

Original Research Article

Risk Factors for Late Rebleeding of Colonic Diverticular Bleeding in Elderly Individuals

Yoshinori Sato, Hiroshi Yasuda, Yusuke Nakamoto, Hirofumi Kiyokawa, Masaki Yamashita, Yasumasa Matsuo, Tadateru Maehata, Hiroyuki Yamamoto and Fumio Itoh

*Division of Gastroenterology and Hepatology, Department of Internal Medicine,
St Marianna University School of Medicine, Kanagawa, Japan*

Abstract

Objectives: This study aimed to examine the clinical characteristics of colonic diverticular bleeding (CDB) in elderly individuals.

Methods: This retrospective case-control study was conducted at a single tertiary center. A total of 519 patients (356 men and 163 women; mean age of 73.1 ± 12.5 years) with CDB and hospitalized between January 2004 and May 2019 were analyzed. The subjects were divided into two groups: the elderly (274 individuals aged ≥ 75 years; mean age, 82.1 ± 5.3 years) and non-elderly (245 individuals aged < 75 years; mean age, 63.0 ± 10.3 years) groups. Primary outcomes were early and late rebleeding rates, and secondary outcomes were the risk factors for late rebleeding in elderly individuals. Rebleeding occurring within 30 days of hospitalization was defined as early rebleeding, whereas rebleeding occurring after 31 days was defined as late rebleeding.

Results: The early rebleeding rates were 30.6% and 33.1% ($p = 0.557$) in the elderly and non-elderly groups, respectively. The late rebleeding rates were 42.3% and 30.6% ($p = 0.005$) in the elderly and non-elderly groups, respectively. The 3-year recurrence-free survival was 63.6% in the elderly group and 75.6% in the non-elderly group (log-rank test: $p < 0.001$). Multivariate analysis revealed the use of non-steroidal anti-inflammatory drugs (NSAIDs) [odds ratio (OR), 3.55], chronic kidney disease (OR, 2.89), and presence of bilateral diverticula (OR, 1.83) as the independent risk factors for late rebleeding in elderly individuals.

Conclusions: Elderly individuals with CDB require careful follow-up even after discharge. Furthermore, it is important to consider discontinuing NSAIDs to prevent rebleeding.

Keywords

colonic diverticular bleeding, elderly patients, rebleeding, non-steroidal anti-inflammatory drug, bilateral diverticula

J Anus Rectum Colon 2021; 5(2): 148-157

Introduction

Recently, the aging society resulting from the declining birth rate and prolonged mean life span has become a problem worldwide[1]. Japan is one of the rapidly aging coun-

tries in the world. The prevalence of diverticula increases with age, and the aging of society in Japan has increased the occurrence of colonic diverticular bleeding (CDB)[2,3]. CDB is the most frequent type of lower gastrointestinal bleeding (LGIB)[4], and its risk factors include the use of

non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin[5,6]. Further, patients with CDB have a high rebleeding rate after discharge, and the reported rebleeding rates after 1 year range from 3.8% to 42%[7-14]. Repeated hospitalization due to CDB impairs elderly individuals from doing the activities of daily living. To date, few studies have focused on the characteristics of CDB in the elderly individuals. The Japan Gastroenterological Association's guidelines for CDB and colonic diverticulitis do not mention the characteristics of CDB in elderly individuals[8]. Therefore, in the study, we examined the difference between elderly and non-elderly individuals with CDB and identified the clinical characteristics of CDB in individuals aged ≥ 75 years.

Methods

Study design

This retrospective case-control study was conducted at a single tertiary center in Japan and in accordance with the Declaration of Helsinki. The local ethics committee of our hospital approved the study protocol. Informed consent was obtained in the form of opt-out on the website. All authors had access to the study data and approved the final draft of the manuscript.

Patients and data collection

The study sample included patients aged ≥ 18 years who were diagnosed with CDB and required hospitalization between January 2004 and May 2019. Those who could be followed up for at least 6 months after discharge were recruited. Recruited patients in this study partly overlapped with those in a previous report[15]. Hospitalization was recommended for all patients who presented to the hospital with LGIB and absence of abdominal pain and in whom the source of bleeding was unclear on abdominal computed tomography (CT) and anoscopy examination, regardless of the presence or absence of shock. The CDB diagnostic criteria were as follows: (i) definitive CDB (an active bleeding, non-bleeding visible vessel, and adherent clot observed from a specific diverticulum by colonoscopy)[16] and (ii) presumptive CDB (the source of bleeding could not be identified by colonoscopy and no other lesion could be observed that could cause bloody stools). Patients who required hospitalization were classified into two groups according to age: the elderly group that comprised patients aged ≥ 75 years and the non-elderly group that comprised those aged < 75 years. In each group, we examined patient data including sex, average age, performance status, comorbidities, the presence or absence of shock on or after admission, hemoglobin (Hb) level on admission, blood transfusion dose during hospitalization, length of hospitalization, mortality, the presence or absence of bilateral diverticula, and oral agents taken includ-

ing antithrombotic agents and NSAIDs. Furthermore, we examined the timing of colonoscopy, rate of identification of the bleeding source, bleeding site, type of stigmata of recent hemorrhage (SRH), hemostasis method, success rate of endoscopic treatment, and rebleeding rate. Patient data were retrospectively collected using the endoscopy database NEXUS[®] (FUJIFILM Holdings Co., Tokyo, Japan) and the patients' electronic medical records. Shock was defined as a shock index of > 1 due to bleeding. Shock index is defined as the ratio of heart rate to systolic blood pressure[17]. Chronic kidney disease (CKD) was considered to be present in patients undergoing hemodialysis or peritoneal dialysis or in those with an estimated glomerular filtration rate of < 60 mL/min. "Bilateral diverticula" was defined as the confirmation of diverticula in both the right and left colons using CT on admission. Mortality was defined as death within 30 days of hospitalization.

Colonoscopy

All patients underwent colonoscopy after admission. Before colonoscopy, an intestinal lavage solution containing 2 L of polyethylene-glycol (PEG) was administered. If there was no history of renal failure or allergy to the contrast medium, all patients underwent contrast-enhanced CT at hospital arrival. When there was extravasation on contrast-enhanced CT or when the vital signs were unstable, colonoscopy was performed without PEG at the discretion of the attending physician. PCF-Q260AZI or PCF-290AZI (Olympus Co., LTD, Tokyo, Japan) was used for colonoscopy. When SRH were identified, endoscopic hemostasis was performed using a hemoclip[18-20] or endoscopic band ligation (EBL)[7,21]. The clipping method used was the direct method, in which the blood vessels within diverticula were directly clipped[19,20]. The indirect method was used only for patients in whom the direct method was difficult to perform. The HX-610-135S or HX-610-135 device (Olympus Co., Ltd., Tokyo, Japan) was used as the hemoclip. The EBL method was introduced in 2015 as a method for endoscopic hemostasis; however, since its introduction, there was one case of delayed perforation following EBL[22]. Therefore, EBL was subsequently discontinued and clipping method was mainly used. Interventional radiology (IVR) or surgery was required when endoscopic hemostasis was difficult.

Outcomes

The primary outcomes were early and late rebleeding rates, and the secondary outcomes were the risk factors of late rebleeding in all patients and elderly patients. Early rebleeding was defined as bloody stools occurring within 30 days after admission or a reduction in Hb to ≥ 2 g/dL on blood tests. Late rebleeding was defined as new bloody stools due to CDB occurring 31 days or later after admis-

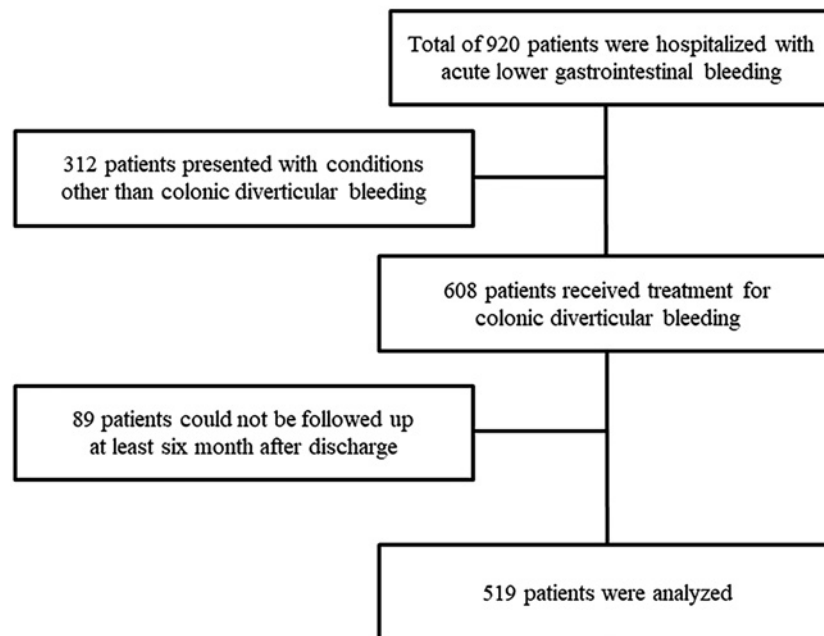


Figure 1. Flowchart of patient enrollment.

sion.

Statistical analysis

Results are presented as median and average for continuous variables. χ^2 -test and Fisher's exact test were used to compare categorical data, and Student's *t*-test and Mann-Whitney *U*-test were used to compare continuous data. Logistic regression analysis was performed to calculate the odds ratios (OR) of the risk factors for late rebleeding in all patients and in elderly patients with CDB. Furthermore, multivariate analysis was performed for risk factors that demonstrated statistical significance on univariate analysis. Comparison of the recurrence-free survival period was performed by log-rank test using Kaplan-Meier method. *P* values of <0.05 were used to indicate statistical significance. Statistical analyses were performed using Statistical Package for the Social Sciences (version 22.0; IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Figure 1 shows patient enrollment. During the study period, 608 patients received treatment for CDB. Among them, 519 patients (356 men and 163 women; mean age, 73.1 ± 12.5 years) who could be followed up for at least 6 months after discharge were recruited. The clinical characteristics of the patients are summarized in Table 1. The elderly group comprised 274 patients, whereas the non-elderly group comprised 245 patients with mean ages of 82.1 ± 5.3 and $63.0 \pm$

10.3 years, respectively. The non-elderly group had a significantly higher proportion of patients with performance status scores of 0 and 1 than the elderly group. The elderly group had significantly more patients with underlying comorbidities such as hypertension, CKD, cardiovascular disease, respiratory disease, and malignant disease than the non-elderly group. Furthermore, the elderly group had significantly more patients taking antithrombotic agents, particularly aspirin ($p < 0.001$). Moreover, the percentage of patients taking NSAIDs was 20.8% and 8.9% in the elderly and non-elderly group, respectively, indicating a significant difference between the groups ($p < 0.001$). Note that the elderly group had significantly more patients with bilateral diverticula than the non-elderly group ($p < 0.001$). Moreover, no significant difference in the proportion of patients with a shock index of >1 was observed between the groups; however, the Hb level on admission was significantly lower in the elderly group than in the non-elderly group (10.84 ± 1.88 vs. 11.90 ± 2.41 g/dL; $p < 0.001$). The mean volume of blood transfusion was significantly higher in the elderly group than in the non-elderly group (1.70 ± 3.69 vs. 1.01 ± 2.29 pacs; $p = 0.003$). In this study, all subjects underwent colonoscopy after hospitalization. The time from admission to colonoscopy was 17.3 ± 21.3 h in the elderly group and 15.8 ± 17.8 h in the non-elderly group, with no significant difference between the groups ($p = 0.465$). The PEG administration rate before colonoscopy in both groups exceeded 80%, with no significant difference observed ($p = 0.717$). The bleeding source was identified in 45.6% of the participants in the elderly group, which was not significantly different from 40.4% in the non-elderly group ($p = 0.231$). The mean length of

Table 1. Clinical Characteristics of Patients.

Characteristics		Elderly group (N = 274)	Non-elderly group (N = 245)	<i>p</i> value
Sex	Male	174 (63.5%)	182 (74.3%)	0.010
	Female	100 (36.5%)	63 (25.7%)	
Age	Average \pm SD	82.1 \pm 5.3	63.0 \pm 10.3	<0.001
Performance status	0	249 (90.8%)	239 (97.6%)	0.001
	1	12 (4.3%)	2 (0.8%)	0.012
	2	10 (3.6%)	3 (1.2%)	0.077
	3	4 (1.3%)	1 (0.4%)	0.489
Comorbidities	Hypertension	215 (78.4%)	128 (52.3%)	<0.001
	Diabetes mellitus	45 (16.4%)	47 (19.1%)	0.411
	Chronic kidney disease	129 (47.0%)	73 (29.7%)	<0.001
	Cardiovascular disease	79 (28.8%)	23 (9.4%)	<0.001
	Cerebrovascular disease	42 (15.3%)	35 (14.2%)	0.738
	Respiratory disease	21 (7.7%)	3 (1.2%)	<0.001
	Liver cirrhosis	2 (0.7%)	4 (1.6%)	0.336
	Malignant disease	31 (11.3%)	10 (4.0%)	0.002
Medication	Antithrombotic agents	142 (51.8%)	76 (31.0%)	<0.001
	Aspirin	95 (34.7%)	52 (21.2%)	<0.001
	Thienopyridine	24 (8.8%)	18 (7.3%)	0.556
	Warfarin	30 (10.9%)	18 (7.3%)	0.157
	DOACs	16 (5.8%)	10 (4.1%)	0.359
	DAPT	18 (6.6%)	14 (5.7%)	0.686
	NSAIDs	57 (20.8%)	22 (8.9%)	<0.001
	Diverticula	Bilateral	144 (52.5%)	22 (8.9%)
Shock	Shock index > 1	38 (13.8%)	33 (13.4%)	0.894
Hb on admission	g/dL (average \pm SD)	10.84 \pm 1.88	11.90 \pm 2.41	<0.001
Blood transfusion	Pacs (average \pm SD)	1.70 \pm 3.69	1.01 \pm 2.29	0.003
Time to colonoscopy	Average \pm SD (hour)	17.3 \pm 21.3	15.8 \pm 17.8	0.465
PEG administration		226 (82.4%)	205 (83.7%)	0.717
Bleeding source	Identification rate	125 (45.6%)	99 (40.4%)	0.231
Length of hospital stay	Days (average \pm SD)	11.8 \pm 10.1	10.2 \pm 5.7	0.028
Mortality		4 (1.4%)	1 (0.4%)	0.220

Hb, hemoglobin; PEG, polyethylene glycol; DOACs, direct oral anticoagulants; DAPT, dual anti-platelet therapy; NSAIDs, non-steroidal anti-inflammatory drugs

hospitalization was significantly longer in the elderly group than in the non-elderly group (11.8 \pm 10.1 vs. 10.2 \pm 5.7 days; $p = 0.028$). Moreover, no significant difference in the mortality rate was observed between the elderly and non-elderly groups (1.4% vs. 0.4%; $p = 0.220$), and not a single case of death directly caused by bleeding was noted in either group.

Table 2 shows the results of endoscopic treatment. In 44.0% of participants in the elderly group, the bleeding site was identified in the left colon. This proportion was significantly higher than that (20.2%) of the non-elderly group ($p < 0.001$). Endoscopic hemostasis was performed on all patients in whom SRH was identified. In terms of the endoscopic hemostasis method used, hemostasis using a hemoclip was frequently performed in both groups with no significant difference observed between the two groups ($p = 0.215$). Furthermore, regarding the clip method, the direct

method was performed in 106 patients (94.6%) in the elderly group and in 88 patients (93.6%) in the non-elderly group ($p = 0.773$). In the elderly group, there were significantly more cases of active bleeding; however, endoscopic treatment was unsuccessful in 15 patients (12%) in the elderly group and in 8 patients (8.1%) in the non-elderly group, with no statistically significant difference ($p = 0.382$). EBL treatment was unsuccessful only in one patient in the elderly group. In case that endoscopic treatment was unsuccessful, IVR and surgery were selected as additional treatment in both groups.

Outcome

The primary and secondary outcomes are presented in Table 3. No statistically significant difference in the early rebleeding rate was observed between the elderly and non-elderly groups (30.6% vs. 33.1%; $p = 0.557$). In addition,

Table 2. Results of Endoscopic Treatment for Patients with SRH.

Characteristics		Elderly group (N = 125)	Non-elderly group (N = 99)	p value
Bleeding site	Right colon	70 (56.0%)	79 (79.8%)	<0.001
	Left colon	55 (44.0%)	20 (20.2%)	
Type of SRH	Active bleeding	83 (66.4%)	49 (50.0%)	0.010
	Visible vessel	15 (12.0%)	14 (14.4%)	0.635
	Adherent clot	27 (21.6%)	36 (35.6%)	0.014
Endoscopic hemostasis method	Hemoclip	112 (89.6%)	94 (95.0%)	0.215
	Band ligation	13 (10.4%)	5 (5.1%)	0.215
Endoscopic treatment	Success	110 (88.0%)	91 (91.9%)	0.382
	Fail	15 (12.0%)	8 (8.1%)	
Additional treatment	IVR	13 (10.4%)	6 (6.0%)	0.335
	Surgery	2 (1.6%)	2 (2.0%)	

SRH, stigmata of recent hemorrhage; IVR, interventional radiology

Table 3. Early and Late Rebleeding Rate.

		Elderly group (N = 274)	Non-elderly group (N = 245)	p value
Early rebleeding		84 (30.6%)	81 (33.1%)	0.557
Period until rebleeding	Median (range: days)	2 (1–14)	1 (0–23)	0.177
Rebleeding times	Median (range)	1 (1–6)	1 (1–8)	0.313
Late rebleeding		116 (42.3%)	75 (30.6%)	0.005
Period until rebleeding	Median (range: months)	12 (1–146)	15 (1–132)	0.850
Rebleeding times	Median (range)	1 (1–10)	1 (1–9)	0.301
Follow-up period	Median (range: months)	34 (6–207)	42.5 (6–185)	0.134

both groups had a median number of rebleeding episode of one ($p = 0.313$). The late rebleeding rate was 42.3% in the elderly group and 30.6% in the non-elderly group, indicating a statistically significant difference ($p = 0.005$). No statistically significant difference in the time to rebleeding was observed between the elderly and non-elderly groups (12 months vs. 15 months; $p = 0.850$). No statistically significant difference in the follow-up period was observed between the elderly and non-elderly groups (34 months vs. 42.5 months; $p = 0.134$).

The results of univariate analysis for the risk factors of late rebleeding in all patients, as secondary outcomes, are presented in Table 4. A total of 191 patients experienced late rebleeding, whereas 328 did not. In univariate analysis, statistically significant differences were observed in terms of age ≥ 75 years ($p = 0.005$), CKD ($p < 0.001$), cardiovascular disease ($p = 0.030$), use of NSAIDs ($p < 0.001$), and the presence of bilateral diverticula ($p < 0.001$). The results of multivariate analysis are presented in Table 5. Multivariate analysis revealed that the risk factors for late rebleeding in all patients were CKD (OR, 2.221; 95% CI, 1.493-3.270; $p < 0.001$), use of NSAIDs (OR, 2.273; 95% CI, 1.365-3.783; $p < 0.002$), and bilateral diverticula (OR, 1.985; 95% CI, 1.361-2.895; $p < 0.001$). A statistically significant difference

was not observed in elderly aged ≥ 75 years (OR, 1.225; 95% CI, 0.845-1.862; $p = 0.260$). The results of univariate analysis for the risk factors of late rebleeding in elderly individuals are presented in Table 6. In the elderly group, 116 patients experienced late rebleeding, whereas 158 did not. Univariate analysis revealed statistically significant differences in CKD ($p < 0.001$), cardiovascular disease ($p = 0.041$), use of NSAIDs ($p < 0.001$), and the presence of bilateral diverticula ($p = 0.049$). The results of the multivariate analysis are presented in Table 7. Multivariate analysis showed that the risk factors for late rebleeding in the elderly group were CKD (OR, 2.889; 95% CI, 1.687-4.949; $p < 0.001$), use of NSAIDs (OR, 3.550; 95% CI, 1.865-6.757; $p < 0.001$), and bilateral diverticula (OR, 1.836; 95% CI, 1.081-3.120; $p = 0.025$). In the follow-up examinations over the course of 3 years, the recurrence-free survival rates at the 1st, 2nd, and 3rd years were 77.1%, 67.2%, and 63.6%, respectively, in the elderly group, and 85.8%, 78.4%, and 75.6%, respectively, in the non-elderly group (Figure 2). The elderly group showed higher frequencies of late rebleeding than the non-elderly group (log-rank test: $p < 0.001$).

Table 4. Risk Factors for Late Rebleeding in All Patients Using Univariate Analysis.

Variables	With recurrent bleeding (N = 191)	Without recurrent bleeding (N = 328)	<i>p</i> value
Sex Male	134 (70.1%)	222 (67.7%)	0.558
Female	57 (29.9%)	106 (32.3%)	
Age ≥75	116 (60.7%)	158 (48.1%)	0.005
<75	75 (39.3%)	170 (51.9%)	
Comorbidities			
Hypertension	128 (67.0%)	215 (65.5%)	0.733
Diabetes mellitus	28 (14.7%)	64 (19.5%)	0.162
Chronic kidney disease	99 (51.8%)	103 (31.4%)	<0.001
Cardiovascular disease	47 (24.6%)	55 (16.7%)	0.030
Cerebrovascular disease	27 (14.1%)	45 (13.7%)	0.894
Respiratory disease	12 (6.3%)	12 (3.6%)	0.169
Medication			
Antithrombotic agents	79 (41.3%)	139 (42.3%)	0.820
Aspirin	57 (29.8%)	90 (27.4%)	0.582
Thienopyridine	17 (8.9%)	25 (7.6%)	0.606
Warfarin	15 (7.8%)	33 (10.0%)	0.402
DOACs	11 (5.8%)	15 (4.5%)	0.550
DAPT	13 (6.8%)	19 (5.8%)	0.643
NSAIDs	44 (23.0%)	35 (10.6%)	<0.001
Bilateral diverticula			
Present	112 (58.6%)	139 (42.3%)	<0.001
Absent	79 (41.4%)	189 (57.7%)	
Bleeding source			
Identified	84 (44.0%)	140 (42.6%)	0.089
Not identified	107 (56.0%)	188 (57.4%)	
Type of SRH			
Active bleeding	55 (28.8%)	77 (23.5%)	0.179
Visible vessel	8 (4.2%)	21 (6.4%)	0.327
Adherent clot	21 (10.1%)	42 (12.8%)	0.542
CT extravasation			
Present	55 (28.8%)	73 (22.2%)	0.095
Absent	136 (71.2%)	255 (78.8%)	
Endoscopic hemostasis method			
Hemoclip	76 (40.0%)	130 (40.0%)	0.971
Band ligation	8 (4.1%)	10 (3.0%)	0.422
Endoscopic hemostasis			
Success	78 (40.8%)	123 (37.5%)	0.451
Fail	9 (4.7%)	14 (4.2%)	0.667
Shock index >1			
Present	21 (11.0%)	50 (15.2%)	0.174
Absent	170 (89.0%)	278 (84.8%)	
Blood transfusion >2pacs	58 (30.3%)	79 (24.1%)	0.117

DOACs, direct oral anticoagulants; DAPT, dual anti-platelet therapy; NSAIDs, non-steroidal anti-inflammatory drugs; SRH, stigmata of recent hemorrhage

Discussion

In Japan, the number of CDB cases has been increasing due to aging of the population[2,3,8]. However, the characteristics of CDB in elderly individuals have not been completely elucidated. First, in this study, compared with the non-elderly group, there were significantly more patients

with poor performance status, patients using antithrombotic agents or NSAIDs, and prevalence of an underlying condition in the elderly group. Furthermore, compared with the non-elderly group, there was significantly more bleeding from the left colon, active bleeding, and the mean blood transfusion amount after hospitalization in the elderly group. While there were various differences in patients' back-

Table 5. Independent Risk Factors for Late Rebleeding in All Patients Using Multivariate Analysis.

Variables	Odds ratio	95% confidence interval	p value
Age \geq 75	1.225	0.845–1.862	0.260
Cardiovascular disease	1.204	0.741–1.958	0.453
Chronic kidney disease	2.221	1.493–3.270	<0.001
NSAIDs	2.273	1.365–3.783	0.002
Bilateral diverticula	1.985	1.361–2.895	<0.001

NSAIDs, non-steroidal anti-inflammatory drugs

grounds, no statistically significant difference was observed in the endoscopic hemostasis method, endoscopic treatment failure rate, early rebleeding rate, and mortality rate within 30 days of hospitalization in both groups. Kaise et al. reported that performing early endoscopic intervention and multimodal treatment, even in elderly individuals, can lower the risk of mortality[3]. In this study, in the elderly group, similar to the non-elderly group, we performed early colonoscopy and obtained comparable hemostasis results, which could have attributed to the absence of a difference in mortality.

Second, in this study, the late rebleeding rate was significantly higher in the elderly group (42.3%) than in the non-elderly group (30.6%) in univariate analysis. However, there was no statistically significant difference on multivariate analysis for age \geq 75 years. In both the elderly group and all patients, the independent risk factors for late rebleeding were bilateral diverticula, use of NSAIDs, and CKD. There were significantly more patients with these independent risk factors for late rebleeding in the elderly group than in the non-elderly group. This result may be attributed to the fact that the late rebleeding rate was significantly more common in the elderly group than in the non-elderly group on univariate analysis. With regard to age, reports have indicated that age is a risk factor for rebleeding. In a retrospective cohort study involving 14,925 individuals in the USA, the late rebleeding rate in individuals with CDB gradually increased with age[9]. Furthermore, it has been reported that LGIB increases the risk of death in elderly patients[23-26]; therefore, it is important to reduce the risk of rebleeding particularly in elderly patients. Regarding other risks of CBD, bilateral diverticula has been reported to be a risk factor for the onset of CDB[27,28]. A cohort study of 1,514 patients by Niikura et al. reported that during the follow-up period of 46 months, 35 patients developed CDB and that the elderly aged \geq 70 years [hazard ratio (HR) 3.7] and bilateral diverticula (HR 2.4) were significant risks for the onset of CBD[27]. Furthermore, a retrospective age- and sex-matched, case-control study by Taki et al. reported that bilateral diverticulosis was a significant risk factor for the onset of CDB (OR, 3.0)[28]. In Asia, although right-side diver-

ticula are common, with age, diverticula increase in number and extend to both sides[3]. How many diverticula could increase the risk of late rebleeding is unknown. However, bilateral diverticula suggested that it is a risk factor both of onset and late rebleeding of CBD. The use of NSAIDs is also a risk factor for rebleeding in patients with CDB[10-13]. In a study by Nagata et al., the rebleeding rate 1 year after discharge was 9.4% in the group with the discontinuation of NSAIDs and 77% in the group that continued the use of NSAIDs, and rebleeding was inhibited by the discontinuation of NSAIDs[10]. Tsuruoka et al. reported that the use of NSAIDs is a risk factor for rebleeding in individuals with CDB (OR, 5.4)[13]. In the American guideline, it is recommended to discontinue drugs that increase the risk of CDB[29]. Thus, the discontinuation of NSAIDs should be considered to prevent rebleeding. However, it is possible that the discontinuation of NSAIDs could result in the inability to control pain, thus reducing patients' quality of life particularly in elderly patients. Therefore, we believe that the discontinuation of NSAIDs should be carefully considered along with their risks and benefits. Furthermore, in this study, CKD was shown to be a risk factor for late rebleeding. Wada et al. reported that CKD was a risk factor for rebleeding in CBD (OR 2.3)[30]. Studies have also reported that diverticulosis develops at a young age in some patients with renal failure[31,32]. In patients with renal failure, the presence of uremic platelet dysfunction is considered as a cause of gastrointestinal bleeding[33]. As there could be a risk of rebleeding with CBD in CKD patients, careful follow-up is needed. Another risk factor for late rebleeding is a history of CBD[30], and the use of aspirin and other antithrombotic agents has also been reported[26,27,34]. However, in this study, antithrombotic agents, including aspirin, did not increase the risk of rebleeding. This may be because antithrombotic agents were discontinued or changed after discharge to reduce the risks. However, as risk reduction was not examined in detail, the specific reason is not clear on the basis of the results of the present study.

This study has several limitations. First, this was a retrospective single-center study. Second, this study was conducted over a long period of 15 years and included many physicians within the study period. Therefore, decisions on the timing of colonoscopy, hemostasis methods, and inpatient management were at the discretion of the attending physician and differed depending on the period. Third, among the endoscopic hemostasis methods, the EBL method was performed in only 18 patients. The EBL method has been reported to reduce the late rebleeding rate more than the hemoclip method[7]. Therefore, the rebleeding rates might have been reduced if the EBL method had been selected as the main hemostasis method.

In conclusion, no significant differences in the results of endoscopic treatment and early rebleeding rates were ob-

Table 6. Risk Factors for Late Rebleeding in the Elderly Group Using Univariate Analysis.

Variables	With recurrent bleeding (N = 116)	Without recurrent bleeding (N = 158)	<i>p</i> value
Sex Male	80 (69.0%)	94 (59.4%)	0.107
Female	36 (31.0%)	65 (40.6%)	
Comorbidities			
Hypertension	92 (79.3%)	123 (77.8%)	0.771
Diabetes mellitus	19 (16.4%)	26 (16.4%)	0.986
Chronic kidney disease	72 (62.0%)	57 (36.1%)	<0.001
Cardiovascular disease	41 (35.3%)	38 (24.1%)	0.041
Cerebrovascular disease	17 (14.6%)	25 (15.7%)	0.790
Respiratory disease	12 (10.3%)	9 (5.7%)	0.152
Medication			
Antithrombotic agents	59 (50.8%)	83 (52.5%)	0.307
Aspirin	44 (37.9%)	51 (32.2%)	0.331
Thienopyridine	13 (11.2%)	11 (7.0%)	0.219
Warfarin	9 (7.8%)	21 (13.3%)	0.147
DOACs	5 (4.3%)	11 (7.0%)	0.355
DAPT	9 (7.8%)	9 (6.7%)	0.495
NSAIDs	38 (32.8%)	19 (12.0%)	<0.001
Bilateral diverticula			
Present	69 (59.4%)	75 (47.5%)	0.049
Absent	47 (40.6%)	83 (52.5%)	
Bleeding source			
Identified	49 (42.2%)	76 (48.1%)	0.335
Not identified	67 (57.8%)	82 (51.9%)	
Type of SRH			
Active bleeding	32 (27.6%)	51 (32.2%)	0.403
Visible vessel	5 (4.3%)	10 (6.3%)	0.594
Adherent clot	12 (10.3%)	15 (9.5%)	0.839
CT extravasation			
Present	35 (30.2%)	45 (28.4%)	0.760
Absent	81 (69.8%)	113 (71.6%)	
Endoscopic hemostasis method			
Hemoclip	45 (38.8%)	67 (42.4%)	0.548
Band ligation	4 (3.4%)	9 (5.6%)	0.387
Endoscopic hemostasis			
Success	46 (40.0%)	64 (40.5%)	0.887
Fail	4 (3.4%)	11 (7.0%)	0.206
Shock index >1			
Present	15 (12.9%)	23 (14.6%)	0.700
Absent	101 (87.1%)	135 (85.4%)	
Blood transfusion >2 pacs	37 (31.9%)	60 (37.9%)	0.298

DOACs, direct oral anticoagulants; DAPT, dual anti-platelet therapy; NSAIDs, non-steroidal anti-inflammatory drugs; SRH, stigmata of recent hemorrhage

Table 7. Independent Risk Factors for Late Rebleeding in the Elderly Group Using Multivariate Analysis.

Variables	Odds ratio	95% confidence interval	<i>p</i> value
Cardiovascular disease	1.480	0.827–2.647	0.187
Chronic kidney disease	2.889	1.687–4.949	<0.001
NSAIDs	3.550	1.865–6.757	<0.001
Bilateral diverticula	1.836	1.081–3.120	0.025

NSAIDs, non-steroidal anti-inflammatory drugs

served between the elderly and non-elderly groups. However, the elderly group had a significantly higher late rebleeding rate than the non-elderly group. The risk factors for late rebleeding in both all patients and elderly individuals include the presence of bilateral diverticula, use of NSAIDs, and history of CKD. Elderly patients with CDB with these risk factors require a particularly careful follow-up, even after discharge. In addition, it is important to discontinue drugs that increase the risk of CDB to prevent

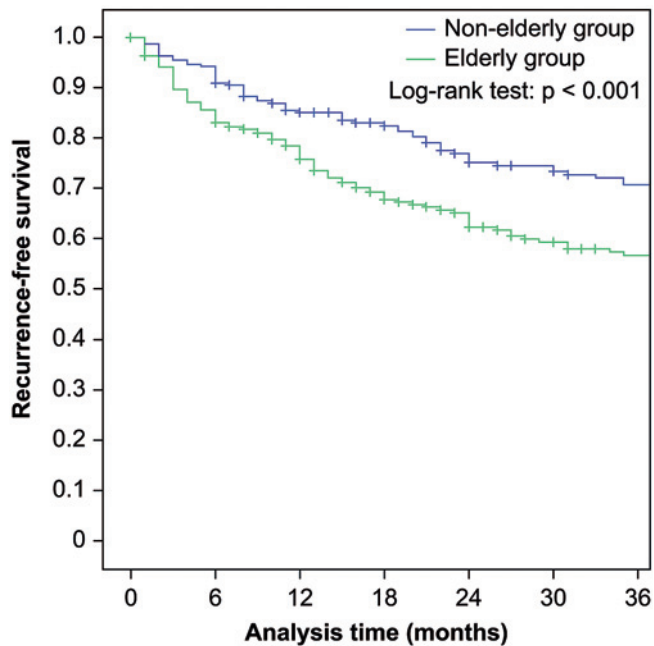


Figure 2. Recurrence-free survival rate between elderly and non-elderly patients.

rebleeding.

Acknowledgements

The authors thank Crimson Interactive Pvt. Ltd. (Ulatus) (www.ulatus.jp) for their assistance in manuscript translation and editing.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. All other authors have contributed to data collection and interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Approval by Institutional Review Board (IRB)

The local ethics committee of St. Marianna University School of Medicine approved the study protocol (approval number: 4775).

Informed Consent

Informed consent was obtained in the form of opt-out on the website.

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