Risk factors and prediction of bleeding after gastric endoscopic submucosal dissection in patients on antithrombotic therapy: newly developed bleeding prediction application software, SAMURAI model

Akitoshi Hakoda,1,2 Toshihisa Takeuchi,1,3,4 Yuichi Kojima,1 Yasuhiro Fujiwara,4 Yasuaki Nagami,4 Yuji Naito,5 Shinsaku Fukuda,6 Tomoyuki Koike,5 Mitsuhige Sugimoto,5 Kenta Hamada,7 Hideki Kobara,10 Norimasa Yoshida,11 Tomoki Inaba,12 Akihito Nagahara,13 Eriko Koizumi,14 Kazunari Murakami,15 Takahisa Furuta,16 Naotaka Ogawara,17 Hajime Isomoto,18 Kotaro Shibagaki,19 Hiromi Kataoka,20 Hidekazu Suzuki,21 and Kazuhide Higuchi1

12nd Department of Internal Medicine and 1Endoscopic Center, Osaka Medical and Pharmaceutical University Hospital, 2-7 Daigakumachi Takatsuki, Osaka 569-8686, Japan
2Department of Medical Statistics and 3Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka 545-8585, Japan
4Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan
5Division of Endoscopy, Hiroaki University Hospital, Amorii 036-8216, Japan
6Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Okayama 700-8530, Japan
7Department of Gastroenterology, Kagawa University Faculty of Medicine, Kagawa 760-0016, Japan
8Division of Gastroenterology, Tohoku University Graduate School of Medicine, Miyagi 980-8575, Japan
9Department of Gastroenterological Endoscopy, Tokyo Medical University Hospital, Tokyo 160-0023, Japan
10Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Okayama 700-8530, Japan
11Department of Gastroenterology, Kagawa Prefectural Central Hospital, Kagawa 760-8557, Japan
12Department of Gastroenterology, Juntendo University School of Medicine, Tokyo 113-0003, Japan
13Department of Gastroenterology, Graduate School of Medicine, Kitasato University, Tokyo 113-8603, Japan
14Department of Gastroenterology, Kagawa Prefectural Central Hospital, Kagawa 760-8557, Japan
15Department of Gastroenterology, Kyorin University School of Medicine, Tokyo 160-8582, Japan
16Department of Gastroenterology, Faculty of Medicine, Kitasato University, Tokyo 160-8582, Japan
17Department of Gastroenterology, Aichi Medical University Hospital, Aichi 480-1195, Japan
18Division of Gastroenterology and Nephrology, Department of Multidisciplinary Internal Medicine, Faculty of Medicine, Tottori University, Tottori 680-8550, Japan
19Department of Gastroenterology, Faculty of Medicine, Shimane University, Shimane 690-8523, Japan
20Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Aichi 467-8601, Japan
21Department of Gastroenterology and Hepatology, Keio University School of Medicine, Tokyo 160-8582, Japan

(Received 4 October, 2021; Accepted 20 October, 2021)

Bleeding after gastric endoscopic submucosal dissection (ESD) remains problematic, especially in patients receiving antithrombotic therapy. Therefore, this study aimed to identify the risk factors. In this prospective study, patients (n = 1,207) who underwent gastric ESD while receiving antithrombotic therapy were enrolled at Osaka Medical and Pharmaceutical University Hospital and 18 other referral hospitals in Japan. Risks of post-ESD bleeding were calculated using multivariable logistic regression. The dataset was divided into a derivation cohort and a validation cohort. We created a prediction model using the derivation cohort. The accuracy of the model was evaluated using the validation cohort. Post-ESD bleeding occurred in 142 (11.8%) participants. Multivariable analysis yielded an odds ratio of 2.33 for aspirin, 4.90 for P2Y12 receptor antagonist, 1.79 for clopidogrel, 0.95 for other antithrombotic agents, 6.53 for warfarin, 5.65 for dabigatran, 7.84 for apixaban, 10.45 for edoxaban, 6.02 for rivaroxaban, and 1.46 for heparin bridging. The created prediction model was called safe ESD management using the risk analysis of post-bleeding in patients with antithrombotic therapy (SAMURAI). This model had good predictability, with a C-statistic of 0.77. In conclusion, use of the SAMURAI model will allow proactive management of post-ESD bleeding risk in patients receiving antithrombotic therapy.

Key Words: bleeding, antithrombotic agents, multivariable analysis, prediction model, validation

Endoscopic submucosal dissection (ESD) is a widely used procedure for treating early gastric cancers and gastric adenomas.1,2 One of the major complications of this procedure is post-ESD bleeding. Previous studies have shown that post-ESD bleeding occurred in 4.1% to 8.5% of patients who underwent gastric ESD.3,4 Furthermore, an increasing number of patients received antithrombotic therapy for the treatment of ischemic heart disease, cerebrovascular disease, arrhythmia, postoperative valvular heart disease, and other arteriosclerotic diseases. Therefore, ESD is frequently performed in people receiving antithrombotic therapy. The Japan Gastroenterological Endoscopy Society (JGES) guidelines for gastroenterological endoscopy in patients undergoing antithrombotic therapy were published in July 2012.5 These guidelines discussed the dilemma that although there is a risk of gastroenterological hemorrhage associated with the continuation of antithrombotic therapy, its discontinuation is associated with the risk of thromboembolism.6 Even when ESD is performed based on these guidelines, post-ESD bleeding occurs more frequently in patients receiving antithrombotic therapy than in patients not receiving antithrombotic therapy.7 Despite numerous reports on the risk factors for post-ESD bleeding, there is a lack of consensus regarding the appropriate use of ESD for patients with antithrombotic therapy.

*To whom correspondence should be addressed.
E-mail: toshihisa.takeuchi@ompu.ac.jp
Thus, this study aimed to identify the risk factors and create a prediction model for post-ESD bleeding in patients receiving antithrombotic therapy.

Many factors, including male sex, comorbidities, tumor characteristics, tumor location, and ESD procedure time, have been identified as high-risk factors for post-ESD bleeding. In addition, antithrombotic therapies are considered important risk factors.\textsuperscript{5,11-13} Although certain models predict post-ESD bleeding, most of the target cases in these models are patients who are not receiving antithrombotic therapy.\textsuperscript{16} We suspect that the mechanism of post-ESD bleeding may be different with and without antithrombotic therapy. Moreover, different antithrombotic agents can be used, such as anticoagulants and antiplatelet agents, and risk factors for each therapy must be evaluated and compared. Patients with antithrombotic therapy made up 18.3\% of all ESD cases.\textsuperscript{10} Thus, it is difficult to enroll sufficient number of patients receiving antithrombotic therapy and undergoing ESD from a single center. Therefore, patients had to be enrolled from numerous hospitals to create a prediction model of post-ESD bleeding for patients receiving antithrombotic therapy. Determining the risk of antithrombotic therapies and accurately predicting the probability of post-ESD bleeding will allow better preparation for the management of post-ESD bleeding complications.

Methods

This study was conducted according to the guidelines of the Declaration of Helsinki. The study was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University and by the institutional review board of each participating institution before the recruitment of patients. Informed consent for this study was obtained in the form of opt-out on the website of each participating hospital.

Data collection. Demographic and clinical data were collected using the Research Electronic Data Capture management system. The institution’s collaborators entered the data needed for this study from the medical records and endoscopy and pathology reports.

Patients. We recruited patients who received antithrombotic therapy and underwent gastric ESD at either Osaka Medical and Pharmaceutical University Hospital or any of the other 18 other referral hospitals in Japan between January 2013 and July 2018, for participation in this study. Patients who had undergone surgery with heavy bleeding or perforation during ESD were excluded. Because this study enrolled patients who were using antithrombotic agents, patients who did not receive antithrombotic agents during the preoperative period were excluded. Patients who underwent ESD for multiple simultaneous lesions were not recruited.

ESD procedure. ESD was performed according to the ESD procedure criteria at all the participating institutions.\textsuperscript{17} The ESD procedure consisted of the following: marking around the lesion, submucosal injection, mucosal incision outside the lesion mark, submucosal dissection of the specimen after incision around the lesion, collection of the specimen, and assessment for ESD ulcer. For visible blood vessels at the base of the ulcer, hemostasis may be performed prophylactically.\textsuperscript{17}

Second-look endoscopy was defined as endoscopy scheduled for wound confirmation of post-ESD ulcers on the day after ESD. In this study, second-look endoscopy was performed in all cases. After ESD, proton pump inhibitor (PPI) or potassium-competitive acid blocker (PCAB) was administered to all patients according to the discretion of the clinicians. Standard doses of PPI and PCAB were administered.

 Interruption and resumption of antithrombotic agents. The interruption of antithrombotic agents before gastric ESD is determined according to the guidelines of JGES,\textsuperscript{9} which are similar to the European and American guidelines: 3–5 days for low-dose aspirin, 5–7 days for P2Y12 receptor antagonist (P2Y12RA), 1 day for cilostazol and 1 day for other antithrombotic agents.\textsuperscript{14,19} In addition, orally administered low-dose aspirin and cilostazol can be continued in cases at high risk of thromboembolism. In patients taking warfarin, if the prothrombin time-international normalized ratio (PT-INR) was confirmed to be >1.5 by blood sampling before ESD, patients continue to take warfarin. Furthermore, the guidelines were revised in 2017 to allow warfarin to be continued during ESD if the PT-INR is below the effective range. Direct oral anticoagulants (DOACs) were withdrawn only on the day of ESD. In patients taking these drugs with a high risk of thromboembolism, heparin bridging is acceptable when the above antithrombotic drugs are withdrawn and should be discontinued at least 3 h before ESD and resumed after confirming postoperative hemostasis. The guidelines also recommend that dabigatran, apixaban, edoxaban, and rivaroxaban should not be taken the day of ESD.

However, the prescribing physician commonly determines the days of interruption for antithrombotic agents. For cases where antithrombotic agents had been suspended for durations longer than the period of drug action, the drugs were considered ineffective at the time of ESD and were considered not to be taken.

Patients who only received antithrombotic agents with long-term suspension were excluded from the analysis. Resumption of antithrombotic agents was performed as soon as possible after identifying the absence of bleeding using blood sampling or endoscopy.

Post-ESD bleeding. Based on a previous report, post-ESD bleeding was defined as hematemesis and/or melena or a >2 g/dl decrease in hemoglobin value in the patient’s most recent laboratory test, requiring an unscheduled esophagogastro-duodenoscopy, during which the bleeding was confirmed to be from a post-ESD ulcer.\textsuperscript{11,16,20} Preventive hemostasis of visible vessels during second-look endoscopy was not regarded as post-ESD bleeding. In this study, post-ESD bleeding was monitored by esophagogastro-duodenoscopy to check for scarring of the ulcer, approximately 2 months after ESD.

Statistical analysis. Categorical variables are expressed as percentages and numbers. Continuous variables are summarized as medians and interquartile ranges. Categorical variables were compared using $\chi^2$ tests; continuous variables were compared using the Kruskal–Wallis test.

The patients were divided into a group with post-ESD bleeding and a group without post-ESD bleeding to investigate the potential risk factors associated with post-ESD bleeding. The following variables were analyzed: age, sex, body mass index (BMI), diabetes, hypertension, hemodialysis, tumor diameter, tumor location, gastric atrophy, postoperative oral administration of PPI or PCAB, use of gastroprotective agents, use of two or more antiplatelet therapies, and taking both antiplatelet drug and anticoagulant or DOAC. In addition, the incidence of post-ESD bleeding in the aspirin- and cilostazol-using groups was examined separately for continuation and withdrawal of medication.

In the multivariable regression analysis, logistic regression was performed considering post-ESD bleeding as an outcome, using clinically important factors (e.g., age, sex, BMI, hemodialysis, tumor diameter, and taking both antiplatelet drug and anticoagulant or DOAC) as explanatory variables. In the analysis, age was used as a nonlinear factor with five knots. By incorporating it into the analysis as a nonlinear factor, even if age and risk do not have a simple proportional relationship, they can be accurately reflected in the analysis results. Since the study was carried out to evaluate preoperative risk factors, information such as administration of PPI or PCAB and the results of pathological examination were not included in the multivariable regression analysis.
The dataset was randomly divided into the derivation cohort and validation cohort using the random numbers created in the analysis software. The derivation and validation cohorts consisted of 70% (n = 845) and 30% (n = 362) of the patients, respectively. The ratio of this split is considered to be the best ratio for prediction model creation and validation.21

A predictive model for post-ESD bleeding was created using the derivation cohort. Factors required to predict post-ESD bleeding rate were age, sex, BMI, hemodialysis, tumor diameter, and presence or absence of each antithrombotic therapy.

The prediction accuracy of the model was evaluated by receiver operating characteristic (ROC) analysis and the areas under the curve (AUC).

Statistical analyses were performed using R ver. 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided, and p<0.05 was considered significant.

**Results**

We recruited 1,245 patients. Of these patients, 38 were eventually excluded from this retrospective study because of either the lack of information on postoperative bleeding (n = 2) or not having used long-term antithrombotic therapy before ESD (n = 36).

**Study flow diagram and patient background.** The flowchart of patient enrolment is shown in Fig. 1. The clinical characteristics of the 1,207 patients are summarized in Table 1. The median age of the patients was 76.0 ± 5.0 years. Post-ESD bleeding occurred in 142 (11.8%) patients. There were 5.6% (68 cases) of patients on dialysis, and 21.0% (253 cases) of the patients were taking two or more antiplatelet agents.

Details of the antithrombotic therapy are as follows: aspirin, 648 cases (of which 290 continued and 358 withdrew the therapy); P2Y12RA, 185 cases; cilostazol, 144 cases (of which 40 cases continued and 104 withdrew the therapy); other antiplatelet agents, 103 cases; warfarin, 228 cases; dabigatran, 34 cases; apixaban, 51 cases; edoxaban, 25 cases; rivaroxaban, 64 cases; and taking both antiplatelet drugs and anticoagulants or DOAC, 162 cases. Oral anticoagulant therapy was replaced by heparin in 180 cases. The median period of heparin bridging before ESD was 5 days. The median units of heparin were 10,000 units per day.

**Univariate analysis and multivariable analysis.** In the univariate analysis, young age, low BMI, hemodialysis, large tumor diameter, and use of two or more antithrombotic agents were significant risk factors for postoperative bleeding (Table 2). In addition, no significant differences emerged in the study of posterior bleeding in the groups where aspirin and cilostazol were continued compared to when the therapies were withdrawn (Table 2). The multivariable analysis adjusted using explanatory variables (i.e., age, sex, BMI, use or non-use of hemodialysis, tumor diameter, and taking both antiplatelet drug and anticoagulants or DOAC) revealed the following odds for postoperative bleeding with regard to the different antithrombotic therapies (Table 3): aspirin [odds ratio (OR), 2.23; 95% confidence interval (CI), 1.19–4.57], P2Y12RA (OR, 4.90; 95% CI, 2.76–8.70), cilostazol (OR, 1.79; 95% CI, 0.80–4.03), other antiplatelet agents (OR, 0.95; 95% CI, 0.35–2.59), warfarin (OR, 6.53; 95% CI, 2.29–18.62), dabigatran (OR, 5.65; 95% CI, 1.48–21.52), apixaban (OR, 7.84; 95% CI, 2.67–23.01), edoxaban (OR, 10.45; 95% CI, 2.89–37.83), rivaroxaban (OR, 6.02; 95% CI, 2.04–17.76), and heparin bridging (OR, 1.46; 95% CI, 0.72–2.97).

**Prediction model creation and validation.** The derivation and validation cohorts consisted of 845 and 362 patients, respectively. The clinical characteristics of these datasets are summarized in Table 4. Factors such as post-ESD bleeding rate, age, sex, BMI, comorbidities, tumor information, post-ESD medication, and use of two or more antithrombotic therapies were considered. No significant difference was found between the clinical characteristics of the derivation and validation cohorts.

The prediction model was created using the derivation cohort. Predictor variables were age, sex, BMI, use or non-use of hemodialysis, tumor diameter, and each antithrombotic therapy. This model can calculate the risk of post-ESD bleeding by entering the predictor variables into a multivariate logistic regression model. For aspirin and cilostazol, which were allowed to continue, there was no significant difference between withdrawal and continuation, so the items for withdrawal and continuation were not separated. We named the prediction model – safe ESD management using the risk analysis of post-bleeding in patients with antithrombotic therapy (SAMURAI) (https://hakodakah.shinyapps.io/ESDpostbleed/). The AUC for the validation cohort was 0.77 (0.70–0.84) for the SAMURAI model (Fig. 2).

A. Hakoda et al.  J. Clin. Biochem. Nutr. | Published online: 3 December 2021 | 3
### Table 1. Clinical characteristics of patients included in this study

| Overall | Number | 1,207 |
|---------|--------|-------|
| Post-ESD bleeding % (n) | 11.8 (142) |
| Age [median (IQR)] | 76.00 (71.00, 81.00) |
| Sex % (n) | Male 82.2 (992) |
| BMI [median (IQR)] | 22.89 (20.79, 25.22) |
| Diabetes % (n) | 28.4 (343) |
| Hypertension % (n) | 75.5 (911) |
| Hemodialysis % (n) | 5.6 (68) |
| Tumor diameter [median (IQR)] | 15.00 (10.00, 20.00) |
| Gastric area of the tumor % (n) | Upper 17.8 (215) |
| | Middle 41.1 (496) |
| | Lower 41.1 (496) |
| Gastric atrophy % (n) | Close type 18.5 (223) |
| | Open type 81.5 (984) |
| Postoperative oral administration of PPI or PCAB % (n) | PPI 68.0 (790) |
| | PCAB 32.0 (372) |
| Use of gastroprotective agents % (n) | 53.5 (646) |
| Use of two or more antithrombotic therapies % (n) | 21.0 (253) |

**Antithrombotic therapy**

- Aspirin % (n) 53.7 (648)
- Continue to take aspirin % (n) 24.0 (290)
- P2Y12RA % (n) 15.3 (185)
- Cilostazol % (n) 11.9 (144)
- Continue to take cilostazol % (n) 0.03 (40)
- Other antiplatelet agents % (n) 8.5 (103)
- Warfarin % (n) 18.9 (228)
- Dabigatran % (n) 2.8 (34)
- Apixaban % (n) 4.2 (51)
- Edoxaban % (n) 2.1 (25)
- Rivaroxaban % (n) 5.3 (64)
- Heparin bridging % (n) 14.9 (180)
- Period of heparin bridging, days [median (IQR)] 5.00 (4.00, 7.00)
- Units of heparin bridging, /day [median (IQR)] 10,000 (10,000, 15,000)
- Taking antiplatelet drugs and anticoagulants (DOAC) % (n) 13.4 (162)

### Table 2. Univariate analysis of risk factors for post-endoscopic submucosal dissection bleeding

| Overall | Non-bleeding | Bleeding | p value |
|---------|--------------|----------|---------|
| Number | 1,065 | 142 | |
| Age [median (IQR)] | 76.00 (71.00, 81.00) | 74.00 (69.00, 79.75) | 0.002 |
| Sex % (n) | Male 81.7 (870) | 85.9 (122) | 0.216 |
| BMI [median (IQR)] | 22.97 (20.92, 25.30) | 22.39 (20.33, 24.52) | 0.02 |
| Diabetes % (n) | 28.7 (306) | 26.1 (37) | 0.507 |
| Hypertension % (n) | 75.0 (799) | 78.9 (112) | 0.317 |
| Hemodialysis % (n) | 4.2 (45) | 16.2 (23) | <0.001 |
| Tumor diameter [median (IQR)] | 14.00 (10.00, 20.00) | 15.00 (10.25, 25.00) | 0.001 |
| Gastric area of the tumor % (n) | Upper 18.4 (196) | 13.4 (19) | 0.325 |
| | Middle 40.7 (433) | 44.4 (63) |
| | Lower 40.9 (436) | 42.3 (60) |
| Gastric atrophy % (n) | Close type 18.2 (194) | 20.4 (29) | 0.525 |
| | Open type 81.8 (871) | 79.6 (113) |
| Postoperative oral administration of PPI or PCAB % (n) | PPI 68.5 (701) | 64.5 (89) | 0.349 |
| | PCAB 31.5 (323) | 35.5 (49) |
| Use of gastroprotective agents % (n) | 53.3 (568) | 54.9 (78) | 0.72 |
| Use of two or more antithrombotic therapies % (n) | 19.0 (202) | 35.9 (51) | <0.001 |
| Taking both antiplatelet drugs and anticoagulants or DOAC % (n) | 7.1 (76) | 16.9 (24) | <0.001 |
| Continue to take aspirin % (n) total number = 648 | 45.7 (265) | 36.8 (25) | 0.161 |
| Continue to take cilostazol % (n) total number = 144 | 28.0 (37) | 27.8 (3) | 0.822 |
Table 3. Multivariable analysis of post-endoscopic submucosal dissection bleeding for the risk assessment of each antithrombotic therapy

| Drug                | Adjusted OR | Lower 95% CI | Upper 95% CI | p value |
|---------------------|-------------|--------------|--------------|---------|
| Aspirin             | 2.23        | 1.19         | 4.57         | 0.014   |
| P2Y12RA             | 4.9         | 2.76         | 8.7          | <0.001  |
| Cilostazol          | 1.79        | 0.8          | 4.03         | 0.156   |
| Other antiplatelet agents | 0.95  | 0.35         | 2.59         | 0.926   |
| Warfarin            | 6.53        | 2.29         | 18.62        | <0.001  |
| Dabigatran          | 5.65        | 1.48         | 21.52        | 0.011   |
| Apixaban            | 7.84        | 2.67         | 23.01        | <0.001  |
| Edoxaban            | 10.45       | 2.89         | 37.83        | <0.001  |
| Rivaroxaban         | 6.02        | 2.04         | 17.76        | 0.001   |
| Heparin bridging    | 1.46        | 0.72         | 2.97         | 0.295   |

All variables were adjusted using age, sex, body mass index, hemodialysis, tumor diameter, and taking both antiplatelet drug and anticoagulant or DOAC.

Table 4. Clinical characteristics of patients in the derivation and validation cohorts

|                                      | Derivation cohort | Validation cohort | p value |
|--------------------------------------|-------------------|------------------|---------|
| Number                               | 845               | 362              |         |
| Post-ESD bleeding % (n)              | 12.3 (104)        | 10.5 (38)        | 0.371   |
| Age [median (IQR)]                   | 76.00 (70.00, 81.00) | 76.00 (71.25, 81.00) | 0.522   |
| Sex % (n)                            | Male 82.6 (698)   | 81.2 (294)       | 0.564   |
| BMI [median (IQR)]                   | 22.94 (20.87, 25.24) | 22.80 (20.50, 25.18) | 0.439   |
| Diabetes % (n)                       | 29.5 (249)        | 26.0 (94)        | 0.217   |
| Hypertension % (n)                   | 76.2 (644)        | 73.8 (267)       | 0.363   |
| Hemodialysis % (n)                   | 5.2 (44)          | 6.6 (24)         | 0.326   |
| Tumor diameter [median (IQR)]        | 15.00 (10.00, 20.00) | 13.00 (10.00, 20.75) | 0.465   |
| Gastric area of the tumor % (n)      | Upper 18.1 (153)  | 17.1 (62)        | 0.912   |
|                                       | Middle 41.1 (347) | 41.2 (149)       |         |
|                                       | Lower 40.8 (345)  | 41.7 (151)       |         |
| Gastric atrophy % (n)                | Close type 18.6 (157) | 18.2 (66)        | 0.887   |
|                                       | Open type 81.4 (688) | 81.8 (296)       |         |
| Postoperative oral administration of PPI or PCAB % (n) | PPI 66.3 (538) | 72.0 (252) | 0.054 |
|                                       | PCAB 33.7 (274)   | 28.0 (98)        |         |
| Use of gastroprotective agents % (n)  | 53.7 (454)        | 53.0 (192)       | 0.836   |
| Use of two or more antithrombotic therapies % (n) | 20.2 (171) | 22.9 (83) | 0.293 |
| Taking both antiplatelet drugs and anticoagulants or DOAC % (n) | 7.5 (63) | 10.2 (37) | 0.11   |

Discussion

Post-ESD bleeding is one of the common complications in patients receiving antithrombotic therapy, and it is important to predict its occurrence accurately. The strength of this study is that only patients receiving antithrombotic therapy were enrolled. Moreover, the study enrolled patients from all over Japan and was able to examine the risks of all 10 antithrombotic therapies by multivariable analysis.

In this study, the overall post-ESD bleeding rate was 11.8%, while in a previous study, the post-ESD bleeding rate with antithrombotic therapy was 23.3%. In the post-ESD bleeding rate has been decreasing because of the improvements in the performance of the surgeon and the technology of the instruments used, as well as the increasing proper use of JGES guidelines.

In the univariate analysis, factors such as dialysis, large tumor diameter, and use of multiple antithrombotic therapies were noted as risk factors, although this fact has already been established by previous reports. In the treatment of hemorrhagic peptic ulcers, suppressors of acid secretion such as PPIs promote ulcer healing and reduce the risk of hemorrhage. In addition, in the treatment of post-ESD ulcers, combination therapy with PPI and mucosal protective agents is reported to yield better healing rates and similar postoperative bleeding rates to those with PPI monotherapy. In this study, we also examined this assumption; however, our results did not yield supporting evidence. In clinical practice, it is assumed that there is no difference between PPI monotherapy and combination therapy because the combination of PPI and mucosal protective agent is often used for cases that are likely to bleed after ESD.

In this study, the overall post-ESD bleeding rate was 11.8%, while in a previous study, the post-ESD bleeding rate with antithrombotic therapy was 23.3%. The post-ESD bleeding rate has been decreasing because of the improvements in the performance of the surgeon and the technology of the instruments used, as well as the increasing proper use of JGES guidelines.

In the univariate analysis, factors such as dialysis, large tumor diameter, and use of multiple antithrombotic therapies were noted as risk factors, although this fact has already been established by previous reports. In the treatment of hemorrhagic peptic ulcers, suppressors of acid secretion such as PPIs promote ulcer healing and reduce the risk of hemorrhage. In addition, in the treatment of post-ESD ulcers, combination therapy with PPI and mucosal protective agents is reported to yield better healing rates and similar postoperative bleeding rates to those with PPI monotherapy. In this study, we also examined this assumption; however, our results did not yield supporting evidence. In clinical practice, it is assumed that there is no difference between PPI monotherapy and combination therapy because the combination of PPI and mucosal protective agent is often used for cases that are likely to bleed after ESD.

In addition, patients who are thin or malnourished may have a strong reaction to their regular dose of antithrombotic drugs. Another new finding is that for aspirin and cilostazol, there is no apparent significant difference between the continuing and withdrawing the therapy.

The result of the multivariable analysis revealed the OR of each antithrombotic therapy. This allowed a comparison of post-

A. Hakoda et al.

J. Clin. Biochem. Nutr. | Published online: 3 December 2021 | 5
bleeding rates based on the type of antithrombotic therapy received by the patient. To our knowledge, this study is the first to evaluate the OR of each antithrombotic agent simultaneously. Among the antiplatelet agents, P2Y12RA had the highest OR. Replacing P2Y12RA with other appropriate antiplatelet agents may lead to lower bleeding rates. The JGES guidelines suggest changing P2Y12RA to aspirin and cilostazol before ESD; the results of this study further validate this recommendation.\(^{19}\) However, in this study, warfarin and direct oral anticoagulants had a higher OR than heparin bridging. When heparin bridging is performed, 10,000–15,000 units per day is often administered, and it is possible that the dose of heparin per body weight is insufficient. In this respect, our result was different from previous reports.\(^{11,26,27}\)

The SAMURAI model succeeded in accurately calculating the post-ESD bleeding rate for each patient using simple input variables. One of the accuracy indicators, the AUC of the SAMURAI model was 0.77. AUC ≥ 0.70 is typically considered sufficient to make clinically useful predictions.\(^{21}\) This prediction may be informative in the post-ESD management of patients receiving antithrombotic therapy. Specifically, in cases where there is a high possibility of post-ESD bleeding, drug suspension or drug reduction can be considered. In addition, the SAMURAI model can be used to evaluate and stratify the risk of bleeding in future research on prevention of post-ESD bleeding, and effective measures to prevent post-ESD bleeding can be considered in groups with each low and high bleeding rates.

As an example of using SAMURAI model, consider a 75-year-old male, whose BMI is 25, and who takes warfarin and aspirin, does not receive hemodialysis and heparin bridging, and has a lesion with a maximum diameter of 10 mm. His post-bleeding risk is calculated to be 10.8% (Fig. 3). This probability is in line with clinical experience.

This study had several limitations. First, this study was retrospective. Second, validation of the model using external data, especially from other countries, has not been performed. Although the handling of antithrombotic agents and gastric ESD procedures are similar worldwide, it is necessary to evaluate how accurately the SAMURAI model can be used internationally.

In summary, we created a prediction model (SAMURAI model) for post-ESD bleeding in patients receiving antithrombotic therapy. We believe that this model will be a useful tool to assess the risk of bleeding and help improve patient outcomes in daily practice.

**Author Contributions**

AH: writing—original draft, writing—review and editing, data curation, formal analysis, methodology, visualization. TT: writing—review and editing, project administration. YK: writing—review and editing, YF, YNagami, YNaito, SF, TK, MS, KHamada, HKobara, NY, TI, AN, EK, KM, TF, NO, HI, KS, HKataoka, and HS: investigation, resources. KHiguchi: writing—review and editing, supervision.

**Acknowledgments**

We thank Takumi Imai, Daijiro Kabata, and Ayumi Shintani.
References

1. Oda I, Saito D, Tada M, et al. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; 9: 262–270.

2. Oka S, Tanaka S, Kaneko I, et al. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; 64: 877–883.

3. Yano T, Tanabe S, Ishido K, et al. Different clinical characteristics associated with acute bleeding and delayed bleeding after endoscopic submucosal dissection in patients with early gastric cancer. *Surg Endosc* 2017; 31: 4542–4550.

4. Sato C, Hirasawa K, Koh R, et al. Postoperative bleeding in patients on antithrombotic therapy after gastric endoscopic submucosal dissection. *World J Gastroenterol* 2017; 23: 5557–5566.

5. Miyahara K, Iwakiri R, Shimoda R, et al. Perforation and postoperative bleeding of endoscopic submucosal dissection in gastric tumors: analysis of 1190 lesions in low- and high-volume centers in Saga, Japan. *Digestion* 2012; 86: 273–280.

6. Toyokawa T, Inaba T, Omote S, et al. Risk factors for perforation and delayed bleeding associated with endoscopic submucosal dissection for early gastric neoplasms: analysis of 1123 lesions. *J Gastroenterol Hepatol* 2012; 27: 907–912.

7. Nam HS, Choi CW, Kim SJ, et al. Risk factors for delayed bleeding by onset time after endoscopic submucosal dissection for gastric neoplasm. *Sci Rep* 2019; 9: 2674.

8. Lim JH, Kim SG, Kim JW, et al. Do antiplatelets increase the risk of bleeding after endoscopic submucosal dissection of gastric neoplasms? *Gastrointest Endosc* 2012; 75: 719–727.

9. Fujimoto K, Fujishiro M, Kato M, et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig Endosc* 2014; 26: 1–14.

10. Shindo Y, Matsumoto S, Miyatani H, et al. Risk factors for postoperative bleeding after gastric endoscopic submucosal dissection in patients under antithromboses. *World J Gastroenterol* 2016; 8: 349–356.

11. Takeuchi T, Ota K, Harada S, et al. The postoperative bleeding rate and its risk factors in patients on antithrombotic therapy who undergo gastric endoscopic submucosal dissection. *BMC Gastroenterol* 2013; 13: 136.

12. Toya Y, Endo M, Oizumi T, et al. Risk factors for post-gastric endoscopic submucosal dissection bleeding with a special emphasis on anticoagulant therapy. *Dig Dis Sci* 2020; 65: 557–564.

13. Mannen K, Tsunada S, Hara M, et al. Risk factors for complications of endoscopic submucosal dissection in gastric tumors: analysis of 478 lesions. *J Gastroenterol* 2010; 45: 30–36.

14. Okada K, Yamamoto Y, Kasuga A, et al. Risk factors for delayed bleeding after endoscopic submucosal dissection for gastric neoplasm. *Surg Endosc* 2011; 25: 98–107.

15. Mukai S, Cho S, Kotachi T, et al. Analysis of delayed bleeding after endoscopic submucosal dissection for gastric epithelial neoplasms. *Gastroenterol Res Pract* 2012; 2012: 875323.

16. Hatta W, Tsuji Y, Yoshio T, et al. Prediction model of bleeding after endoscopic submucosal dissection for early gastric cancer: BEST-4 score. *Gastrointest Endosc* 2020; 81: 1023–1031.

17. Veitch AM, Vaniervliet G, Gershlick AH, et al. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines. *Gut* 2016; 65: 374–389.

18. Mochizuki S, Uedo N, Oda I, et al. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. *Gut* 2015; 64: 397–405.

19. Nguyen QH, LY HB, Ho LS, et al. Influence of data splitting on performance of machine learning model in prediction of shear strength of soil. *Math Probl Eng* 2021; 2021: 4832864.

20. Selby NM, Kubbah AK, Hawkey CJ. Acid suppression in peptic ulcer haemorrhage: a “meta-analysis”. *Aliment Pharmacol Ther* 2000; 14: 1119–1126.

21. Kaviani MJ, Hashemi MR, Kazemifar AR, et al. Effect of oral omeprazole in reducing re-bleeding in peptic ulcer patients: a prospective, double-blind, randomized, clinical trial. *Aliment Pharmacol Ther* 2003; 17: 211–216.

22. Kato T, Araki H, Onogi F, et al. Clinical trial: rebamipide promotes gastric ulcer healing by proton pump inhibitor after endoscopic submucosal dissection—a randomized controlled study. *J Gastroenterol* 2010; 45: 285–290.

23. Fujiwara S, Morita Y, Toyonaga T, et al. A randomized controlled trial of rebamipide plus rabeprazole for the healing of artificial ulcers after endoscopic submucosal dissection. *J Gastroenterol* 2011; 46: 595–602.

24. Birnie DH, Healey JS, Wells GA, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013; 368: 2084–2093.

25. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med* 2015; 373: 823–833.

A. Hakoda et al.

J. Clin. Biochem. Nutr. | Published online: 3 December 2021 | 7
Pencina MJ, D'Agostino RB Sr, Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. Stat Med 2012; 31: 101–113.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/).