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Complete omission of second-look endoscopy after gastric endoscopic submucosal dissection in real-world practice

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Abstract

Gastric endoscopic submucosal dissection (ESD) is increasingly performed in patients receiving antithrombotic therapy. Second-look endoscopy (SLE) has been performed empirically in several clinical settings. We investigated whether SLE omission was associated with an increased risk of postESD bleeding in all patients, including those administered antithrombotic agents.

Between July 2016 and June 2018, 229 patients were treated with a clinical pathway for gastric ESD that involved SLE on the day after ESD (SLE group). Between September 2018 and May 2020, 215 patients were treated using a clinical pathway that did not include SLE (nonSLE group). We retrospectively compared the incidence of postESD bleeding among the propensity score-matched cohorts and determined the risk factors for postESD bleeding using multivariate analysis.

The propensity score-matched cohorts showed no significant differences in the incidence of postESD bleeding between the SLE (3.2%) and nonSLE (5.1%) groups. Multivariate analysis revealed that the presence of lesions in the lower gastric body (adjusted odds ratio [OR] 2.17, 95% confidence interval [CI] 1.06–4.35, *P*.03) was a significant risk factor for postESD bleeding during admission, whereas resected specimen size ≥ 40 mm (adjusted OR 3.21, 95% CI 1.19–8.19, *P*.02) and antiplatelet therapy (adjusted OR 4.16, 95% CI 1.47–11.80, *P*.007) were significant risk factors after discharge.

Complete omission of SLE after gastric ESD does not increase postESD bleeding in clinical practice.

Abbreviations: EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, POD = postoperative day, SLE = second-look endoscopy, TLE = third-look endoscopy

Keywords: endoscopic submucosal dissection, gastric neoplasms, postoperative bleeding, second-look endoscopy

1. Introduction

Gastric cancer screening is widely performed in Japan; therefore, many gastric cancers are detected at an early stage.[1,2] Usually, a less invasive endoscopic treatment is preferred for the management of intramucosal cancers. Endoscopic submucosal dissection (ESD) was introduced in 2000 and is preferred over endoscopic mucosal resection (EMR). ESD is a promising approach to achieve en-bloc resection for early gastric cancer.[3] Postoperative bleeding (postESD bleeding) is the most common complication of ESD with a reported incidence of approximately 5%.[4–11] Age, histological findings, tumor location, resected specimen size, antithrombotic therapy, and hemodialysis are among several risk factors associated with postESD bleeding.[4–6,9,10,12]

Second-look endoscopy (SLE) is conventionally performed after primary endoscopic hemostasis for bleeding peptic ulcers, which improves clinical outcomes and reduces mortality.[13,14] SLE performed within a few days after gastric ESD was empirically introduced and widely accepted in Japan, and was as popular as gastric ESD. However, several retrospective studies performed in 2010 have reported that SLE did not reduce the frequency of postESD bleeding.[4] A prospective randomized study reported that omission of SLE was not inferior to SLE for the prevention of postESD bleeding in patients at an average risk of bleeding.[15,16] A meta-analysis also reported that SLE does not reduce the risk of postESD bleeding.[17] However, these previous studies excluded high-risk patients who received antithrombotic agents or hemodialysis.

In recent years, antithrombotic therapy has been widely prescribed in clinical practice worldwide.[18,19] The Japan Gastroenterological Endoscopy Society (JGES) guidelines (2017) recommend continuation of aspirin for high-risk procedures,

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such as ESD.[20] Therefore, an increasing number of patients undergo ESD with antithrombotic agents, and the practice of performing SLE has continued because these patients are at high risk of bleeding.[10,21–23] However, it remains unclear whether SLE can reduce the risk of postESD bleeding in these patients.

Per our hospital policy, we previously followed a clinical pathway for gastric ESD that included SLE performed on the day following ESD and 9 days of admission. In July 2018, we introduced a new clinical pathway that includes 7 days of admission without SLE. We performed an observational study that compared the incidence of bleeding between the 2 clinical pathways to investigate whether SLE omission is associated with a high risk of postESD bleeding in real-world clinical practice.

2. Methods

2.1. Study design

Between July 2016 and May 2020, 499 consecutive patients with gastric neoplasms underwent ESD at the Fujita Health University Hospital. Between July 2016 and June 2018, postESD SLE was performed in all patients according to the previous clinical pathway (SLE group). Between September 2018 and May 2020, postESD SLE was not performed according to the latest clinical pathway (nonSLE group). Patients treated between July and August 2018 were excluded from the study because both the clinical pathways were used. We retrospectively investigated the postESD bleeding rates in the SLE and nonSLE groups using medical records in July 2020. The exclusion criteria were as follows: perforation during ESD (n = 2), EMR (n = 2), withdrawal from ESD (n = 1), no SLE performed during the SLE period (n = 19), and SLE performed during the nonSLE period (n = 3). All 3 who were excluded from the nonSLE group underwent ESD in September or October 2018. Since that, SLE had never been done in the nonSLE group. postESD bleeding was defined as overt bleeding manifested as hematemesis, hematochezia, or melena within 1 month after ESD. Emergency endoscopic hemostasis was performed in these patients. Patients who required hemostasis without any of the aforementioned bleeding episodes during SLE were not counted as having postESD bleeding in this study. The timing of postESD bleeding events was categorized as during the admission phase if bleeding occurred within 5 days after ESD and during the discharge phase if bleeding occurred ≥6 days postESD. Acute bleeding was defined as bleeding that occurred on the day of ESD. Bleeding rate was calculated for each patient. We compared the clinical characteristics of the patients and gastric neoplasms between the SLE and nonSLE groups. Multiple lesions in 1 patient were dealt with per lesion according to the gross type, location, resected size, invasion depth, and pathological diagnosis. On the other hand, age, gender, SLE, and antithrombotic agents were dealt with per patient. After a propensity score-matched analysis of both groups, we compared the frequency of postESD bleeding during the acute, admission, and discharge phases. We determined the factors independently associated with postESD bleeding using a multivariate analysis. This study was performed in accordance with the Declaration of Helsinki guidelines. Written informed consent for ESD was obtained from all the patients, and this clinical observational study was approved by the Ethics Committee of Fujita University. Patients were allowed to withdraw from the study via the opt-out method provided on the hospital website.

2.2. Antithrombotic management

Considering the risk of bleeding and thrombosis, continuation or cessation of antithrombotic therapy was decided by prescribing physicians. The timing of cessation of antithrombotic therapy before ESD was based on JGES guidelines.[20,24] The following discontinuation regimen was recommended: aspirin for at least 3 days, thienopyridine for at least 5 days, cilostazol for at least 1 day, warfarin for at least 3 days, and direct oral anticoagulants for at least 1 day before ESD. If the cessation period was shorter than the recommended duration, antithrombotic therapy was regarded as continuation. In the case of aspirin replacement with ticlopidine, aspirin was continued around ESD. In patients who received multiple antithrombotic agents, such as double antiplatelet therapy or antiplatelet and anticoagulant therapy, cessation was defined as the discontinuation of all medicines. Continuation of aspirin, but cessation of another agent, was considered continuation of aspirin. Heparin bridge therapy was used as a substitute for anticoagulant therapy. Heparin was withdrawn 3 hours before ESD and resumed on the day following the procedure. The timing of resumption was categorized as within 2 days or ≥ 3 days after ESD.

2.3. Indications for and procedure of endoscopic submucosal dissection

Before ESD, all patients underwent a detailed endoscopic evaluation using narrow-band imaging with magnifying endoscopy (GIF-H260Z; Olympus Medical Systems Corporation, Tokyo, Japan) to confirm the margin and depth of the neoplasm. The indications for ESD were determined based on the 2014 Japanese Gastric Cancer Treatment Guidelines (ver. 4).[25] We used a specific endoscope with a water jet (GIF-Q260J; Olympus, Tokyo, Japan) and high-frequency power supply unit (VIO300D; ERBE, Tübingen, Germany) for electrocoagulation. Gastric ESD was performed using midazolam and pentazocine for conscious sedation, and the standard method of carbon dioxide insufflation. The area around the neoplasm was marked, and 10% glycerin solution mixed with sodium hyaluronate (MucoUp; Johnson & Johnson Medical Company, Tokyo, Japan) was injected into the submucosal layer. We created a mucosal incision using a dual knife or insulated-tip knife-2 (Olympus Medical Systems Co. Tokyo. Japan) and ESD was performed, followed by retrieval of the resected specimen. Prophylactic hemostasis was performed using hemostatic forceps (Coagrasper; Olympus Medical Systems Co., Tokyo, Japan) to control bleeding from visible vessels at the site of the ESD-induced ulcer. The method of prophylactic hemostasis immediately after ESD in the nonSLE group was similar to that used in the SLE group. Finally, we dispersed a mixture of liquid magnesium hydroxide and thrombin (20,000 U).

2.4. Clinical pathway protocols

Both clinical pathways involved hospitalization 1 day before ESD. Omeprazole (20 mg) was injected intravenously twice daily on the day before ESD until the day after ESD. Patients in the SLE group underwent SLE on the first day after ESD. Therapeutic endoscopic hemostasis was performed using electrocoagulation or clipping in patients with active bleeding, oozing blood, or visible vessels. Water intake was resumed in patients who showed no findings. In the nonSLE group, water intake resumed on the first day after ESD. Patients received a proton-pump inhibitor (vonoprazan 20 mg) once a day with resumption of food intake on the second day after ESD via both clinical pathways. In the SLE group, patients were discharged on the ninth day after they underwent third-look endoscopy (TLE) on the eighth day of admission. In the nonSLE group, patients were discharged on the seventh day of admission. After 1 month, we confirmed patients whether had any events indicated postESD bleeding.

2.5. Statistical analysis

SPSS Statistics software (version 25.0; IBM Japan Ltd., Tokyo, Japan) was used for all analyses. Variables with P values < 0.05 on univariate analyses were subjected to multivariate logistic regression analyses. A propensity score-matched analysis was conducted to reduce the effects of possible confounding factors and treatment-related selection bias. Other statistical differences were analyzed using the chi-square test, Fisher exact test, or Mann–Whitney U-test. Statistical significance was set at $P = .05$.

3. Results

3.1. Patients' characteristics

The study included 229 patients, 262 lesions in the SLE group, and 215 patients, 261 lesions in the nonSLE group. We could follow every patient's condition after the discharge. Table 1 summarizes the clinical characteristics of the patients and gastric neoplasms. The percentage of men, antiplatelet users, and lesions in the lower gastric body was significantly higher in the nonSLE group. To adjust for differences in the background of the SLE and nonSLE groups, propensity score-matched analysis was performed for variables of sex, antithrombotic agents, resected size, and tumor location, and new data sets were established (Table 2). The adjusted new data sets included 157 patients (177 lesions in the SLE group) and 157 patients (189 lesions in the nonSLE group). The flow diagram of the study is shown in Figure 1.

Table 1

Clinical characteristics of patients with gastric neoplasm.

	SLE group (n = 229) 262 lesions	nonSLE group (n = 215) 261 lesions	*P* value
Age, y, median, range	73 (42–91)	73 (30–93)	0.985
Gender			0.028
Male	171	179	
Female	58	36	
Hemodialysis	1	3	0.347
Anticoagulants	6	13	0.079
Antiplatelets	15	34	0.002
Maximum diameter of resected specimen (mm), median, range	30 (15–90)	30 (13–75)	0.085
Location			0.006
U	30	43	
M	123	84	
L	99	121	
Post gastrectomy	10	13	
Gross type			0.094
0-I	14	11	
0-IIa	88	110	
0-IIb	1	7	
0-IIc	129	115	
0-IIa + IIc	29	16	
Others	1	2	
Pathological diagnosis			0.791
Adenoma	32	41	
tub1	161	151	
tub2	45	53	
Por/sig	7	5	
Others	11	11	
Invasion depth			0.624
m	194	179	
sm1*	13	17	
sm2†	12	13	

*The definition of sm1: cancer invaded into submucosal layer within 500 μm.

†The definition of sm2: cancer invaded into submucosal layer deeper than 500 μm.

SLE = second look endoscopy.

3.2. postendoscopic submucosal dissection bleeding

In the adjusted cohorts, postESD bleeding was observed in 5 patients (3.2%) in the SLE group and 8 patients (5.1%) in the nonSLE group. However, there were no significant intergroup differences ($P = .397$) (Table 3). The cumulative incidence curve of postESD bleeding also showed no statistically significant intergroup differences ($P = .392$) (Fig. 2). Acute bleeding (postoperative day [POD] 0) occurred in 2 patients only in the nonSLE group. PostESD bleeding during the admission phase (POD 0 to 5) was observed in 2 patients (1.3%) in the SLE group and in 5 patients (3.2%) in the nonSLE group. PostESD bleeding during the discharge phase (POD 6-) occurred each in 3 patients (1.9%) in the SLE and nonSLE groups. No significant intergroup differences were observed in these phases.

Figure 3 shows the number and timing of hemorrhages after ESD in both groups without adjustment. Although no postESD bleeding was observed on the day of ESD or the following day in the SLE group, 11 patients underwent hemostasis because of fresh blood in the stomach. In addition, we treated as many vessels on the ulcer bed as possible prophylactically in 2nd look endoscopy.

We observed antithrombotic agent administration around the ESD in 20 and 46 patients in the SLE and nonSLE groups, respectively. The detailed kinds of the antithrombotic agents were described (see Table, Supplemental Digital Content 1, http://links.lww.com/MD/G882). The management of antithrombotic agents pre or post ESD referred to the JGES recommendations, 10 patients discontinued and continued antithrombotic agents around the ESD in the SLE group, and 26 patients discontinued, and 20 patients continued antithrombotic agents in the nonSLE group (see Table,

Table 2

Clinical characteristics of patients after propensity-score matched analysis.

	SLE group (n = 157) 177 lesions	nonSLE group (n = 157) 189 lesions	*P* value
Age, y, median, range	73 (42–89)	73 (30–93)	0.601
Gender			0.755
Male	134	132	
Female	23	25	
Hemodialysis	0	0	–
Anticoagulants	5	5	1
Antiplatelets	15	13	0.692
Maximum diameter of resected specimen (mm), median, range	30 (15–90)	32 (13–75)	0.283
Location			0.863
U	22	20	
M	63	68	
L	85	89	
Post gastrectomy	7	12	
Gross type			0.351
0-I	4	5	
0-IIa	63	83	
0-IIb	1	6	
0-IIc	100	91	
0-IIa + IIc	8	4	
Others	1	0	
Pathological diagnosis			0.693
Adenoma	18	30	
tub1	114	113	
tub2	34	34	
Por/sig	0	0	
Others	11	12	
Invasion depth			0.654
m	135	130	
sm1	18	17	
sm2	4	8	

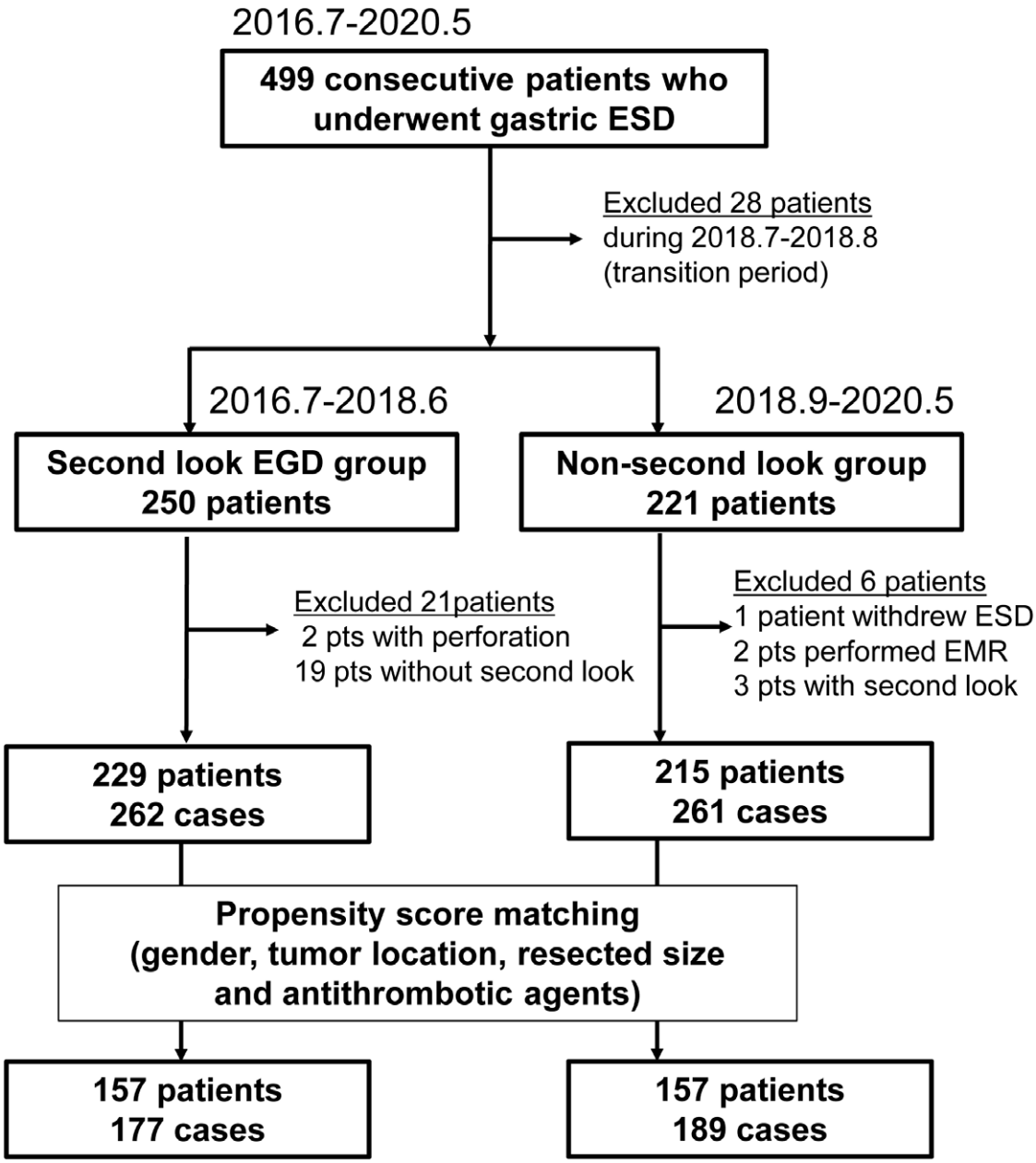

Figure 1. Flow diagram of patients investigated in this study.

Table 3

The comparison of postESD complications in Propensity score-matched cohorts.

	SLE group(n = 157)	nonSLE group(n = 157)	*P*-value
postESD bleeding	5 (3.2%)	8 (5.1%)	0.397
Acute postESD bleeding (d0)	0	2 (1.3%)	0.158
postESD bleeding (day0–5)	2 (1.3%)	5 (3.3%)	0.253
postESD bleeding (day6-)	3 (1.9%)	3 (1.9%)	1
Blood transfusion	1 (0.6%)	2 (1.3%)	0.563
Delayed perforation	0	0	–

ESD = endoscopic submucosal dissection, SLE = second look endoscopy.

Supplemental Digital Content 2, http://links.lww.com/MD/G882). In the SLE group, 12 and 8 patients resumed antithrombotic agents within 2 and 3 days after ESD, respectively. In the nonSLE group, 36 and 10 patients resumed antithrombotic agents within 2 and 3 days after ESD, respectively (see Table, Supplemental Digital Content 3, http://links.lww.com/MD/G882). No patient developed thromboembolic complications during ESD in this study.

3.3. Risk factors associated with postESD bleeding

Risk factors for postESD bleeding were analyzed using data from both groups (444 patients). Univariate and multivariate analyses revealed that resected specimen size ≥ 40 mm (adjusted OR 3.21, 95% CI 1.19–8.19, P = .02) and antiplatelet medication administration (adjusted OR 4.16, 95% CI 1.47–11.80, P = .007) were significantly associated with postESD bleeding.

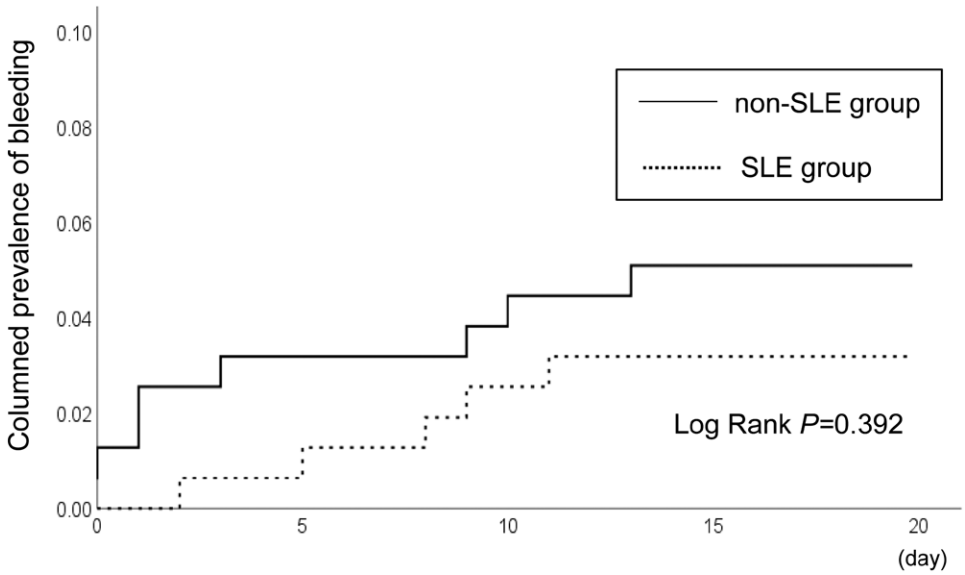

Figure 2. The cumulative incidence curve of postESD bleeding in adjusted patients of the SLE and nonSLE groups. ESD = endoscopic submucosal dissection, SLE = second-look endoscopy.

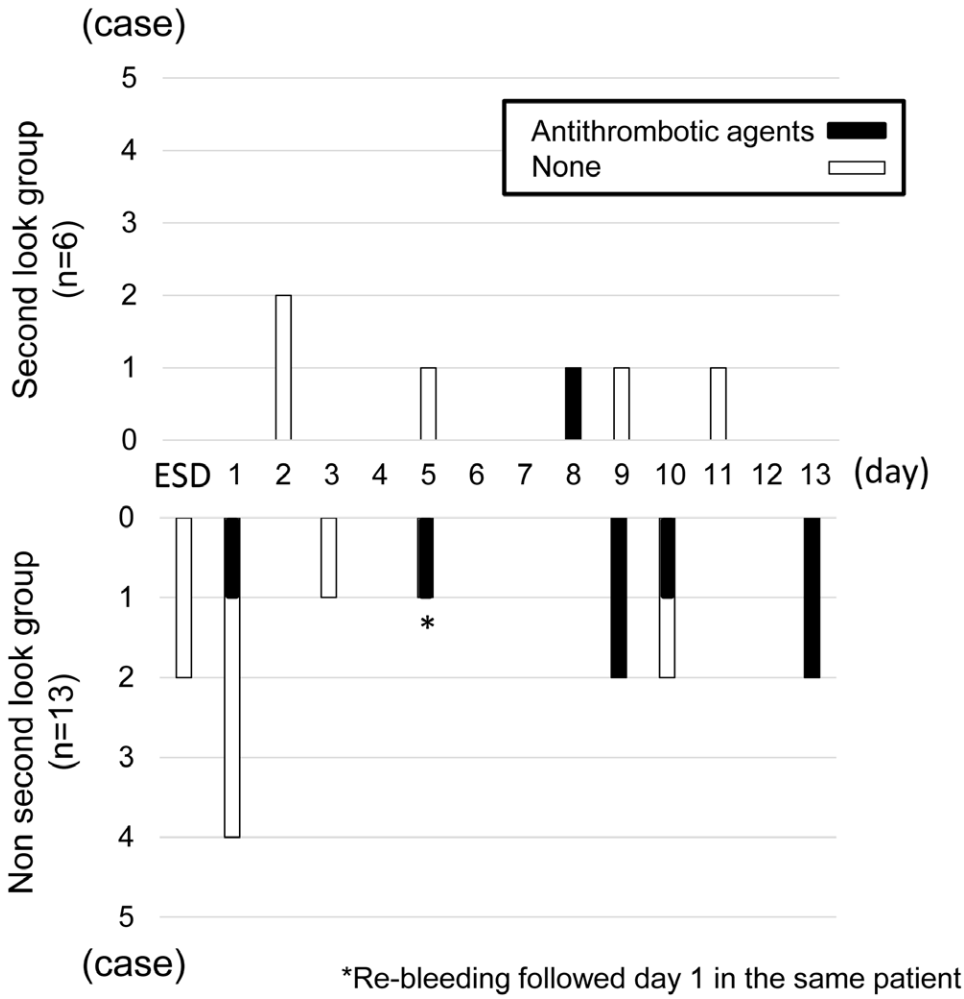

Figure 3. The number and timing of postESD bleeding events in all patients of the SLE and nonSLE groups.

The crude odds ratios of SLE and hemodialysis were calculated as 0.42 and 7.82 on univariate analysis; however, these were not statistically significant (P = .08 and 0.08, respectively, Table 4).

Stratification of risk factors of postESD bleeding based on the timing of hemorrhage showed that lesions in the lower gastric body (adjusted OR 2.17, 95% CI 1.06–4.35, P = .03) were independent risk factors during the admission phase (until the fifth day). Notably, SLE was not a statistically significant risk factor for postESD bleeding during the admission phase (adjusted OR 0.26, P = .09). In contrast, resected specimen size ≥ 40 mm (adjusted OR 3.94, 95% CI 1.06–14.70, P = .041) and antiplatelet medication administration (adjusted OR 9.56, 95% CI 2.60–35.13, P = .001) were independent risk factors for postESD bleeding during the discharge phase (after day 6). Notably, SLE was not a statistically significant factor during either the admission or discharge phases (crude OR 0.62, P = .46).

3.4. Effects on the postESD bleeding among preoperative and postoperative management of antithrombotic agents

In the SLE group, the postESD bleeding rate in patients who took antithrombotic agents was similar to that in patients who did not (P = .50, Fig. 4). In the nonSLE group, the postESD bleeding rate tended to be higher in patients who received antithrombotic agents than in those who did not (P = .078).

The postESD bleeding rate was 3 of 36 (8.3%) among patients who discontinued antithrombotic therapy, in contrast to 4 of 30 (13.3%) patients who continued antithrombotic agents. The postESD bleeding rate was 8.3% (4 48) in patients who resumed antithrombotic agents within 2 days (including continuation) and 16.6% (3 18) in those who resumed these agents after ≥3 days. Cession or late resumption of antithrombotic agents during ESD did not reduce postESD bleeding in this study.

4. Discussion

In the current study, the postgastric ESD bleeding rate was not significantly high, even in a clinical pathway protocol that omitted SLE, including in patients who received hemodialysis or antithrombotic agents. A resected specimen size ≥ 40 mm and antiplatelet agent administration were independently significantly associated with postESD bleeding; however, SLE showed no such association. Furthermore, the risk factors for hemorrhage differed between the admission and discharge phases. The location of lesions in the lower gastric body was the only risk factor associated with postESD bleeding during the admission phase (until the fifth day); however, resected specimen size ≥40 mm and antiplatelet medication administration were significant risk factors during the discharge phase (≥6 days).

Usually, patients administered antithrombotic agents are considered to be at a high risk of postESD bleeding.[10,21,23,26–29] However, cessation of antithrombotic therapy in patients at a high risk of thromboembolism predisposes them to cardiovascular and cerebrovascular events.[30–33] In 2017, the JGES modified the guidelines that recommend continuation of aspirin through ESD.[20] However, in this propensity score-matched cohort study, no significant difference was observed in the incidence of hemorrhage between the SLE and nonSLE groups, despite complete omission of SLE. The multivariate analysis did not suggest that SLE was a significant protective factor against postESD bleeding. Usually, the risk of thromboembolism is estimated before ESD in patients who receive antithrombotic agents, which is referred to as deciding continuation vs cessation of medications. In cases of discontinuation, antithrombotic agents should be resumed immediately after ESD to prevent thromboembolism. Notably, antiplatelet agent administration was significantly associated with a risk of hemorrhage, regardless of continuation or cessation of this therapy during ESD. The present study indicates that routine omission of postESD SLE in all patients did not increase the incidence of postESD bleeding in real-world practice. Interestingly, the risk factors for hemorrhage that occurred within 5 days differed from those associated with hemorrhage that occurred after ≥6 days. Detailed analysis revealed that although oral administration of antiplatelet agents was associated with a high risk of hemorrhage throughout the study period, it was a significant risk only after ≥6 days. This finding may explain why SLE did not reduce the risk of postESD bleeding in patients administered with antithrombotic agents. Most recently, 2 retrospective studies reported that SLE did not reduce the incidence of postESD bleeding in high-risk patients such as taking antithrombotic agents.[34,35] Therefore, not only SLE, but also a novel approach is warranted to prevent bleeding in these patients. However, this study does not

Table 4

Univariate and Multivariate analysis associated with postESD bleeding.

			Univariate analysis			Multivariate analysis		
The timing of bleeding			**OR**	**95%CI**	***P* value**	**OR**	**95%CI**	***P* value**
All period	Age (yr)	≥75	0.76	0.29–1.96	0.57			
	Gender	F	0.2	0.03–1.51	0.12			
	Hemodialysis	+	7.82	0.77–78.87	0.08	–	–	0.06
	SLE	+	0.42	0.16–1.12	0.08	–	–	0.13
	No. of lesions	≥2	1.56	0.50–4.86	0.44			
	Gross type	Elevated	0.59	0.22–1.59	0.3			
	Location (U/M/L)	L	1.29	0.94–1.78	0.11	–	–	0.08
	Resected specimen size (mm)	≥40	2.69	1.07–6.79	0.035	3.21	1.19–8.19	0.02
	Invasion depth	SM	0.71	0.16–3.14	0.65			
	Pathological diagnosis	Undifferentiated	1.35	0.79–2.31	0.27			
	Anticoagulants	+	1.26	0.16–9.94	0.83			
	Antiplatelets	+	4.1	1.48–11.34	0.007	4.16	1.47–11.80	0.007
Day 0–5	SLE	+	0.26	0.05–1.27	0.09			
	Location (U/M/L)	L	2.07	1.03–4.18	0.04	2.17	1.08–4.35	0.03
	Resected specimen size (mm)	≥40	1.87	0.49–7.10	0.35			
	Antiplatelets	+	1	0.12–8.23	0.99			
Day 6–	SLE	+	0.62	0.17–2.26	0.46			
	Location (U/M/L)	L	0.94	0.61–1.43	0.76			
	Resected specimen size (mm)	≥40	3.59	0.99–12.92	0.051	3.94	1.06–14.70	0.041
	Antiplatelets	+	8.86	2.47–31.82	0.001	9.56	2.60–35.13	0.001

ESD = endoscopic submucosal dissection, SLE = second look endoscopy.

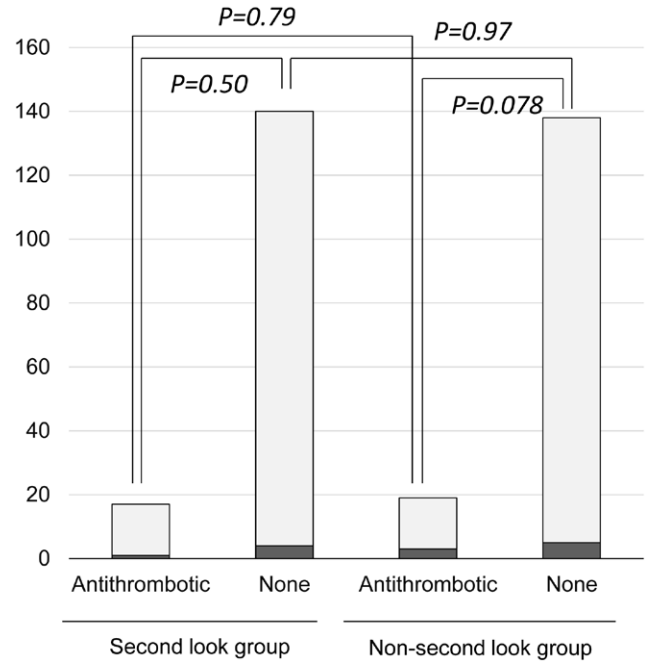

Figure 4. Comparison between the SLE and nonSLE groups with regard to the percentage of postESD bleeding events in adjusted patients who did and did not receive antithrombotic agent.

completely deny SLE itself because 11 patients, which was equivalent to 4.8% of the SLE group, underwent endoscopic hemostasis in 2nd look endoscopy. If these patients had not undergone SLE, almost all were considered to have postESD hemorrhage. We believe that this was reflected in the difference in bleeding on POD1. Therefore, we still believe in the role of SLE in acute bleeding within a day after ESD, although its number might be limited owing to the development of the gastric ESD technique. Some clinical studies have reported various methods for preventing hemorrhage in patients administered with antithrombotic agents. A recent study by Ikeda et al reported that, in addition to SLE, TLE reduced the incidence of postESD bleeding in patients who received antithrombotic agents.[36] In our study, only 1 patient underwent endoscopic hemostasis at TLE among 20 patients who were administered antithrombotic agents, even though we performed TLE on the 8th day in the SLE group. Other studies have suggested that polyglycolic acid sheets covering the ESD-induced ulcer bed may be useful in prevent hemorrhage.[37–39] However, to date, there is a lack of consensus regarding methods that can reduce hemorrhage in patients receiving antithrombotic agents.

The limitations of this study are as follows: (a) The single-center design is a drawback of this study. (b) The admission days for the different clinical pathways were different. (c) The cessation of antithrombotic agents was at the discretion of doctors. (d) The incidence of hemorrhage could not be directly compared among patients who received antithrombotic agents. (e) Only 4 patients underwent hemodialysis in this study.

In conclusion, the complete omission of SLE after gastric ESD does not increase postESD bleeding in real-world practice. ESD for lower gastric body lesions is associated with bleeding during the admission phase. A resected specimen size ≥40 mm and antiplatelet agent administration were associated with bleeding during the discharge phase.

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