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# Analysis of risk factors for colonic diverticular bleeding and recurrence

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**Abstract**

The increase in incidence of colonic diverticular bleeding is relative to an age-related rise in the incidence of colonic diverticulosis and use of antithrombotic medication. However, risk factors related to the onset, recurrence, and prophylaxis have not been established. Therefore, we aimed to determine risk factors for the onset and recurrence of colonic diverticular bleeding.

An age- and sex-matched case-control study was performed to assess the risk factors for the onset of colonic diverticular bleeding. The distribution of diverticulosis, comorbidity, and medication were evaluated from medical records. We also assigned patients with a first-time bleeding into groups with and without rebleeding during follow-up to determine risk factors for recurrence.

Bilateral colonic diverticulosis, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin (LDA), and anticoagulants were significant risk factors for the onset of colonic diverticular bleeding on multivariate analysis. In contrast, the use of selective cyclooxygenase-2 (COX-2) inhibitor was not a risk factor for the onset. The incidence of bleeding in direct oral anticoagulant and warfarin users was not different between the 2 groups. The cumulative recurrence rate at 1 year was 15%. Recurrence rate was significantly higher in patients with a prior history of colonic diverticular bleeding than those without. Steroid use was associated with recurrence.

Extensive distribution of diverticulosis and use of nonselective NSAIDs, LDA, and anticoagulants are regarded as risk factors for the onset of colonic diverticular bleeding. In addition, a prior history of colonic diverticular bleeding is related to the recurrence.

**Abbreviations:** BMI = body mass index, CI = confidence interval, COX = cyclooxygenase, DOAC = direct oral anticoagulant, HR = hazard ratio, LDA = low-dose aspirin, NSAIDs = nonsteroidal anti-inflammatory drugs, OR = odds ratio, PH = prior history, PPI = proton-pump inhibitor, PT-INR = prothrombin time international normalized ratio, SD = standard deviation.

**Keywords:** colonic diverticular bleeding, low-dose aspirin, nonsteroidal anti-inflammatory drugs, risk factor, steroids

## 1. Introduction

Diverticula are the most frequently encountered anatomic alteration of the colon. Colonic diverticula are characterized by herniation of the mucosa and submucosa through defects in the muscular layer of the colonic wall at the sites of penetration by vasa recta.[1] Colonic diverticulosis is highly prevalent and is increasing in incidence in both Asian and Western countries.[2,3] The colonic distribution of diverticula vary between countries, with diverticula found primarily in the left-sided colon in Western countries and the right-sided colon in Asia.[4–6]

The cases of colonic diverticular bleeding are increasing in relation to the rising incidence of colonic diverticulosis and antithrombotic drug use.[7] Although the mechanism of colonic diverticular bleeding is not fully understood, it is thought to be caused by a rupture of the vasa rectum at the neck or dome of the diverticulum.[8] Colonic diverticular bleeding ceases spontaneously in 70% to 90% of cases.[9,10] However, approximately 4% of patients with colonic diverticulosis suffer from severe diverticular bleeding.[11] Patients with colonic diverticular bleeding are at increased risk for recurrence.[1,12] Therefore, understanding the risk factors for diverticular bleeding is crucial for guiding the clinical management of patients. The risk factors related to colonic diverticular bleeding and appropriate prophylaxis have not been fully elucidated. In this study, we aimed to determine the risk factors for the onset and recurrence of colonic diverticular bleeding.

## 2. Materials and methods

### 2.1. Study design, setting, and participants

We performed an age- and sex-matched, case-control study to investigate the various risk factors (listed in the following section) for the onset and recurrence of colonic diverticular bleeding. Medical records of inpatients were retrospectively evaluated to get detailed information. Between January 2009 and December 2016, 102 patients with colonic diverticular bleeding were admitted at the Hyogo College of Medicine. Two bleeding patients with colonoscopy withdrawal time less than 6 minutes

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were excluded to maintain the accuracy of detection.[13] Finally, this study included 100 patients admitted with colonic diverticular bleeding, and 200 age- and sex-matched controls with asymptomatic colonic diverticulosis. Control patients had undergone colonoscopy with a withdrawal time more than 6 minutes during the same period, but had not experienced colonic diverticular bleeding or any intestinal surgery. The reasons for endoscopy of control patients included polyp treatment and screening for colorectal neoplasm and inflammation. Detection of colorectal cancer extending beyond the mucosa or inflammatory bowel disease was criterion for exclusion of control patients. Of the 100 patients with diverticular bleeding, 5 underwent surgical treatment and 95 were managed nonoperatively when first admitted to our hospital. The 95 nonoperative patients were further categorized as either having a first-time bleed (n = 71), or prior history of bleed (n = 24). Both patient groups (those with first-time bleeding and those with prior history of bleeding), were monitored for recurrence. Furthermore, the former patient group was compared to identify risk factors for rebleeding. Recurrence was defined as rebleeding after initial discharge. Data of patients who were not followed up, or who died, were considered censored. When medical records were not sufficient, telephone interviews were performed. The study protocol was approved by the Ethics Committee/Institutional Review Board of Hyogo College of Medicine, Japan (No. 201701-024).

### 2.2. Risk factors

Risk factors were identified by comparisons between the patients and controls. Patient information used for this study included location of diverticulosis, height, body weight, medication use, comorbidities, and whether they underwent hemostasis and colonoscopy within 24 hours of admission. Location of diverticulosis was defined as right sided, involving the transverse or proximal colon; left sided, the descending or distal colon; or bilateral, the entire colon. Patients were asked about the use of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, low-dose aspirin (LDA), non-aspirin antiplatelet drugs, anticoagulants, steroids, and proton-pump inhibitors (PPI). For this study, LDA was defined as being separate from nonselective NSAIDs because of its antiplatelet function. Anticoagulants consisted of direct oral anticoagulant (DOAC) and warfarin. If medications were used intermittently, they were not included. Comorbidities encompassed hypertension, dyslipidemia, diabetes mellitus, cerebrovascular disease, and ischemic heart disease. Patients were considered to have a specific comorbidity if they had been diagnosed with it in the past or were currently taking medication to treat that particular condition. Vascular disease was defined as a history of cerebrovascular disease and/or ischemic heart disease.

### 2.3. Diagnosis of colonic diverticular bleeding

Patients and controls underwent a complete colonoscopy following bowel preparation with a cleansing agent containing polyethylene glycol. However, a few patients who were unable to tolerate the bowel preparation, given their poor functional status, underwent an enema. The timing of colonoscopy was decided at the discretion of the physicians. A definitive diagnosis of diverticular bleeding was made by colonoscopic visualization of diverticulum exhibiting the stigmata of recent hemorrhage (such as active bleeding, a visible vessel, or an adherent clot). A presumptive diagnoses of recent diverticular bleeding was made when bright blood clots were found in the colon in the presence of diverticulosis and no alternative source of potential bleeding could be identified by additional testing, including esophagogastroduodenoscopy and/or capsule endoscopy.[14,15]

### 2.4. Statistical analysis

The number of participants in each arm of this case-control study was calculated to obtain results with an $\alpha$ of .05 and a power of .90. We calculated that 231 subjects including 77 cases and 154 controls were needed.

To determine the risk factors of colonic diverticular bleeding, we estimated the odds ratio (OR), the hazard ratio (HR), and 95% confidence interval (CI). Body mass index (BMI) was compared using the Mann-Whitney *U* test, whereas location of diverticulosis, comorbidities, and medications were compared using the chi-square test or Fisher exact test by univariate analysis and the unconditional logistic regression by multivariate analysis. Recurrence rate was calculated using the Kaplan-Meier method. Risk factors for recurrence of colonic diverticular bleeding and HR were evaluated using the Mann-Whitney *U* test and the log-rank test. Factors that had *P* values less than .05 on univariate analysis were used in multivariate analysis. All reported *P* values were 2-sided and those less than .05 were considered to be statistically significant. SPSS 22.0 (SPSS Inc., Chicago, IL), was used for statistical analyses.

## 3. Results

### 3.1. Characteristics of patients

The demographics and characteristics of cases and controls are summarized in Table 1. The age range of cases and controls were 29 to 90 and 35 to 93 years, respectively. Mean of the BMI was not different between the 2 groups. Nineteen cases (19.0%) were diagnosed as definite colonic diverticular bleeding. Colonoscopy was performed within 24 hours of admission in definitive cases (15/19, 78.9%) and presumptive cases (57/81, 70.4%) ($P = .576$). The timing of colonoscopy was not related to the identification rate of responsible diverticulum. In presumptive cases, 48 cases (59.3%) received esophagogastroduodenoscopy and 15 cases (18.5%) received capsule endoscopy. Transfusions were needed in 35 cases (35.0%). No patient died of diverticular bleeding.

### 3.2. Risk factors of colonic diverticular bleeding

By using age and sex as the matching variables, we performed a case-control study to analyze the risk factors for the onset of colonic diverticular bleeding. Univariate analysis showed that bilateral colonic diverticulosis (OR, 3.06; 95% CI, 1.84–5.07; $P < .001$), vascular disease (OR, 2.10; 95% CI, 1.22–3.63; $P = .007$), nonselective NSAIDs (OR, 3.59; 95% CI, 1.43–8.97, $P = .004$), LDA (OR, 2.12; 95% CI, 1.21–3.71, $P = .008$), and anticoagulants (OR, 2.95; 95% CI, 1.37–6.34, $P = .004$) were

**Table 1**

**Characteristics of patients.**

| | Control (n = 200) | Case (n = 100) | *P* value |
|---|---|---|---|
| Mean age ± SD, y | 70.7 ± 10.8 | 70.7 ± 11.6 | — |
| Men, % | 124 (62.0) | 62 (62.0) | — |
| BMI, kg/m$^2$ | 23.5 ± 3.1 | 23.0 ± 3.6 | .241 |

BMI = body mass index, SD = standard deviation.

**Table 2**

**Risk factors for the onset of colonic diverticular bleeding.**

| | Control (n = 200) | Case (n = 100) | Univariate OR (95% CI) | *P* value | Multivariate OR (95% CI) | *P* value |
|---|---|---|---|---|---|---|
| Bilateral diverticulosis | 82 (41.0)* | 68 (68.0) | 3.06 (1.84–5.07) | <.001 | 3.00 (1.77–5.10) | <.001 |
| Hypertension | 111 (55.5) | 55 (55.0) | 0.98 (0.61–1.59) | .935 | | |
| Dyslipidemia | 70 (35.0) | 29 (29.0) | 0.76 (0.45–1.28) | .297 | | |
| Diabetes mellitus | 37 (18.5) | 22 (22.0) | 1.24 (0.69–2.25) | .472 | | |
| Vascular disease | 38 (19.0) | 33 (33.0) | 2.10 (1.22–3.63) | .007 | 1.21 (0.61–2.41) | .582 |
| Cerebrovascular disease | 16 (8.0) | 19 (19.0) | 2.70 (1.32–5.51) | .005 | | |
| Ischemic heart disease | 24 (12.0) | 21 (21.0) | 1.95 (1.03–3.71) | .040 | | |
| Nonselective NSAIDs | 8 (4.0) | 13 (13.0) | 3.59 (1.43–8.97) | .004 | 3.47 (1.33–9.04) | .011 |
| Selective COX-2 inhibitor | 8 (4.0) | 4 (4.0) | 1.00 (0.29–3.40) | 1.00 | | |
| LDA | 35 (17.5) | 31 (31.0) | 2.12 (1.21–3.71) | .008 | 2.23 (1.11–4.48) | .024 |
| Non-aspirin antiplatelet drugs | 37 (18.5) | 23 (23.0) | 1.32 (0.73–2.37) | .358 | | |
| Anticoagulants | 13 (6.5) | 17 (17.0) | 2.95 (1.37–6.34) | .004 | 3.09 (1.35–7.09) | .008 |
| Steroids | 18 (9.0) | 11 (11.0) | 1.25 (0.57–2.76) | .581 | | |
| PPI | 65 (32.5) | 42 (42.0) | 1.50 (0.92–2.47) | .105 | | |
| Dialysis | 9 (4.5) | 8 (8.0) | 1.85 (0.69–4.94) | .216 | | |

CI = confidence interval, COX = cyclooxygenase, LDA = low-dose aspirin, NSAIDs = nonsteroidal anti-inflammatory drugs, PPI = proton-pump inhibitor, OR = odds ratio.
* Numbers in parentheses show percentage values.

significant risk factors. Multivariate analysis showed that bilateral colonic diverticulosis (OR, 3.00; 95% CI, 1.77–5.10; $P < .001$), nonselective NSAIDs (OR, 3.47; 95% CI, 1.33–9.04, $P = .011$), LDA (OR, 2.23; 95% CI, 1.11–4.48, $P = .024$), and anticoagulants (OR, 3.09; 95% CI, 1.35–7.09, $P = .008$) were independent risk factors (Table 2). Of the 13 bleeding patients using nonselective NSAIDs, 1 took 1 tablet daily, 3 took 2 tablets, 8 took 3 tablets, and 1 was unknown. As for the control cases, 5 took 1 tablet daily, 2 took 2 tablets, and 1 took 3 tablets. The dose of nonselective NSAIDs was significantly different between cases and controls ($P = .001$). Taking 3 tablets daily was a significant risk factor of colonic diverticular bleeding (OR, 17.7; 95% CI, 2.17–143.4; $P < .001$). Among LDA (81 and 100 mg) users, 29 of 31 bleeding cases (93.5%) and 33 of 35 control cases (94.3%) were taking 100 mg daily. Regarding the bleeding cases, 7 patients were using DOAC (rivaroxaban, 4; edoxaban, 1; dabigatran, 1; and apixaban, 1) and 10 were using warfarin. Prothrombin time international normalized ratio (PT-INR) of warfarin users were significantly higher in the bleeding cases compared to control cases ($2.02 \pm 0.49$ vs $1.32 \pm 0.23$, $P = .009$). As for the control cases, 6 patients were using DOAC (rivaroxaban, 3; edoxaban, 1; and dabigatran, 2) and 7 were using warfarin. There was no difference in the incidence of bleeding between DOAC and warfarin users.

### 3.3. Risk factors for the recurrence of colonic diverticular bleeding

Cumulative recurrence rate for patients being managed non-operatively at the initial admission to our hospital is shown in Figure 1A. Mean follow-up period was 26.2 months. The recurrence rates at 12, 24, and 36 months were 15%, 27%, and 33%, respectively. Cumulative recurrence rate of patients with or without prior history of colonic diverticular bleeding was significantly different (HR, 2.39; 95% CI, 1.19–6.79; $P = .019$) (Fig. 1B). We also assigned patients with a first-time bleeding (n = 71), into groups with and without rebleeding to determine risk factors for recurrence (Table 3). The age ranges of patients with and without recurrence were 44 to 86 and 29 to 90 years, respectively. Age, gender, and BMI were not different between the recurrence and nonrecurrence group. Only steroid use was a significant risk factor for recurrence (Fig. 2). Furthermore, 50%

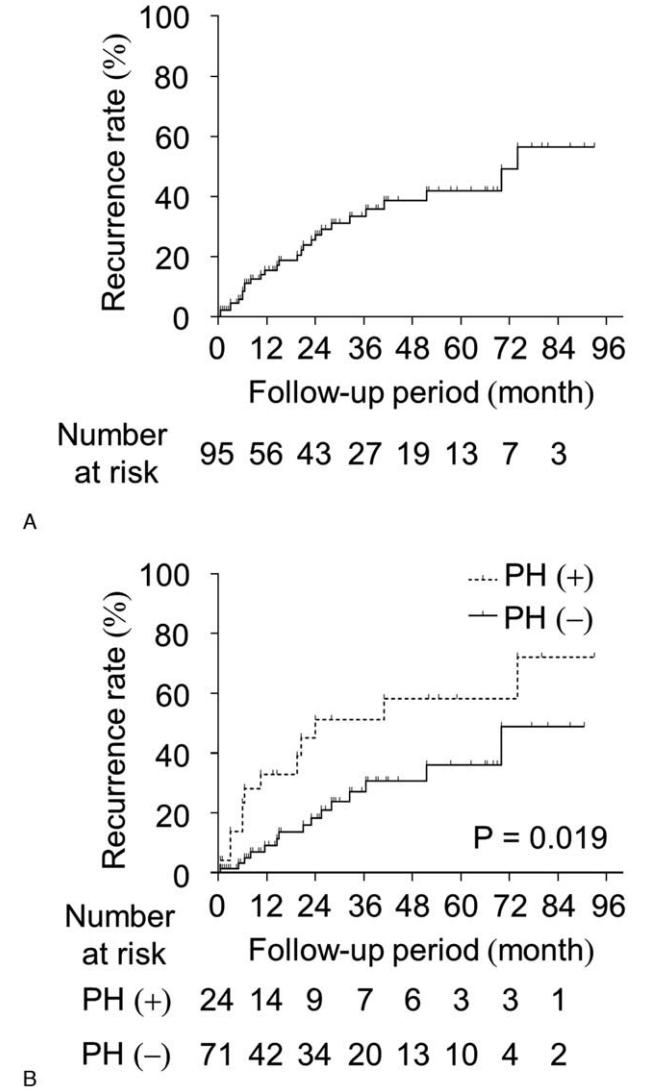


**Figure 1.** Kaplan-Meier estimates of cumulative recurrence rate at the initial admission (A) and for patients who had PH and those that did not (B). PH = prior history.

**Table 3**

**Risk factors for recurrence of colonic diverticular bleeding with a first bleed.**

| | Recurrence (n = 15) | Nonrecurrence (n = 56) | Hazard ratio (95% CI) | *P* value |
|---|---|---|---|---|
| Mean age ± SD, y | 71.6 ± 11.0 | 70.8 ± 11.8 | | .730 |
| Men | 8 (53.3)* | 34 (60.7) | 0.74 (0.26–2.08) | .565 |
| Mean BMI, kg/m$^2$ | 22.8 ± 4.9 | 22.6 ± 3.5 | | .752 |
| Bilateral diverticulosis | 11 (73.3) | 35 (62.5) | 1.26 (0.42–3.73) | .686 |
| Hypertension | 6 (40.0) | 31 (55.4) | 0.40 (0.12–1.01) | .060 |
| Dyslipidemia | 5 (33.3) | 17 (30.4) | 1.00 (0.34–2.94) | .994 |
| Diabetes mellitus | 3 (20.0) | 11 (19.6) | 0.89 (0.26–3.03) | .854 |
| Vascular disease | 4 (26.7) | 16 (28.6) | 0.68 (0.24–2.00) | .504 |
| Cerebrovascular disease | 2 (13.3) | 9 (16.1) | 0.52 (0.17–1.86) | .360 |
| Ischemic heart disease | 2 (13.3) | 11 (19.6) | 0.67 (0.19–2.57) | .594 |
| Nonselective NSAIDs | 2 (13.3) | 7 (12.5) | 0.87 (0.21–3.58) | .850 |
| selective COX-2 inhibitor | 0 (0.0) | 4 (7.1) | 0.00 (0.04–2.81) | .320 |
| LDA | 4 (26.7) | 18 (32.1) | 0.80 (0.27–2.39) | .693 |
| Non-aspirin antiplatelet drugs | 3 (20.0) | 13 (23.2) | 0.79 (0.24–2.61) | .714 |
| Anticoagulants | 2 (13.3) | 12 (21.4) | 0.84 (0.21–3.42) | .816 |
| Steroids | 6 (40.0) | 4 (7.1) | 4.31 (2.35–45.84) | .002 |
| PPI | 8 (53.3) | 25 (44.6) | 1.82 (0.69–5.53) | .223 |
| Dialysis | 1 (6.7) | 6 (10.7) | 0.90 (0.11–7.48) | .921 |
| Hemostasis | 7 (46.7) | 22 (39.3) | 1.07 (0.39–2.98) | .888 |
| Colonoscopy within 24 h | 12 (80.0) | 44 (78.6) | 1.31 (0.40–4.18) | .669 |

BMI = body mass index, CI = confidence interval, COX = cyclooxygenase, LDA = low-dose aspirin, NSAIDs = nonsteroidal anti-inflammatory drugs, PPI = proton-pump inhibitor, SD = standard deviation.
* Numbers in parentheses show percentage values.

(3/6) patients in the recurrence group and 75% (3/4) patients in the nonrecurrence group were using LDA/nonselective NSAIDs with steroids ($P = .571$).

## 4. Discussion

In this case-control study, we found that bilateral diverticulosis, nonselective NSAID use, LDA use, and anticoagulant use were independent risk factors for colonic diverticular bleeding onset. In contrast, selective COX-2 inhibitor use was not identified as an independent risk factor. Regarding anticoagulants, the risk of diverticular bleeding onset between DOAC and warfarin use did not differ. Finally, steroid use was the only risk factor identified for the recurrence of diverticular bleeding.

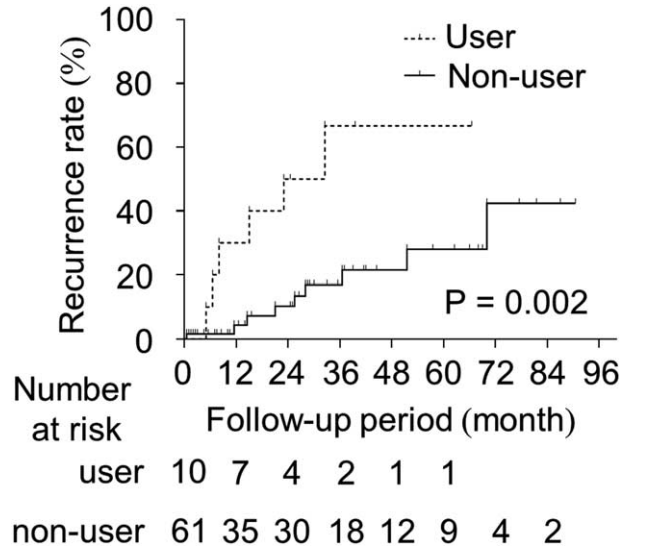


**Figure 2.** Kaplan-Meier estimates of cumulative recurrence rate for steroid user and nonuser.

The mean age and male-to-female ratio of patients with initial bleeding of colonic diverticular bleeding were similar to other studies.[16–18] Early colonoscopy did not contribute to the identification rate of responsible diverticulum in this study. It is not established whether the timing of colonoscopy affects the identification of a bleeding source for patients with lower gastrointestinal bleeding.[19,20] Some studies consistently reported that bilateral diverticulosis was a risk factor for the onset of colonic diverticular bleeding.[21–23] It is difficult to evaluate the precise number and location of diverticula by colonoscopy. Although a barium enema study might be the best examination, opportunities for using the examination are decreasing. This study included only patients who had undergone colonoscopy with a withdrawal time more than 6 minutes to reduce oversight.[13] A reason why bilateral diverticulosis may increase the risk for bleeding is that the greater the distribution of diverticula along the colon, the larger the potential for blood vessels to become exposed and the greater the propensity for bleeding.

NSAIDs, including LDA, were reported as risk factors for the onset of colonic diverticular bleeding.[17,24–26] NSAIDs reduce prostaglandin synthesis and decrease platelet function through COX-1 inhibition.[27,28] Therefore, mucosal injury may lead to the development of intestinal erosions and ulcers with a high likelihood of bleeding. In this study, increased dose of nonselective NSAIDs was a significant risk factor. However, the sample size was not enough to conclude that the onset risk depends on the dose. In addition, LDA has a higher affinity for COX-1 than COX-2 and decreases platelet function through the inhibition of thromboxane $A_2$ production.

Celecoxib, a selective COX-2 inhibitor, has sustained anti-inflammatory and analgesic activity similar to nonselective NSAIDs with a lower frequency of upper gastrointestinal ulceration or adverse events.[28–30] To our knowledge, only 1 study had evaluated whether selective COX-2 inhibitor use was a

risk factor for the onset of colonic diverticular bleeding.[17] Both studies, including ours, showed that selective COX-2 inhibitor use was not associated with the onset of colonic diverticular bleeding, although the number of patients using selective COX-2 inhibitors were few. When NSAID withdrawal is difficult, replacement with a selective COX-2 inhibitor might reduce the risk of colonic diverticular bleeding.

In this study, anticoagulant use was an independent risk factor for inducing the onset of colonic diverticular bleeding. This result contradicts findings from previous studies.[24,31] Although anticoagulants theoretically do not have an effect on diverticular bleeding onset, many patients who use anticoagulants often receive medical care for gastrointestinal bleeding. A possible reason for this observation is that anticoagulants prevent spontaneous resolution of bleeding from impaired mucosa, leading to symptomatic patient presentation. Although previous studies have been imprecise in identifying the difference between DOAC and warfarin,[32,33] our study demonstrated no difference between DOAC and warfarin in inducing the onset of colonic diverticular bleeding.

PPI is widely used for prophylaxis of upper gastrointestinal bleeding. However, a recent study by Miyake et al reported a worrisome relationship between PPI use and an increased risk of lower gastrointestinal bleeding in LDA users.[34] Another study by Nagata et al had contradictory results, demonstrating no association between concurrent PPI and anticoagulant use with lower gastrointestinal bleeding.[35] Subanalysis of this study further indicated that PPI was not a risk factor for colonic diverticular bleeding.[36] In the present study, PPI use was not an independent risk factor for the onset of colonic diverticular bleeding. To firmly establish the relationship between PPI and colonic diverticular bleeding, additional prospective studies are warranted.

We also evaluated risk factors for recurrence of colonic diverticular bleeding. Our results demonstrate recurrence rate and mean follow-up period similar to previous reports.[9,15,37–40] Interestingly, there was a significant difference between recurrence rate for patients who had a prior history of colonic diverticular bleeding and those that did not. In patients who had already experienced at least 1 prior bleeding episode, the recurrence rate was as high as 51% over 2 years. Although it has been reported that the recurrence within 1 month from the initial bleeding was not associated with a prior history of colonic diverticular bleeding,[41] McGuire et al reported that the chance of a third bleeding after a second episode was as high as 50%.[11] Our result was in agreement with the latter report. Despite these high recurrence rates of bleeding, surgery was often not used as a treatment modality for recurrent colonic diverticular bleeding. In fact, only 7 patients underwent surgery among 100 patients during the follow-up period in the present study. The most common reason cited for avoiding surgery was risk, as patients with colonic diverticular bleeding are often elderly with multiple comorbidities. Additionally, the identification of diverticulum responsible for bleeding is challenging, with only 17% to 40% being identified via colonoscopy.[16,39,42,43] Therefore, without knowing the origin of the bleeding, it is difficult to discern which colonic segment should be resected. However, when colonic diverticular bleeding recurs, patients invariably require hospitalization. In turn, hospitalization detrimentally affects patient's quality of life and increases risk of mortality. Our study results can guide clinical decision making to reduce the likelihood of initial diverticular bleeding, rebleeding, and prevent hospitalization.

We also assigned patients with first-time bleeding into groups with and without rebleeding during the follow-up period to determine the risk factors for bleeding recurrence. We found that steroid use was a significant risk factor for the recurrence. This is likely due to steroids causing impaired and delayed mucosal healing, which in turn increases the probability of rebleeding.[44]

A number of limitations are present in our study, which may require further investigation. First, it was a retrospective study in a single institution. As our institution is a tertiary care center, most patients already have various comorbidities and take numerous medications. A multicenter cohort study would provide strong evidence and reduce the risk of Berkson bias. However, collecting all patient medication information is not easily accomplished in a retrospective analysis, as medications are often prescribed in different hospitals or clinics. A second limitation is that a few patients were unavailable for follow up. To minimize this limitation, we conducted telephone interviews. Finally, the sample size for some factors is small. Especially, there is not enough power for the detailed analysis of medications including type, dosage, and duration. Prospective studies to assess these factors are warranted.

In conclusion, this study indicates that extensive distribution of diverticulosis and use of LDA, nonselective NSAIDs, and anticoagulants are regarded as risk factors for the onset of colonic diverticular bleeding. The risk of colonic diverticular bleeding onset was not different between DOAC and warfarin. In addition, recurrence rate was significantly different between patients who had a prior history of colonic diverticular bleeding and those that did not. Steroid use was regarded as a risk factor for bleeding recurrence in patients with first-time bleeding of colonic diverticular bleeding.

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## References

[1] Stollman N, Raskin JB. Diverticular disease of the colon. Lancet 2004;363:631–9.
[2] Nagata N, Niikura R, Aoki T, et al. Increase in colonic diverticulosis and diverticular hemorrhage in an aging society: lessons from a 9-year colonoscopic study of 28,192 patients in Japan. Int J Colorectal Dis 2014;29:379–85.
[3] Roberts P, Abel M, Rosen L, et al. Practice parameters for sigmoid diverticulitis: The Standards Task Force American Society of Colon and Rectal Surgeons. Dis Colon Rectum 1995;38:125–32.
[4] Chia JG, Wilde CC, Ngoi SS, et al. Trends of diverticular disease of the large bowel in a newly developed country. Dis Colon Rectum 1991;34: 498–501.
[5] Yamada E, Inamori M, Uchida E, et al. Association between the location of diverticular disease and the irritable bowel syndrome: a multicenter study in Japan. Am J Gastroenterol 2014;109:1900–5.
[6] Mehrzad R, Mishra S, Faller G, et al. Right-sided diverticulosis and disparities from left-sided diverticulosis in the Vietnamese population living in Boston, Mass., USA: a retrospective cohort study. Med Princ Pract 2015;24:355–61.
[7] Kinjo K, Matsui T, Hisabe T, et al. Increase in colonic diverticular hemorrhage and confounding factors. World J Gastrointest Pharmacol Ther 2016;7:440–6.
[8] Meyers MA, Alonso DR, Gray GF, et al. Pathogenesis of bleeding colonic diverticulosis. Gastroenterology 1976;71:577–83.
[9] McGuire HHJr. Bleeding colonic diverticula. A reappraisal of natural history and management. Ann Surg 1994;220:653–6.
[10] Lewis M. Bleeding colonic diverticula. J Clin Gastroenterol 2008;42: 1156–8.
[11] McGuire HHJr, Haynes BWJr. Massive hemorrhage for diverticulosis of the colon: guidelines for therapy based on bleeding patterns observed in fifty cases. Ann Surg 1972;175:847–55.

[12] Maykel JA, Opelka FG. Colonic diverticulosis and diverticular hemorrhage. Clin Colon Rectal Surg 2004;17:195–204.
[13] Barclay RL, Vicari JJ, Doughty AS, et al. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. N Engl J Med 2006;355:2533–41.
[14] Jensen DM, Machicado GA, Jutabha R, et al. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. N Engl J Med 2000;342:78–82.
[15] Zuckerman GR, Prakash C. Acute lower intestinal bleeding. Part II: etiology, therapy, and outcomes. Gastrointest Endosc 1999;49:228–38.
[16] Sugihara Y, Kudo SE, Miyachi H, et al. Analysis of risk factors for colonic diverticular bleeding: a matched case-control study. Gut Liver 2016;10:244–9.
[17] Nagata N, Niikura R, Aoki T, et al. Colonic diverticular hemorrhage associated with the use of nonsteroidal anti-inflammatory drugs, low-dose aspirin, antiplatelet drugs, and dual therapy. J Gastroenterol Hepatol 2014;29:1786–93.
[18] Tsuruoka N, Iwakiri R, Hara M, et al. NSAIDs are a significant risk factor for colonic diverticular hemorrhage in elder patients: evaluation by a case-control study. J Gastroenterol Hepatol 2011;26:1047–52.
[19] Kouanda AM, Somsouk M, Sewell JL, et al. Urgent colonoscopy in patients with lower GI bleeding: a systematic review and meta-analysis. Gastrointest Endosc 2017;86:107.e1–17.e1.
[20] Sengupta N, Tapper EB, Feuerstein JD. Early versus delayed colonoscopy in hospitalized patients with lower gastrointestinal bleeding: a meta-analysis. J Clin Gastroenterol 2017;51:352–9.
[21] Niikura R, Nagata N, Shimbo T, et al. Natural history of bleeding risk in colonic diverticulosis patients: a long-term colonoscopy-based cohort study. Aliment Pharmacol Ther 2015;41:888–94.
[22] Suh S, Seo PJ, Park H, et al. The risk factors for colonic diverticular bleeding. Korean J Gastroenterol 2012;60:349–54.
[23] Suzuki K, Uchiyama S, Imajyo K, et al. Risk factors for colonic diverticular hemorrhage: Japanese multicenter study. Digestion 2012; 85:261–5.
[24] Yamada A, Sugimoto T, Kondo S, et al. Assessment of the risk factors for colonic diverticular hemorrhage. Dis Colon Rectum 2008;51:116–20.
[25] Yuhara H, Corley DA, Nakahara F, et al. Aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis. J Gastroenterol 2014;49:992–1000.
[26] Strate LL, Liu YL, Huang ES, et al. Use of aspirin or nonsteroidal anti-inflammatory drugs increases risk for diverticulitis and diverticular bleeding. Gastroenterology 2011;140:1427–33.
[27] Hollander D. Gastrointestinal complications of nonsteroidal anti-inflammatory drugs: prophylactic and therapeutic strategies. Am J Med 1994;96:274–81.
[28] Ballinger A, Smith G. COX-2 inhibitors vs. NSAIDs in gastrointestinal damage and prevention. Expert Opin Pharmacother 2001;2:31–40.
[29] Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. Lancet 1999;354:2106–11.
[30] Chen YF, Jobanputra P, Barton P, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess 2008;12:1–278.
[31] Niikura R, Nagata N, Akiyama J, et al. Hypertension and concomitant arteriosclerotic diseases are risk factors for colonic diverticular bleeding: a case-control study. Int J Colorectal Dis 2012;27:1137–43.
[32] Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383:955–62.
[33] Caldeira D, Barra M, Ferreira A, et al. Systematic review with meta-analysis: the risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants. Aliment Pharmacol Ther 2015;42: 1239–49.
[34] Miyake K, Akimoto T, Hanada Y, et al. Proton pump inhibitors are associated with lower gastrointestinal tract bleeding in low-dose aspirin users with ischaemic heart disease. Dig Liver Dis 2015;47:757–62.
[35] Nagata N, Niikura R, Aoki T, et al. Effect of proton-pump inhibitors on the risk of lower gastrointestinal bleeding associated with NSAIDs, aspirin, clopidogrel, and warfarin. J Gastroenterol 2015;50:1079–86.
[36] Nagata N, Shimbo T. Reply to the letter by Kawada entitled "Combined effect of proton-pump inhibitors and other drugs with regard to lower gastrointestinal tract bleeding with special reference to low-dose aspirin". J Gastroenterol 2016;51:174–5.
[37] Okamoto T, Watabe H, Yamada A, et al. The association between arteriosclerosis related diseases and diverticular bleeding. Int J Colorectal Dis 2012;27:1161–6.
[38] Niikura R, Nagata N, Yamada A, et al. Recurrence of colonic diverticular bleeding and associated risk factors. Colorectal Dis 2012;14: 302–5.
[39] Nishikawa H, Maruo T, Tsumura T, et al. Risk factors associated with recurrent hemorrhage after the initial improvement of colonic diverticular bleeding. Acta Gastroenterol Belg 2013;76:20–4.
[40] Aytac E, Stocchi L, Gorgun E, et al. Risk of recurrence and long-term outcomes after colonic diverticular bleeding. Int J Colorectal Dis 2014; 29:373–8.
[41] Fujino Y, Inoue Y, Onodera M, et al. Risk factors for early re-bleeding and associated hospitalization in patients with colonic diverticular bleeding. Colorectal Dis 2013;15:982–6.
[42] Tanaka Y, Motomura Y, Akahoshi K, et al. Predictive factors for colonic diverticular rebleeding: a retrospective analysis of the clinical and colonoscopic features of 111 patients. Gut Liver 2012;6:334–8.
[43] Sugiyama T, Hirata Y, Kojima Y, et al. Efficacy of contrast-enhanced computed tomography for the treatment strategy of colonic diverticular bleeding. Intern Med 2015;54:2961–7.
[44] Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open 2014;4:e004587.