic submucosal dissection; DXals = direct oral Xa inhibitors.

Table 1. Comparison of characteristics of patients

| Patients | Control (n=156) | Antiplatelets (n=50) | DXals (n=23) |
|------------------------------------|------------------|----------------------|------------------|
| Age* (yr) | 73 (67–78.3) | 75 (71–81) | 78 (71–80) |
| Male | 114 | 43 | 17 |
| Antiplatelet agents | | | |
| Aspirin | | 23 | 6 |
| Thienopyridine | | 20 | 2 |
| Cilostazole | | 11 | 0 |
| Others | | 14 | 1 |
| DXals | | | |
| Rivaroxaban | | | 8 |
| Apixaban | | | 10 |
| Edoxaban | | | 5 |
| eGFR† (mL/min/1.73m ²) | 73.4 (60.4–83.6) | 65.5 (54.6–86.7) | 56.6 (53.3–71.3) |
| PT‡ (sec) | 11.4 (10.9–11.9) | 11.6 (11.1–12.0) | 13.0 (12.1–13.8) |
| APTT‡ (sec) | 28.9 (27.5–30.8) | 29.1 (27.8–31.4) | 32.4 (30.7–35.9) |

Values are presented as median (interquartile range) or number (%).

DXals = direct oral Xa inhibitors; eGFR = estimated glomerular filtration rate; PT = prothrombin time; APTT = activated partial thromboplastin time.

*P=0.018; †P=0.025; ‡P<0.001.

Table 2. Comparison of gastric lesions and procedures

| Gastric lesions | Control (n=173) | Antiplatelets (n=56) | DXals (n=24) |
|---|-----------------|----------------------|--------------|
| Size of gastric cancer (mm) | 12 (8–18) | 13 (8–19) | 11 (8–15) |
| Size of resected specimens (mm) | 31 (25–39) | 29 (22.3–35) | 28 (26–33) |
| Location (lower/middle/upper thirds of stomach) | 98/53/22 | 27/23/6 | 11/10/3 |
| Histological type (intestinal type) | 164 (94.8) | 56 (100) | 23 (95.8) |
| Submucosal invasion | 17 (9.8) | 7 (12.5) | 0 |
| Positive for ulceration | 4 (2.3) | 2 (3.6) | 0 |
| Lymphovascular invasion | 7 (4.0) | 2 (3.6) | 0 |
| Procedure time for ESD (min) | 56 (30–84) | 55 (24–89) | 50 (30–68) |

Values are presented as median (interquartile range) or number (%).

DXals = direct oral Xa inhibitors; ESD = endoscopic submucosal dissection.

In the DXaI group, the delayed bleeding rate was significantly ($P<0.01$) higher than that in the other groups and the adjusted OR of bleeding in the control group was 5.7 (95% CI, 1.4–23.7; $P=0.016$) (Table 3).

Bleeding and coagulation time in patients using DXals

A comparison of bleeding and non-bleeding cases is shown in Table 4. Intravenous administration of heparin was performed after the procedure in 8 patients with a high risk of thrombosis. Only RITG as the actual coagulation time was significantly ($P=0.046$) higher in the bleeding cases (18.6%) than in the non-bleeding cases (3.8%). All bleeding cases were treated using endoscopic hemostasis.

Table 3. Bleeding rates and adjusted odds ratio after gastric ESD

| Bleeding | Control | Antiplatelets | DXals | Total |
|-----------------------------------|--------------|---------------|---------------------------|--------------|
| Bleeding per patient | 8/156 (5.1) | 2/50 (4.0) | 7/23 (30.4 [*]) | 17/229 (7.4) |
| Bleeding per lesion | 8/173 (4.6) | 3/56 (4.4) | 7/24 (28.6 [*]) | 21/253 (7.1) |
| Bleeding per patient (odds) | 1 | 1.2 | 5.7 | - |
| 95% CI | - | 0.22–6.2 | 1.4–23.7 | - |
| P-value | - | 0.85 | 0.016 | - |
| Median time of bleeding after ESD | Day 6 (2–11) | Day 3 (2–4) | Day 5 (0–6) | - |

Values are presented as number (%).

ESD = endoscopic submucosal dissection; DXals = direct oral Xa inhibitors; CI = confidence interval.

^{*} $P<0.01$ (vs. control and antiplatelets).

Table 4. Comparison between bleeding cases and non-bleeding cases in patients using DXals

| Factors of patients and procedures | Bleeding (n=7) | Non-bleeding (n=16) | P-value |
|------------------------------------|------------------|---------------------|---------|
| Age (yr) | 80 (73–82) | 78 (71–80) | 0.434 |
| Sex (male:female) | 6:1 | 11:5 | 0.621 |
| DXals | | | |
| Rivaroxaban | 2 | 6 | |
| Apixaban | 4 | 6 | 0.725 |
| Edoxaban | 1 | 4 | |
| Using antiplatelets | 2 | 5 | 0.676 |
| Administration of heparin | 2 | 6 | 1.000 |
| eGFR (mL/min/1.73 m ²) | 60.4 (55.6–65.4) | 57.3 (44.9–78.8) | 0.852 |
| HAS-BLED score >3 | 2 | 3 | 0.564 |
| PT (sec) (trough) | 13.6 (12.7–13.9) | 12.8 (12.1–13) | 0.112 |
| APTT (sec) (trough) | 33.1 (30.7–43) | 32.5 (29.2–35.9) | 0.549 |
| RITG (trough) | 18.6 (3.6–19.9) | 3.8 (–0.7–12.7) | 0.0463 |
| Size of gastric cancer (mm) | 11 (7–28) | 12 (8–14) | 0.916 |
| Procedure time (min) | 52 (17–68) | 50 (29–68) | 0.860 |

Values are presented as median (interquartile range).

DXals = direct oral Xa inhibitors; eGFR = estimated glomerular filtration rate; PT = prothrombin time; APTT = activated partial thromboplastin time; RITG = ratio of inhibited thrombin generation.

Table 5. Cases with delayed bleeding in the patients using DXaIs

| Case | Age | Sex | Size (mm) | Onset of bleeding* | Antithrombotics at bleeding [†] | At trough | | At bleeding | |
|------|-----|--------|-----------|--------------------|--|-----------------|-------------------|-------------|------|
| | | | | | | PT [‡] | RITG [§] | PT | RITG |
| 1 | 73 | Male | 15 | 1, 2 | H | 14.7 | 34.5 | 14.8 | - |
| 2 | 77 | Female | 28 | 1 | H | 12.7 | 3.6 | 12.6 | - |
| 3 | 84 | Male | 7 | 2 | R | 13.7 | 18.6 | 16.5 | 41.8 |
| 4 | 71 | Male | 16 | 5 | E, C | 13.9 | 19.6 | 18.8 | 24.2 |
| 5 | 80 | Male | 5 | 5 | A | 13.6 | 16.9 | 14.0 | - |
| 6 | 82 | Male | 8 | 6 | A | 13.0 | 19.9 | 14.0 | 34.7 |
| 7 | 79 | Male | 30 | 6 | A | 11.8 | 0.4 | 13.4 | 10.6 |

DXaIs = direct oral Xa inhibitors; PT = prothrombin time; RITG = ratio of inhibited thrombin generation.

*Postoperative day; [†]H: heparin, R: rivaroxaban, E: edoxaban, C: clopidogrel, A: apixaban; [‡]PT from 10.2–12.6 seconds; [§]RITG ranged from –18.2 to 13.7.

All the cases in which delayed bleeding occurred are presented in **Table 5**. During the administration of heparin, bleeding occurred in 2 cases before restarting the administration of DXaIs. The trough levels of PT and RITG were high, and coagulation activity remained. In 3 cases, RITG was not measured at the time of bleeding. Furthermore, no thrombotic events occurred during the observation period.

Correlations of RITG, PT, and drug concentrations at trough

Blood sampling was performed 18 hours after the last dose. There was a strong correlation between RITG and PT ($R^2=0.66$, $P<0.01$). The serum concentrations of rivaroxaban, apixaban, and edoxaban were 81.3 ± 29.7 , 87.4 ± 39.5 , and 20.6 ± 24.9 ng/mL, respectively. There were no significant correlations between RITG and DXaI concentrations (rivaroxaban: $R^2=0.20$, $P=0.37$; apixaban: $R^2=0.30$, $P=0.16$; edoxaban: $R^2=0.85$, $P=0.08$).

DISCUSSION

To the best of our knowledge, this is the first report on the measurement of molecular markers related to coagulation activity for the perioperative management of anticoagulants for gastric ESD. For patients receiving anticoagulation therapy, the JGES recommends heparin replacement therapy (HRT) in patients scheduled to undergo endoscopic resection with a high bleeding risk [14]. However, perioperative management of HRT is complicated and there are high bleeding rates after endoscopic resection; therefore, the JGES updated the guidelines regarding the use of anticoagulants in 2017 [10,18,19]. A one-day cessation of DOACs, equivalent to HRT, is now recommended for perioperative management.

The 2016 updated guidelines of the American Society for Gastrointestinal Endoscopy recommend cessation of DOACs for 1 to 3 days before endoscopic resection, and the European Society of Gastrointestinal Endoscopy 2016 guidelines recommend cessation of DOACs for at least 2 days before endoscopic resection [8,9]. In addition, the APAGE-APSDE guidelines recommend withholding DOACs for at least 48 hours before the high-risk procedure [20]. DOACs are re-administered after confirmation of hemostasis, and anticoagulant therapy is stopped for several days. Japanese guidelines recommend the shortest cessation of DOACs for 1 day prior to endoscopic resection [10].

Recently, there have been reports on the high bleeding risk after endoscopic resection in the management of one-day cessations of DOACs [17,21,22]. The occurrence of delayed bleeding after gastric ESD in DOAC users was high ($\leq 20\%$) according to previous Japanese studies; however, previous studies reported that taking DOACs was not statistically associated with

post-ESD bleeding (8.7%) [23-25]. Moreover, the discrepancy in bleeding rates depends on the withdrawal time of the DOACs.

Meanwhile, withdrawal of DOACs for more than 48 hours may increase thromboembolic events due to the complete disappearance of the anticoagulant effect. In fact, a prospective observational study showed that thrombotic events occurred in 0.4% of patients, which is an incidence higher than that reported previously [26]. Although the bleeding risk is high in the management of a short cessation of DXaIs (as recommended by Japanese guidelines), endoscopic hemostasis would provide complete hemostasis and prevent unfortunate thrombotic events.

The guidelines mentioned above also recommend that preoperative cessation of DOACs depends on renal function; however, molecular markers that predict delayed bleeding after endoscopic resection have not been determined yet. We believe that monitoring the anticoagulant activity of DOACs (for instance, with warfarin) is necessary to reduce bleeding after gastric ESD. To determine the residual coagulation activity of DXaIs, there have been reports on the evaluation of PT, dPT, and Russell's viper venom time [27-29]. RITG is a new dPT-based assay used as a confirmation test for DxaI therapy. Moreover, RITG fluctuation during the peak and trough periods reflects anticoagulant activity, which is different from the blood concentration of DxaIs [15]. The effects of DxaIs are somewhat reflected in PT, but the sensitivity of DXaIs to PT reagents varies [30]. In addition, dPT showed a higher correlation with the concentration of each DXaI than with PT. RITG was also shown to be related to bleeding and thrombotic events in patients administered DXaIs [15]. This study also showed that RITG is associated with delayed bleeding after gastric ESD. For GI bleeding related to DOACs, it has been hypothesized that non-absorbed active anticoagulant agents within the GI tract cause bleeding due to vulnerable mucosal breaks [7]. However, our data reveals that residual coagulation activity at the trough increases the bleeding risk after restarting the administration of DXaIs. It might be useful to measure the actual coagulation time at trough levels and individually determine the cessation of DXaIs according to residual coagulation activity.

This study had several limitations. First, it was conducted at a single institution with a small sample size. Second, the heterogeneity of DxaIs was limited. Third, the molecular markers were measured only during the perioperative period. Although the blood concentrations of DXaIs can be measured, the actual anticoagulant effects vary between individuals who receive the same drug dose. Unfortunately, RITG has not been commercialized; however, we recommend monitoring some molecular markers. Recently, the validity of confirmation tests for DOACs has been verified, and global data are needed in the field of endoscopy to provide safe treatment [31,32].

In conclusion, a one-day cessation of DXaIs for gastric ESD is associated with a high risk of delayed bleeding, and monitoring residual coagulation activity could be helpful for preventing delayed bleeding.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Comparison of characteristics between bleeding cases and non-bleeding cases

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