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Original Article

Antithrombotic Agents are not Associated with Outcomes of Diverticular Bleeding but Prolonged the Length of Hospital Stay

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ABSTRACT

Introduction: The prognosis of diverticular bleeding is subject to patient comorbidity and medication although colonic diverticular bleeding stopped spontaneously in 70-90% of cases. The aim of the study is to elucidate the risk factors of diverticular rebleeding and to determine a clinical approach that will achieve better outcomes.

Methods: We evaluated 140 patients admitted with colonic diverticular bleeding, diagnosed by colonoscopy, from 2004 to 2017. We collected clinical information on age, gender, past history of colonic diverticulitis, comorbidities, ongoing medication, diverticula locations, length of hospital stay, whether the patient required red blood cell transfusions, and the presence of stigmata of recent hemorrhage (SRH) observed by colonoscopy.

Results: Frequency analysis revealed that there were no risk factors for recurrent diverticular bleeding both during hospitalization and during outpatient visits after leaving the hospital. There was no significant independent risk factor for transfusion requirements. The odds ratio for prolonged length of hospital stay was 2:1 for use of antithrombotic drugs and 1:7 for alcohol habits.

Conclusions: Using antithrombotic agents did not affect rebleeding during hospitalization or transfusion requirements in diverticular bleeding, but prolonged the length of hospital stay. This should induce a delay in restarting antithrombotic agents, possibly resulting in poor prognosis of underlying diseases.

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Introduction

Colonic diverticular bleeding is the most common source of lower gastrointestinal bleeding. The condition has become more prevalent and is now an important issue both in Japan and Western countries.[1–4] Since colonic diverticular bleeding stopped spontaneously in 70-90% of cases,[5, 6] it is unlikely that urgent endoscopy was performed in clinical practice. However, analysis of a large national Japanese database indicated 2.5% in-hospital mortal-

ity.[7] Furthermore, a lower survival rate was reported in France, 78% after one year and 64% after three years.[8] This suggests that diverticular bleeding prognosis is subject to patient comorbidity and medications.[5] Ischemic events, such as myocardial infarction and stroke, are often fatal, especially in the elderly. Regrettably, once gastrointestinal bleeding has occurred, antithrombotic treatments for coronary diseases and cerebrovascular diseases cannot continue until hemostasis. Repeated bleeding should lead to poor prognosis. It is very important to identify the risk factors associated with colonic diverticular rebleeding.

The study's aim is to elucidate diverticular rebleeding risk factors and determine a better clinical approach to avoid inducing a poor prognosis, thus leading to better outcomes.

Materials and Methods

After approval from the ethical board of Toho University Medical Center, Omori Hospital (approval number: M17056), a retrospective review of hospitalized patients began. We evaluated 140 patients admitted with colonic diverticular bleeding, diagnosed by colonoscopy, on the day of or the day after overt bleeding, from 2004 to 2017. We collected clinical information on age, gender, past history of colonic diverticulitis, comorbidities (medication for hypertension, diabetes mellitus, and dyslipidemia), ongoing medication (antithrombotic drugs, including anticoagulants, anti-platelet drugs, and low-dose aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs)), the location of diverticula, length of hospital stay, whether red blood cell transfusion was required, and the presence of stigmata of recent hemorrhage (SRH) observed by colonoscopy. Age was categorized into two groups (less than 75 years old and others). Hypertension, diabetes mellitus, and dyslipidemia were assessed as well as underlying diseases requiring antithrombotic drugs. Subjects who usually consumed more than 20 g ethanol were considered drinkers. Both previous and current smokers were classified as smokers. Abnormal kidney function was classified as chronic dialysis, renal transplantation, or serum creatinine ≥ 2.0 g/dL. Abnormal liver function was defined here as aspartate aminotransferase (AST) >90 IU/L, and/or alanine aminotransferase (ALT) >70 IU/L, and/or alkaline phosphatase (ALP) >500 IU/L.

SRH was diagnosed when there was active bleeding, a visible nonbleeding vessel, or an adherent clot observed by colonoscopy. Even when SRH was not found, a presumptive diagnosis of diverticular bleeding was based on the presence of fresh blood within one or more colonic segments and diverticular erosions.[7, 8] The in-hospital recurrence of diverticular bleeding was defined clinically according to different parameters, including melena, a change in vital signs (systolic blood pressure <90 mmHg, heart rate >100 beats/min), or a drop in hemoglobin level.

Exclusion criteria were: (1) not undergoing colonoscopy; (2) <20 years old; (3) a past history of diverticular bleeding; and (4) management as an outpatient.

Statistical analysis

The data were evaluated using descriptive statistical methods (mean ± SD, ranges). First, clinical information was compared between patients with and without in-hospital rebleeding and red blood cell transfusion to elucidate the risk factors associated with recurrent acute diverticular bleeding. Next, the potential risk factors for recurrent diverticular bleeding after leaving the hospital were evaluated. Statistical correlation was performed using the Pearson chi-squared test with a 95 percent confidence interval to calculate frequency distribution and odds ratios between the potential risk factors and diverticular bleeding recurrence during both hospitalization and outpatient visits after leaving the hospital. The Kaplan-Meier method was used to investigate whether any clinical prognostic factor was confounding the recurrence of diverticular bleeding and length of hospital stay, and the log rank test was used to compare between the two groups. P values <0.05 were considered significant.

Results

A total of 140 patients were analyzed in this study. The patients' characteristics, including those taking antithrombotic drugs on admission due to acute colonic diverticular bleeding, are shown in Table 1, compared to the controls. The breakdown of the subjects was 95 males and 45 females, ranging in age between 30 and 93 years (average 66.9 years). Patients' comorbidities included 46 cases (32.9%) had hypertension, 21 (15.0%) had diabetes mellitus, and 32 (22.9%) had dyslipidemia. The subjects included 52 current smokers (37.1%) and 41 drinkers (29.3%).

Forty-one patients (29.3%) received antithrombotic drugs (Table 2), such as low-dose aspirin in 28 (68.3%), clopidogrel and warfarin in 10 (each) (24.4%), ticlopidine in 3 (7.3%), and prasugrel and cilostazol in one (each) (2.4%) patients. The mean value of prothrombin time-international normalized ratio in 10 patients using war-

farin was 2.0 ± 0.9. There was no patient who received direct oral anticoagulants in this study. The diseases to be treated by antithrombotic drugs were ischemic heart diseases (IHD) in 18 (43.9%), atrial fibrillation (AF) in 4 (9.8%), cerebrovascular diseases (CVD) in 13 (31.7%), peripheral arterial diseases (PAD) in 5 (12.2%), unknown in 5 (12.2%) patients. There were four patients with plural target diseases (IHD + CVD, IHD + PAD, IHD + PAD + CVD, AF + IHD + CVD). NSAIDs except low dose aspirin were prescribed in 11 cases (7.1%). The mean value of hemoglobin and hematocrit was 11.5 ± 2.2 g/dL and $35.0 \pm 10.6\%$, respectively.

Rebleeding, confirmed by colonoscopy during hospitalization, was found in 17 patients (12.1%) regardless of the length of hospital stay. (Table 3). A frequency analysis revealed that no factor was significantly associated with rebleeding during the hospitalization.

Although SRH was found in 42 patients (30%), the hemoglobin level on admission was almost equal between patients with and without SRH (11.7 ± 2.0 g/dl v.s. 11.7 ± 2.1

Table 1　Patients' characteristics with diverticular bleeding.

Number of patients	140
Age (year, mean +/− SD)	66.9 ± 13.2
Male/Female	95/45
Comorbidities (%)	
Hypertension	46 (32.9)
Diabetes mellitus	21 (15.0)
Dyslipidemia	32 (22.9)
Location of diverticulum (%)	
Right side	76 (54.3)
Left side	45 (32.1)
Bilateral	31 (22.1)
SRH	51 (36.4)
Habits (%)	
Current Smoker	52 (37.1)
Alcohol	41 (29.3)

Table 2　The details of antithrombotic agents and comorbidities.

Medication (%)	
Antithrombotic drugs	45 (32.1)
aspirin	28 (62.2)
clopidogrel	10 (22.2)
ticlopidine	3 (6.7)
cilostazol	1 (2.2)
prasugrel	1 (2.2)
warfarin	10 (22.2)
NSAIDs	11 (24.4)
Disease of antithrombotic drugs	
Ischemic Heart disease	18 (40.0)
Atrial fibrillation	4 (8.9)
Cerebrovascular disease	13 (28.9)
Peripheral arterial disease	5 (11.1)
unknown	5 (11.1)
Comorbidities (%)	
Hypertension	31 (68.9)
Diabetes mellitus	10 (22.2)
Dyslipidemia	15 (33.3)

Table 3　Potential risk factors for recurrent diverticular bleeding during hospitalization.

	Rebleeding (+)	Rebleeding (−)	Odd's ratio (95%CI)	p value
No. of cases	17	123		
≧75 year	4 (23.5)	40 (32.5)	0.638 (0.206-1.993)	0.454
Male	14 (82.4)	81 (65.9)	2.420 (0.700-8.265)	0.172
Hypertension	8 (47.1)	73 (59.3)	0.609 (0.226-1.638)	0.336
Diabetes	4 (23.5)	17 (13.8)	1.919 (0.592-6.311)	0.293
Dyslipidemia	2 (11.8)	30 (24.4)	0.413 (0.100-1.730)	0.245
Left-sided diverticulum	8 (47.1)	62 (50.4)	0.875 (0.326-2.348)	0.796
Antithrombotic drugs	4 (23.5)	37 (30.1)	0.715 (0.231-2.239)	0.578
NSAIDs	2 (11.8)	9 (7.3)	1.689 (0.380-7.732)	0.523
Smoking	9 (52.9)	46 (37.4)	1.883 (0.698-5.076)	0.219
Alcohol	2 (11.8)	39 (31.7)	0.287 (0.07-1.191)	0.09
SRH	9 (52.9)	42 (34.1)	2.170 (0.802-5.865)	0.131
Past history of diverticulitis	2 (11.8)	5 (4.1)	3.147 (0.651-15.63)	0.172
Past history of diverticular bleeding	1 (5.9)	7 (5.7)	1.036 (0.158-7.046)	0.975
Abnormal kidney function	1 (5.9)	1 (0.8)	7.625 (0.760-76.65)	0.099
Abnormal liver function	2 (11.8)	5 (4.1)	3.147 (0.651-15.63)	0.172

Table 4 Potential risk factors for rebleeding after leaving the hospital.

	Recurrence (+)	Recurrence (−)	Odd's ratio (95%CI)	p value
No. of cases	45	95		
≧75 year	12 (26.7)	32 (33.7)	0.716 (0.330-1.558)	0.404
Male	34 (75.6)	61 (64.2)	1.723 (0.782-3.783)	0.179
Hypertension	25 (55.6)	56 (58.9)	0.871 (0.428-1.771)	0.704
Diabetes	8 (17.8)	13 (13.71)	1.364 (0.534-3.499)	0.526
Dyslipidemia	10 (22.2)	22 (23.2)	0.948 (0.412-2.190)	0.903
Left-sided diverticulum	17 (37.8)	53 (55.8)	0.481 (0.234-0.989)	0.047 *
Antithrombotic drugs	11 (24.4)	30 (31.6)	0.701 (0.317-1.554)	0.386
NSAIDs	3 (6.7)	8 (8.4)	0.777 (0.213-2.862)	0.719
Smoking	17 (37.8)	35 (36.7)	1.041 (0.504-2.154)	0.915
Alcohol	18 (45.0)	50 (52.6)	0.600 (0.294-1.226)	0.163
SRH	19 (42.2)	32 (33.7)	1.439 (0.699-2.966)	0.327
Past history of diverticulitis	3 (6.7)	4 (4.2)	1.625 (0.389-6.819)	0.533
Past history of diverticular bleeding	4 (8.9)	4 (4.2)	2.220 (0.578-8.533)	0.265
Abnormal kidney function	1 (2.2)	1 (1.1)	2.1360 (0.218-20.928)	0.586
Abnormal liver function	1 (2.2)	6 (6.3)	0.337 (0.052-2.227)	0.371

*p＜0.05

Table 5 Potential risk factors for transfusion requirements in patients with diverticular bleeding.

	Transfusion (+)	Transfusion (−)	Odd's ratio (95%CI)	p value
No. of cases	6	134		
≧75 year	1 (16.7)	43 (32.1)	0.423 (0.064-2.854)	0.426
Male	6 (100.0)	89 (66.4)	−	0.085
Hypertension	4 (66.7)	77 (57.5)	1.481 (0.304-7.139)	0.655
Diabetes	3 (50.0)	18 (13.4)	6.444 (1.374-30.347)	0.014 *
Dyslipidemia	2 (33.3)	30 (22.4)	1.733 (0.355-8.580)	0.532
Left-sided diverticulum	1 (16.7)	69 (51.5)	0.188 (0.029-1.263)	0.095
Antithrombotic drugs	3 (50.0)	38 (28.4)	2.526 (0.557-11.474)	0.254
NSAIDs	0	11 (8.2)	0 (0-7.745)	0.465
Smoking	5 (83.3)	47 (35.1)	9.255 (1.375-61.114)	0.017 *
Alcohol	3 (50.0)	65 (48.5)	1.062 (0.236-4.777)	0.943
SRH	2 (33.3)	49 (36.6)	0.867 (0.180-4.230)	0.872
Past history of diverticulitis	0	7 (5.2)	0 (0-12.94)	0.566
Past history of diverticular bleeding	0	12 (9.0)	0 (0-7.007)	0.443
Abnormal kidney function	0	2 (1.5)	0 (0-49.145)	0.763
Abnormal liver function	1 (16.7)	6 (4.5)	4.267 (0.590-33.60)	0.269

*p＜0.05

g/dl). Among 42 patients with SRH, endoscopic clipping was performed in 21 patients (50%) by the judgment of endoscopists.

Forty-five patients (32.1%) returned to the hospital after discharge because of the event of a bloody stool. The length of the observation period after discharge was 22.1±33.0 months. Potential risk factors for recurrent diverticular bleeding, both during the hospitalization and during outpatient visits after leaving the hospital, were shown in Table 4. There was no significant factor associated with recurrence of diverticular bleeding except left-sided diverticulum. There was no significant independent risk factor for the recurrence of colonic diverticular bleeding after leaving the hospital.

Twelve patients required red blood cell transfusions (8.6%). Potential risk factors for requiring transfusions are shown in Table 5. Diabetes and smoking habit are significant independent risk factors for requiring transfusions

while hospitalized.

The average length of hospital stay for the entire cohort was 10.8 days. This value of 17 patients with rebleeding during hospitalization was significantly longer than that of 123 patients without rebleeding (14.6±8.0 days y.s. 10.2± 6.6 days, p=0.013), as shown in Fig. 1. The probability of rebleeding after hemostat was compared using the Kaplan-Meier analysis in Fig. 2. The length of hospitalization tended to be prolonged in patients who were taking antithrombotic agents. Two (1.6%) of 123 patients without rebleeding during hospitalization and one (5.9%) of 17 patients with rebleeding were hospitalized for longer than 30 days. Compared to the group not using antithrombotic drugs, the overall hospital stay was longer for patients using antithrombotic drugs, but the difference was not statistically significant (p=0.09, by the log rank test).
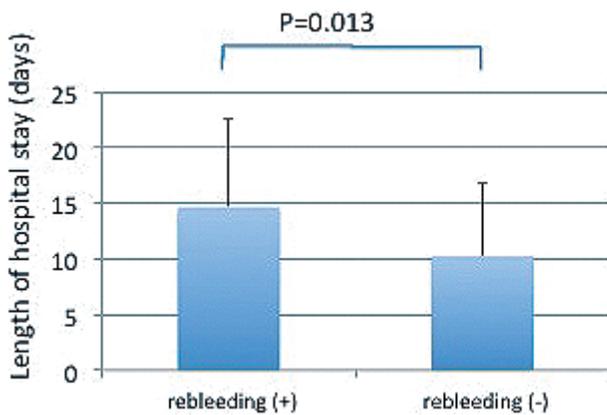

Fig. 1 The average length of hospital stay in patients with and without rebleeding during hospitalization.

Among 41 patients taking antithrombotic agents, oral administration was stopped in 37 patients (90.2%). Sixteen patients (43%) were restarted on antithrombotic agents while hospitalized, whereas 21 patients (57%) were discharged without restarting. Only five (23.8%) of 21 patients were restarted on antithrombotic agents after discharge.

Discussion

Most cases of colonic diverticulosis are asymptomatic; they are accidentally detected on CT examination or colonoscopy performed for another reason. Once diverticula are complicated by abscess, perforation and bleeding, it is clinically significant, especially in the elderly. Patients with ischemic heart disease and cerebral infarction are increasing in an aging society. They are usually taking antithrombotic drugs, including anti-platelet drugs and anticoagulants. While these drugs improved overall prognosis in patients with myocardial infarction and stroke,[9, 10] antithrombotic treatments were associated with an increased risk of bleeding complications. Upper gastrointestinal bleeding is the most common source of bleeding in patients taking aspirin, a powerful inhibitor of platelet aggregation.[11] To prevent aspirin-induced gastric mucosal damage, almost all patients are usually treated with a proton pump inhibitor (PPI) regardless of past gastric ulcer history. Adding a PPI to aspirin and NSAIDs is an evidence-based recommendation because PPIs can heal NSAID-associated ulcers, even if NSAIDs are continued.[12] An official statement of the European Society of Gastrointestinal Endoscopy (ESGE) recommends using a PPI in patients requiring dual anti-platelet therapy.[13] The clinical
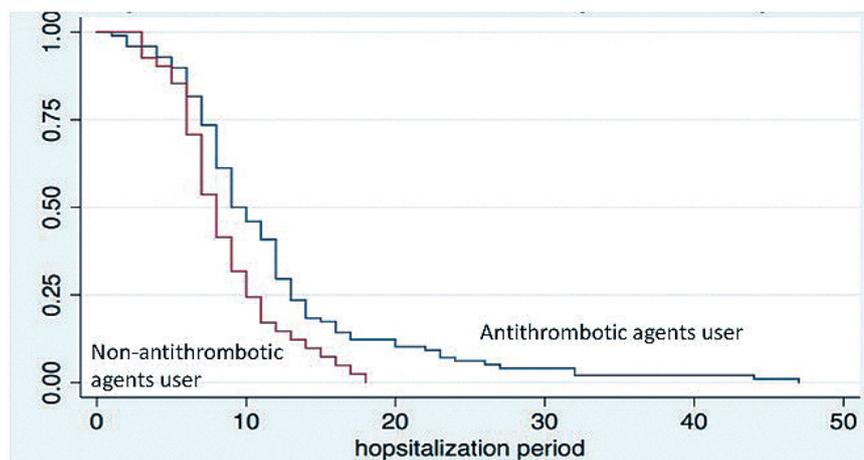

Fig. 2 The probability of rebleeding after hemostat was constructed by the Kaplan-Meier method and compared with the log rank test.

approach to prevent upper gastrointestinal bleeding is now established, but there is no evidence to prevent lower gastrointestinal bleeding yet.

In the present study, 41 patients (29.3%) received antithrombotic drugs due to their comorbidities. Patients older than 75 years accounted for 46.3%, more than those not taking an antithrombotic treatment (25.3%). The mean age of patients taking antithrombotic drugs was significantly older in than in controls (73.4±9.0 v.s. 64.1±13.7 years, p<0.01). Although diverticulum pathogenesis is still poorly understood, diverticular disease affects the elderly both in Japan and Western countries.[1-4] Since arteriosclerosis also increases with age, age itself might not be an independent risk factor for bleeding because diverticular bleeding is thought to be the result of a rupture of an arteriosclerotic altered diverticular vessel.[14] In addition, hypertension and dyslipidemia, considered strong risk factors for arteriosclerosis, were present significantly more often in patients taking antithrombotic agents. Recently, percutaneous coronary intervention (PCI) is almost routinely accompanied by stent placement to reduce the risk of restenosis, requiring maintenance therapy with aspirin and other antiplatelets (dual anti-platelet therapy; DAPT).[15] Although long-term use of NSAIDs should be avoided if possible, more patients should take aspirin due to increased PCI therapy for coronary artery disease. The frequent side effects may cause patients to discontinue therapy for IHD, resulting in determination of overall prognosis. Among 41 patients taking antithrombotic agents, 37 (90.2%) discontinued oral administration. Sixteen patients (43.0%) were restarted on antithrombotic agents while hospitalized, whereas 21 patients (57.0%) were discharged without restarting. This indicates older age might be associated with a more severe bleeding because these drugs produce a tendency toward systemic bleeding by impairing thromboxane-dependent platelet aggregation, consequently prolonging bleeding time.[16]

Contrary to our expectations, antithrombotic agents were not associated with rebleeding both during the hospitalization and after discharge in this study. A Japanese systematic review reveals that using aspirin and non-aspirin NSAIDs was strongly and consistently associated with increased risk of colonic diverticular bleeding,[17] whereas the effect of anticoagulants and non-aspirin antiplatelet agents on diverticular bleeding outcomes is been controversial.[18, 19] Thus, there are still many unclear points regarding the association between antithrombotic agents

and diverticular bleeding, suggesting that it is more complex and multifactorial. Therefore, this retrospective study noted the relationship between using antithrombotic agents and outcomes after an episode of diverticular bleeding.

Although using antithrombotic agents was not an independent risk factor for transfusion, recurrent diverticular bleeding after discharge, or rebleeding during the hospitalization, the length of hospital stay was significantly longer in patients taking antithrombotic agents. Since 57.0% of patients stopped taking these drugs orally upon admission, and were discharged without restarting them, prescribing decisions should be made carefully. Although how long patients should be restarted on warfarin after an episode of diverticular bleeding remains obscure, it was reported that earlier restarting of warfarin was associated with lower risk of thromboembolism.[20] There are too many variables in patients' clinical course to decide whether to restart an antithrombotic therapy after a diverticular bleeding episode and predict the prognostic outcome accurately. Future studies are needed to better identify antithrombotic agent users at risk of diverticular bleeding.

There are other potential risk factors besides antithrombotic agents for diverticular bleeding reported in the previous studies. Diverticula can develop anywhere in the large colon; however, the prevalence of diverticulosis of the left-sided colon is higher in Western countries compared to Eastern countries. In Japan, diverticulosis is more common in the right side.[21] The percentage of complications requiring surgery was higher in patients with left-sided colonic diverticulitis than it was in patients with right-sided diverticulitis.[22] This may be because left diverticula are associated with comparatively more perforations because narrow and degenerative change weakens muscle layers. The frequency of diverticular disease, especially left-sided diverticular disease, is increasing due to the adoption of Westernized diets, aging society, and advances in diagnostic tools.[5, 23] This study revealed that the incidence rate of rebleeding during the hospital was 12.1% after one episode of diverticular bleeding. Although the location of diverticula was not associated with in-hospital rebleeding, left-sided diverticulum was a significant independent risk factor for recurrent colonic diverticular bleeding after initial hemostasis. Since a colonoscope reaches the left-sided colon easily, resulting in successful endoscopic hemostasis, the results might be attributable to

degenerative change weakens the muscle layers of the left-sided colon.

Both colonic diverticulosis and bleeding diverticula were more common in males.[1, 2, 24] As shown in Table 3, male sex tended to be a risk factor for recurrent colonic diverticular bleeding, but the difference was not statistically significant in the present study. This is compatible with previous Japanese reports although there is no consensus on sex differences in diverticulosis and its rebleeding events in Western countries.[8] This gender difference might result from the other risk factors, such as obesity, smoking, and alcohol intake.[6, 25]

Relationship between diverticulitis and diverticular bleeding remains controversial in spite of attention by researchers. In the present study, a past history of diverticulitis was not a significant independent risk factor for the recurrent colonic diverticular bleeding after initial hemostasis. However, Strate et al[26] reported that obesity is associated with an increased risk of diverticulitis and diverticular bleeding, and the magnitude of the increased risk and the dose-response gradient was greater for diverticular bleeding than for diverticulitis. This suggests obese patients will experience more complications of diverticulitis and diverticular bleeding. Cyclooxygenase inhibitors are associated with increased risk of gastrointestinal bleeding as well as diverticulitis and its complications. Since diverticular bleeding is gastrointestinal bleeding, it is quite reasonable to pay clinical attention to a relationship between diverticulitis and diverticular bleeding.

Finally, there was no significant difference in rebleeding between hospitalized patients with and without SRH. This suggests that endoscopic treatment, mainly clipping hemostasis, would not affect the outcome of diverticular bleeding in both short- and long-term follow-up periods. Urgent endoscopy is desirable, especially in emergency situations, for diagnosis and successful treatment. There are previous reports that urgent colonoscopy did not improve rebleeding outcomes or mortality in diverticular bleeding.[27, 28] Since hospital medical equipment is often insufficient for urgent endoscopy in Japan, this result would be suitable for actual medical circumstances.

There are several limitations to the present study. This was a retrospective study in a single institute that could probably have various biases. Furthermore, in a strict sense, not only the similarities in age and sex but also the other factors such as size, location, and numbers of diverticula should have been equalized between the cases and controls. Second, the indication of clipping has been inconsistent, although all subjects underwent colonoscopy. Third, such detailed analysis may be needed in the future to elucidate the risk factors for diverticular bleeding more precisely.

There are some new findings regarding outcomes after diverticular bleeding. What is interesting to us is that use of antithrombotic agents did not affect rebleeding outcomes during hospitalization, or transfusion requirements in diverticular bleeding, but prolonged the length of hospital stay. This should induce the delay in restarting antithrombotic agents, possibly resulting in poor prognoses of underlying diseases.

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