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Endoscopic direct clipping versus indirect clipping for colonic diverticular bleeding: A large multicenter cohort study

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Abstract

Background: Direct and indirect clipping treatments are used worldwide to treat colonic diverticular bleeding (CDB), but their effectiveness has not been examined in multicenter studies with more than 100 cases.

Objective: We sought to determine the short- and long-term effectiveness of direct versus indirect clipping for CDB in a nationwide cohort.

Methods: We studied 1041 patients with CDB who underwent direct clipping ($n = 360$) or indirect clipping ($n = 681$) at 49 hospitals across Japan (CODE BLUE-J Study).

Results: Multivariate analysis adjusted for age, sex, and important confounding factors revealed that, compared with indirect clipping, direct clipping was independently associated with reduced risk of early rebleeding (<30 days; adjusted odds ratio [AOR] 0.592, $p = 0.002$), late rebleeding (<1 year; AOR 0.707, $p = 0.018$), and blood transfusion requirement (AOR 0.741, $p = 0.047$). No significant difference in initial hemostasis rates was observed between the two groups. Propensity-score matching to balance baseline characteristics also showed significant reductions in the early and late rebleeding rates with direct clipping. In subgroup analysis, direct clipping was associated with significantly lower rates of early and late rebleeding and blood transfusion need in cases of stigmata of recent hemorrhage with non-active bleeding

on colonoscopy, right-sided diverticula, and early colonoscopy, but not with active bleeding on colonoscopy, left-sided diverticula, or elective colonoscopy.

Conclusions: Our large nationwide study highlights the use of direct clipping for CDB treatment whenever possible. Differences in bleeding pattern and colonic location can also be considered when deciding which clipping options to use.

KEYWORDS

acute lower gastrointestinal bleeding, colonic diverticular hemorrhage, endoscopic clipping, endoscopic hemostasis, stigmata of recent hemorrhage

INTRODUCTION

Endoscopic therapy for definitive colonic diverticular bleeding (CDB) diagnosed based on stigmata of recent hemorrhage (SRH) potentially prevents recurrence.[1,2] Among the various endoscopic therapies for CDB, the clipping technique is commonly used worldwide because of its simplicity, low cost, and theoretical advantage of causing less damage to adjacent tissues.[3–9] Previous studies have reported the effectiveness of clipping for CDB, but early rebleeding rates differed considerably among them (0%–50%),[4,10–13] likely due to small sample sizes of <100 cases per study, institutional differences such as in physicians' endoscopic skills and emergency settings, and treatment differences such as in clipping methods and combinations with other endoscopic treatments such as hypertonic saline epinephrine solution (HSE). Large-scale multicenter studies are therefore needed to clarify the effectiveness of endoscopic clipping for CDB.

Clipping methods for CDB are classified as direct or indirect,[4,14,15] where direct clipping involves capturing the vessel directly and indirect clipping involves closing the diverticular orifice in a zipper-like manner.[7,8] Hemostasis rates and subsequent rebleeding rates can differ between the two clipping methods, resulting in different transfusion needs, surgery or interventional radiology (IVR) rates, and length of stay. Therefore, it is highly important to elucidate the difference in efficacy between these two treatments. In addition, indirect clipping may cost several times as much as direct clipping.

Three previous studies have sought to elucidate this difference in efficacy but the results were inconsistent[14–16]; two revealed no significant differences in the early rebleeding rate between the two methods,[14,16] whereas one showed a significantly lower rate with direct clipping.[15] These studies were conducted at single institutions and involved ≤87 cases each, so applying the results to clinical practice remains challenging. Data on the long-term effectiveness of the two clipping methods for CDB are also scarce.[14] Moreover, active bleeding or the location of SRH on colonoscopy may affect rebleeding outcomes,[1] but whether these differences in endoscopic findings affect the relationship between clipping methods and clinical outcome is still unclear. Clarifying this issue might expand the options for using different clipping methods, leading to improvement in clinical outcomes.

Against this background, in this study we evaluated the short- and long-term effectiveness of direct clipping versus indirect clipping for CDB, using large-scale data on acute hematochezia in Japan.

Key summary

Established knowledge on this subject

- Among the various endoscopic therapies for colonic diverticular bleeding (CDB), the clipping technique is commonly used worldwide.
- Clipping methods for CDB are classified as direct or indirect, where direct clipping involves capturing the vessel directly and indirect clipping involves closing the diverticular orifice in a zipper-like manner.
- There has been no multicenter study with a large sample size that has evaluated the effectiveness of the two clipping methods for CDB.

What are the significant and/or new findings of this study?

- Our large multicenter cohort study revealed that, compared with indirect clipping, direct clipping was associated with reduced risk of early rebleeding (within 30 days) after endoscopic treatment for CDB.
- Direct clipping also showed significantly reduced rates of late rebleeding (within 1 year) and blood transfusion requirement.
- In the stigmata of recent hemorrhage (SRH) with non-active bleeding group and right-sided CDB group, compared with indirect clipping, direct clipping was associated with lower rates of early and late rebleeding and blood transfusion need, but no associations were seen in the active bleeding group or left-sided CDB group.

METHODS

Patients and study design

This retrospective multicenter cohort study, the CODE BLUE-J Study (COlonic DivErticular Bleeding Leaders Update Evidence from multicenter Japanese Study), was conducted at 49 hospitals across Japan.[17,18] [Correction added on 20 January 2022, after first online publication: In the preceding sentence, the term 'CDB' has been replaced with 'COlonic DivErticular Bleeding']. The ethics committees

and institutional review boards of all 49 participating hospitals approved conducting this study with the opt-out method (Table S1). A total of 10,342 adult patients were emergently hospitalized for acute hematochezia between January 2010 and December 2019. Among 2020 diagnosed with definitive CDB based on the presence of SRH, we analyzed data from 1041 patients who were treated with either direct clipping (n = 360) or indirect clipping (n = 681) as first-line treatment for definitive CDB (Figure 1).

Variables

We assessed 42 items of clinical data, including baseline characteristics such as age, sex, vital signs on admission, lifestyle, presenting symptoms, laboratory data, comorbidities, and medication use within 30 days of admission, and reviewed in-hospital examination findings obtained from the electronic medical records and endoscopic databases, as previously reported.[17,18] Comorbidity was assessed using the modified Charlson Comorbidity Index (CCI), composed of the conventional CCI items[19] plus those for hypertension and hyperlipidemia. The CCI is an index for classifying prognostic comorbidity and has been extensively validated for gastrointestinal bleeding.[20]

Detailed endoscopic factors were collected, such as the timing of colonoscopy, type of bowel preparation, use of an endoscopic distal attachment cap, use of a water-jet device, type of SRH, location of SRH, and method of endoscopic clipping. Stigmata of recent hemorrhage was defined as active bleeding or SRH with non-active bleeding (a densely adherent clot despite vigorous irrigation and/or a non-bleeding visible vessel) on colonoscopy.[2,14] SRH location was classified as left-side colon (descending and sigmoid colon, and rectum) or right-side colon (other locations).

Clipping methods were classified as direct clipping or indirect clipping.[7,14,15] In the direct clipping method, endoclips were placed directly on the vessel[14,15] (Figure 2a,b). In the indirect clipping method, the diverticulum was closed in a zipper-like manner[14,15] (Figure 2c,d).

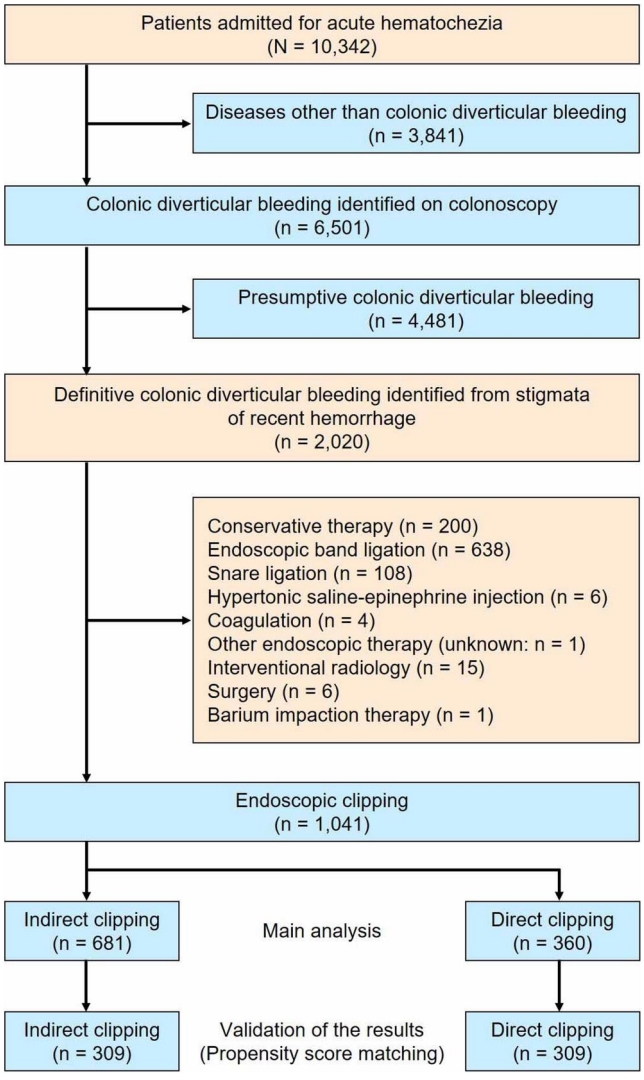

FIGURE 1 Flowchart of patients in this study

Clinical outcomes

The outcome of interest was rebleeding after initial endoscopic treatment, occurring during hospitalization or after discharge. Early rebleeding was defined as rebleeding within 30 days of the initial endoscopic treatment for CDB and late rebleeding as rebleeding within 1 year.[14,21] The secondary outcomes were rate of initial hemostasis, mortality, need for IVR, need for surgery, blood transfusion requirement, and length of stay after initial endoscopic treatment.

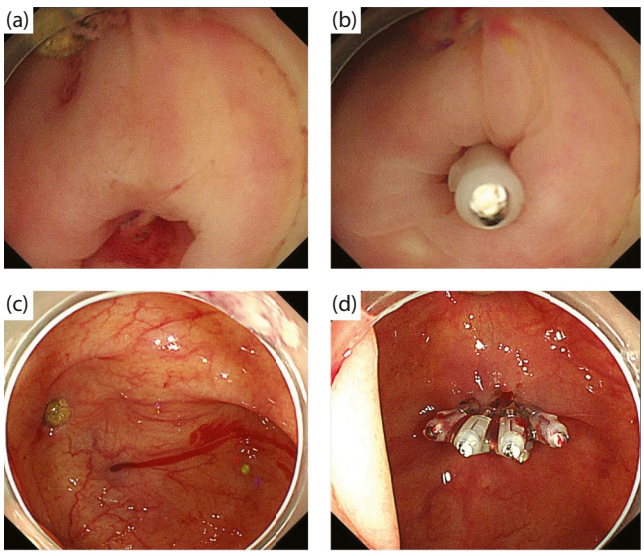

FIGURE 2 Endoscopic findings. (a) Colonic diverticulum with a visible non-bleeding vessel. (b) After direct clip placement. (c) Active bleeding from the colonic diverticulum. (d) The diverticulum closed in a zipper-like manner via indirect clip placement

Statistical analysis

We compared the baseline characteristics of the direct and indirect clipping groups. Categorical data were compared using the χ^2 test or Fisher's exact test, and continuous data were compared using the Mann-Whitney *U* test. The association between clipping method and clinical outcome was analyzed using univariate and multivariate logistic regression models. In multivariate analysis, we adjusted for eight factors that were potentially clinically important variables—age ≥70 years, sex, heart rate ≥100 bpm, modified CCI ≥2, extravasation on computed tomography (CT), active bleeding, use of endoscopic distal attachment cap, and use of water-jet scope—most of which were significantly different ($p < 0.05$) in univariate analysis.

In subgroup analysis, we evaluated the relationship between clipping method and clinical outcome according to SRH type (active bleeding/SRH with non-active bleeding), SRH location (right/left), and timing of colonoscopy (early [within 24 h of initial visit to the hospital]/elective [over 24 h]).

To validate associations found between clipping method and clinical outcome, we used propensity score matching (PSM) analysis to reduce the effect of selection bias and confounders.[22] To estimate the propensity score, we selected a logistic regression model with the recipient of direct clipping as a function of baseline characteristics and endoscopic factors. The model included age ≥70 years, sex, and factors found to have at least borderline significance ($p < 0.10$) on univariate analysis, namely, heart rate ≥100 bpm, hemoglobin <12 g/dl, platelets $<15 \times 10^4/\mu L$, modified CCI ≥2, use of anticoagulant, extravasation on CT, active bleeding, use of endoscopic distal attachment cap, and use of water-jet scope. We performed one-to-one PSM between the direct and indirect clipping groups using the nearest neighbor method within a caliper width of 0.2 of the standard deviation of the logit of the propensity score. Before matching, the area under the receiver operating characteristic curve for propensity scores for direct clipping was 0.684 (95% confidence interval, 0.648–0.719). We selected multivariate logistic regression analysis as the main analysis instead of PSM for two reasons: PSM greatly reduced the number of subjects and important outcomes (e.g., blood transfusion requirement, mortality, need for IVR, and need for surgery), especially in the indirect clipping group; and multivariate logistic regression analysis is more precise and less biased than PSM when there are at least eight events per confounder.[23] Statistical significance was set at $p < 0.05$. All statistical analysis was performed using STATA ver16 (StataCorp, college Station, TX).

RESULTS

Patient characteristics and clinical outcomes

Characteristics of the entire cohort ($n = 1041$) are shown in Table 1. Early and late rebleeding rates after colonoscopy were 24.6% (256/1041) and 37.4% (389/1041) overall, respectively. Significant differences were found between the direct and indirect clipping groups in relation to sex, heart rate ≥100 bpm, modified CCI ≥2, extravasation on CT, active bleeding, use of endoscopic distal attachment cap, and use of water-jet scope, and we therefore included these as confounders in the multivariate model. Multivariate analysis adjusting for these confounders revealed that, compared with indirect clipping, direct clipping was independently associated with reduced risk of early rebleeding, late rebleeding, and blood transfusion requirement (all $p < 0.05$; Table 2). No significant differences were found between the two groups in the rate of initial hemostasis, IVR need during hospitalization, or prolonged hospitalization after endoscopic treatment (≥7 days).

For validation of these results, PSM analysis was performed and identified 618 patients comprising 309 pairs from the direct and indirect clipping groups whose baseline characteristics were closely balanced (Table S2). The association of reduced risk of early and late rebleeding with direct clipping remained unchanged (Table S3). Other outcomes except blood transfusion requirement were also unchanged.

Combined clipping therapy with HSE

From the entire cohort ($n = 1041$), 20 patients had combination therapy with HSE injection (direct clipping: 9; indirect clipping: 11); the remaining 1021 patients were treated with clipping alone (direct clipping: 351; indirect clipping: 670). No significant difference was found in the early rebleeding rate between clipping with HSE and clipping alone (25% [5/20] vs. 24.6% [251/1021], $p = 1.000$). For direct clipping, the early rebleeding rate was not significantly different between clipping with HSE and clipping alone (11.1% [1/9] vs. 18.8% [66/351], $p = 1.000$), nor was it significant for indirect clipping (36.4% [4/11] vs. 27.6% [185/670], $p = 0.508$).

Differences in clinical outcome based on type and location of SRH and timing of colonoscopy

The baseline characteristics of patients treated with direct or indirect clipping are shown according to SRH type, SRH location, and timing of colonoscopy in Table S4, with their clinical outcomes shown in Table 3.

In patients with active bleeding, no associations were seen with direct or indirect clipping. In contrast, in patients without active bleeding, multivariate analysis revealed that direct clipping was associated with significantly lower rates of early and late rebleeding (both $p < 0.05$) and marginally significant lower rates of blood transfusion requirement and IVR need during hospitalization (both $p < 0.1$). No significant difference was found between the two clipping groups in the rates of initial hemostasis or prolonged hospitalization.

In patients with right-sided CDB, direct clipping, compared with indirect clipping, was independently associated with lower rates of early rebleeding, late rebleeding, and blood transfusion requirement

TABLE 1 Baseline characteristics of patients who underwent direct or indirect clipping for definitive colonic diverticular bleeding

	All patients (N = 1041)		
	Direct clipping (n = 360)	Indirect clipping (n = 681)	p value
Age ≥70 years	228 (63.3)	434 (63.7)	0.899
Sex (male)	274 (76.1)	461 (67.7)	**0.005**
Body mass index ≥25	94 (28.5)	193 (30.2)	0.579
Current drinker	165 (50.2)	286 (50.1)	0.985
Current smoker	47 (14.1)	104 (17.8)	0.150
Performance status ≥2	25 (6.9)	67 (9.8)	0.118
Systolic blood pressure ≤100 mmHg	49 (13.8)	85 (12.8)	0.659
Heart rate ≥100 bpm	98 (27.6)	122 (18.6)	**0.001**
Loss of consciousness	21 (5.8)	38 (5.6)	0.897
Laboratory data			
Hemoglobin <12 g/dl	196 (54.4)	408 (59.9)	0.089
White blood cell >10,000/μL	54 (15.0)	89 (13.1)	0.389
Platelets <15 × 10^4/μL	43 (11.9)	109 (16.0)	0.078
Albumin <3.0 g/dl	25 (7.1)	54 (8.4)	0.463
Blood urea nitrogen >25 mg/dl	82 (22.8)	160 (23.7)	0.755
History of colorectal surgery	21 (5.8)	36 (5.3)	0.712
History of colonic diverticular bleeding	145 (40.4)	240 (35.2)	0.102
Modified Charlson comorbidity index ≥2	187 (51.9)	406 (59.6)	**0.017**
Medication			
NSAID	40 (11.1)	67 (9.8)	0.520
Coxib	4 (1.1)	18 (2.6)	0.117
Antiplatelet[a]	115 (31.9)	247 (36.3)	0.163
Anticoagulant[b]	42 (11.7)	110 (16.2)	0.051
Acetaminophen	5 (1.4)	19 (2.8)	0.194
Corticosteroid	22 (6.1)	44 (6.5)	0.826
Extravasation on CT	107 (29.7)	146 (21.4)	**0.003**
Endoscopic factors			
Bowel preparation, use of PEG solution and/or glycerin enema	306 (85.0)	573 (84.1)	0.716
Use of endoscopic distal attachment cap	341 (94.7)	582 (85.5)	**<0.001**
Use of water-jet scope	351 (97.5)	575 (84.4)	**<0.001**
Stigmata of recent hemorrhage			
Active bleeding	195 (54.2)	428 (62.9)	**0.007**
Location, left-side colon	101 (28.1)	210 (30.8)	0.351

Note: Data are presented as n (%). Bold values indicate $p < 0.05$.

Abbreviations: CT, computed tomography; NSAID, nonsteroidal anti-inflammatory drug; PEG, polyethylene glycol.

[a]Antiplatelet is defined as low dose aspirin, thienopyridine, cilostazol, or other antiplatelet drugs.

[b]Anticoagulant is defined as warfarin or direct oral anticoagulants.

but not with rates of initial hemostasis, IVR need during hospitalization, or prolonged hospitalization. No associations were seen with direct or indirect clipping in patients with left-sided CDB.

In relation to the timing of colonoscopy, the early rebleeding rate was not significantly different between early colonoscopy and elective colonoscopy (25.6% [211/825] vs. 20.8% [45/216], p = 0.150).

TABLE 2 Effects of direct clipping on clinical outcome

	Direct clipping (n = 360)	Indirect clipping (n = 681)	Crude OR (95% CI)	p value	AOR (95% CI)	p value
Initial hemostasis	348 (96.7)	646 (94.9)	1.571 (0.805–3.066)	0.182	1.436 (0.705–2.927)	0.319
Early rebleeding[a]	67 (18.6)	189 (27.8)	0.595 (0.435–0.815)	**0.001**	0.592 (0.424–0.827)	**0.002**
Late rebleeding[b]	117 (32.5)	272 (39.9)	0.724 (0.553–0.947)	**0.018**	0.707 (0.531–0.942)	**0.018**
Blood transfusion requirement during hospitalization	104 (28.9)	247 (36.3)	0.714 (0.541–0.941)	**0.017**	0.741 (0.552–0.996)	**0.047**
IVR need during hospitalization	10 (2.8)	40 (5.9)	0.458 (0.226–0.927)	**0.026**	0.536 (0.254–1.131)	0.102
Prolonged hospitalization after endoscopic treatment (≥7 days)	225 (62.5)	442 (64.9)	0.901 (0.691–1.175)	0.442	1.009 (0.758–1.343)	0.952

Note: Values are the number and (%). Bold values indicate $p < 0.05$. Each of the AORs is obtained by multivariate logistic regression analysis. Adjustment for potential confounders included the eight factors of age ≥70 years, sex, heart rate ≥100 bpm, modified Charlson Comorbidity Index ≥2, extravasation on CT, active bleeding, use of distal attachment, and use of water-jet scope, most of which were shown to be significant in univariate analysis ($p < 0.05$).

Abbreviations: AOR, adjusted odd ratio; CI, confidence interval; CT, computed tomography; IVR, interventional radiology; OR, odds ratio.

[a]Early rebleeding is defined as rebleeding within 30 days of initial hemostasis.

[b]Late rebleeding is defined as rebleeding within 1 year of initial hemostasis.

In patients who underwent early colonoscopy, multivariate analysis revealed that direct clipping, compared with indirect clipping, was independently associated with lower rates of early rebleeding, late rebleeding, and blood transfusion requirement. No associations were found with direct or indirect clipping in patients who underwent elective colonoscopy.

DISCUSSION

To our knowledge, this is the largest study to compare outcomes between direct and indirect clipping for CDB, and the following three important points were found. First, direct clipping relative to indirect clipping reduced early and late rebleeding and blood transfusion requirement, which was validated in PSM analysis. Second, direct clipping relative to indirect clipping reduced early and late rebleeding and blood transfusion requirement in patients without active bleeding and in those with right-sided CDB on colonoscopy, but no associations were seen in those with active bleeding or left-sided CDB. Third, both direct clipping and indirect clipping had a high rate of initial hemostasis, and so both are considered generally easy to perform. Based on our findings, we recommend direct clipping for SRH with non-active bleeding or right-sided CDB, but either direct or indirect clipping is acceptable for active bleeding or left-sided CDB.

The three earlier studies examining rebleeding rates for direct and indirect clipping found inconsistent results. Kobayashi et al. found no significant difference in the early rebleeding rate between the two methods (20.0% [3/15] and 24.6% [17/72], respectively).[16] However, Nagata et al. showed lower rates of early rebleeding rates in direct clipping (14.3%: 2/14) versus indirect clipping (24.2%: 8/33), although the difference was not significant.[14] Kishino et al. showed a significantly lower rate of early rebleeding associated with direct clipping (5.9% [2/34]) compared with indirect clipping (35.7% [10/28]).[15] These discrepancies may be due to small sample sizes and differences in the endoscopies performed among the facilities. Although we do not know the exact reason for the significant reduction seen in early and late rebleeding with direct clipping compared with indirect clipping in the present study, we speculate that the underlying blood vessel that nourishes the colonic diverticulum is related to the rebleeding. Indirect clipping merely closes the orifice of the diverticulum and does not take into account the anatomical formation of blood vessels.[24] In contrast, direct clipping at an identified bleeding point enables the penetrating artery to be captured almost to the colonic mucosa, enabling bleeding to be stopped precisely. However, unless the diverticular orifice is large, the direct method can be challenging with vessels at the base of diverticulum. We speculate that the reasons for our early rebleeding rate of 18.6% even after direct clipping were that the penetrating vessel was not grasped by the clips[15] and the rebleeding diverticulum was different from the initial site.[14] When we reviewed previous studies investigating the effectiveness of endoscopic clipping for CDB (Table S5), the mean early rebleeding rate was 23.6%, which is similar to ours (24.6%). Also, the reason direct clipping reduces the long-term rebleeding rate is that direct clip placement can stop the artery from providing nutrients to the diverticulum. However, the late rebleeding rate even in the direct clipping group was high (32.5%) in this study, probably because the rebleeding sites were different from the previously treated sites, as reported previously.[14]

It is noteworthy that, in patients with active bleeding on colonoscopy, no significant differences in rebleeding rates were observed between the two therapies. We speculate that this was because the bleeding point was obscured by active bleeding, making precise direct clipping more difficult. In cases of active bleeding, it is difficult to grasp the bleeding point precisely with clips, but in endoscopic band ligation (EBL),[14] the bleeding diverticulum can be aspirated and ligated to eliminate the diverticulum, which is superior to clipping. Active bleeding is considered a good indication for EBL, although EBL has the disadvantage of requiring the colonoscope to be reinserted. On the other hand, clipping has the advantage of being able to be performed on the spot.

TABLE 3 Clinical outcomes of patients treated with direct or indirect clipping according to the type and location of SRH and timing of colonoscopy

Active bleeding (*n* = 623)	**Direct clipping (*n* = 195)**	**Indirect clipping (*n* = 428)**	**Crude OR (95% CI)**	***p* value**	**AOR (95% CI)**	***p* value**
Initial hemostasis	185 (94.9)	397 (92.8)	1.445 (0.693–3.009)	0.324	1.527 (0.703–3.317)	0.285
Early rebleeding[a]	48 (24.6)	133 (31.1)	0.724 (0.493–1.064)	0.100	0.698 (0.467–1.043)	0.079
Late rebleeding[b]	81 (41.5)	184 (43.0)	0.942 (0.669–1.328)	0.734	0.881 (0.615–1.263)	0.492
Blood transfusion requirement during hospitalization	66 (33.8)	163 (38.1)	0.832 (0.583–1.186)	0.309	0.877 (0.602–1.279)	0.496
IVR need during hospitalization	10 (5.1)	33 (7.7)	0.647 (0.312–1.341)	0.238	0.716 (0.325–1.580)	0.409
Prolonged hospitalization after endoscopic treatment (≥7 days)	137 (70.1)	295 (68.9)	1.065 (0.736–1.540)	0.738	1.132 (0.769–1.667)	0.530
SRH with non-active bleeding (*n* = 418)	**Direct clipping (*n* = 165)**	**Indirect clipping (*n* = 253)**	**Crude OR (95% CI)**	***p* value**	**AOR (95% CI)**	***p* value**
Initial hemostasis	163 (98.8)	249 (98.4)	1.309 (0.237–7.230)	0.757	0.995 (0.152–6.518)	0.996
Early rebleeding[a]	19 (11.5)	56 (22.1)	0.458 (0.261–0.804)	**0.006**	0.457 (0.251–0.830)	**0.010**
Late rebleeding[b]	36 (21.8)	88 (34.8)	0.523 (0.333–0.821)	**0.005**	0.476 (0.294–0.770)	**0.003**
Blood transfusion requirement during hospitalization	38 (23.0)	84 (33.2)	0.602 (0.385–0.941)	**0.025**	0.654 (0.400–1.071)	0.091
IVR need during hospitalization	0 (0)	7 (2.8)	0.156 (0–1.052)	0.058	0.146 (0–1.036)	0.055
Prolonged hospitalization after endoscopic treatment (≥7 days)	88 (53.3)	147 (58.1)	0.824 (0.555–1.223)	0.337	0.947 (0.617–1.453)	0.802
SRH, right-side colon (*n* = 730)	**Direct clipping (*n* = 259)**	**Indirect clipping (*n* = 471)**	**Crude OR (95% CI)**	***p* value**	**AOR (95% CI)**	***p* value**
Initial hemostasis	251 (96.9)	448 (95.1)	1.611 (0.710–3.654)	0.250	1.422 (0.593–3.412)	0.430
Early rebleeding[a]	42 (16.2)	138 (29.3)	0.467 (0.318–0.687)	**<0.001**	0.483 (0.321–0.726)	**<0.001**
Late rebleeding[b]	73 (28.2)	192 (40.8)	0.570 (0.411–0.791)	**0.001**	0.557 (0.394–0.788)	**0.001**
Blood transfusion requirement during hospitalization	82 (31.7)	196 (41.6)	0.650 (0.472–0.895)	**0.008**	0.660 (0.467–0.933)	**0.019**
IVR need during hospitalization	8 (3.1)	30 (6.4)	0.469 (0.212–1.038)	0.056	0.591 (0.255–1.370)	0.220
Prolonged hospitalization after endoscopic treatment (≥7 days)	153 (59.1)	318 (67.5)	0.694 (0.507–0.951)	**0.023**	0.817 (0.582–1.149)	0.245
SRH, left-side colon (*n* = 311)	**Direct clipping (*n* = 101)**	**Indirect clipping (*n* = 210)**	**Crude OR (95% CI)**	***p* value**	**AOR (95% CI)**	***p* value**
Initial hemostasis	97 (96.0)	198 (94.3)	1.470 (0.462–4.676)	0.512	1.368 (0.399–4.691)	0.618
Early rebleeding[a]	25 (24.8)	51 (24.3)	1.026 (0.591–1.779)	0.929	0.900 (0.505–1.602)	0.719
Late rebleeding[b]	44 (43.6)	80 (38.1)	1.254 (0.775–2.031)	0.356	1.104 (0.655–1.863)	0.710
Blood transfusion requirement during hospitalization	22 (21.8)	51 (24.3)	0.868 (0.492–1.532)	0.626	1.003 (0.553–1.819)	0.991
IVR needed during hospitalization	2 (2.0)	10 (4.8)	0.404 (0.087–1.879)	0.233	0.335 (0.067–1.691)	0.186
Prolonged hospitalization after endoscopic treatment (≥7 days)	72 (71.3)	124 (59.0)	1.722 (1.033–2.871)	**0.036**	1.633 (0.960–2.777)	0.070
Early colonoscopy (*n* = 825)	**Direct clipping (*n* = 300)**	**Indirect clipping (*n* = 525)**	**Crude OR (95% CI)**	***p* value**	**AOR (95% CI)**	***p* value**
Achieving initial hemostasis	288 (96.0)	497 (94.7)	1.352 (0.677–2.700)	0.391	1.346 (0.646–2.803)	0.428
Early rebleeding[a]	59 (19.7)	152 (29.0)	0.601 (0.427–0.845)	**0.003**	0.564 (0.393–0.809)	**0.002**
Late rebleeding[b]	102 (34.0)	217 (41.3)	0.731 (0.544–0.982)	**0.037**	0.666 (0.487–0.909)	**0.011**

TABLE 3 (Continued)

Early colonoscopy (n = 825)	Direct clipping (n = 300)	Indirect clipping (n = 525)	Crude OR (95% CI)	p value	AOR (95% CI)	p value
Blood transfusion requirement during hospitalization	85 (28.3)	183 (34.9)	0.739 (0.543–1.006)	0.054	0.709 (0.511–0.984)	**0.040**
IVR needed during hospitalization	10 (3.3)	31 (5.9)	0.549 (0.266–1.137)	0.102	0.599 (0.277–1.294)	0.192
Prolonged hospitalization after endoscopic treatment (≥7 days)	186 (62.0)	326 (62.1)	0.996 (0.744–1.334)	0.978	1.009 (0.739–1.376)	0.956
Elective colonoscopy (n = 216)	**Direct clipping (n = 60)**	**Indirect clipping (n = 156)**	**Crude OR (95% CI)**	**p value**	**AOR (95% CI)**	**p value**
Achieving initial hemostasis	60 (100)	149 (95.5)	3.818 (0.560- Inf)	0.197	2.051 (0.207- Inf)	0.568
Early rebleeding[a]	8 (13.3)	37 (23.7)	0.495 (0.216–1.136)	0.092	0.610 (0.245–1.520)	0.288
Late rebleeding[b]	15 (25.0)	55 (35.3)	0.612 (0.313–1.197)	0.149	0.694 (0.329–1.462)	0.336
Blood transfusion requirement during hospitalization	19 (31.7)	64 (41.0)	0.666 (0.355–1.252)	0.205	1.151 (0.530–2.504)	0.722
IVR need during hospitalization	0 (0)	9 (5.8)	0.199 (0–1.290)	0.100	0.316 (0–2.436)	0.303
Prolonged hospitalization after endoscopic treatment (≥7 days)	39 (65.0)	116 (74.4)	0.640 (0.337–1.215)	0.171	0.844 (0.412–1.728)	0.642

Note: Values are number and (%). Bold values indicate $p < 0.05$. Each of the AORs is obtained by multivariate logistic regression analysis. In the active bleeding group, adjustment for potential confounders included the 6 factors of age ≥70 years, sex, use of coxib, extravasation on CT, use of endoscopic distal attachment cap, and use of water-jet scope. In the SRH with non-active bleeding group, adjustment for potential confounders included the eight factors of age ≥70 years, sex, heart rate ≥100 bpm, hemoglobin <12 g/dl, modified Charlson Comorbidity Index ≥2, use of antiplatelet, use of endoscopic distal attachment cap, and use of water-jet scope. In the right-side colon group, adjustment for potential confounders included the seven factors of age ≥70 years, sex, heart rate ≥100 bpm, modified Charlson Comorbidity Index ≥2, use of endoscopic distal attachment cap, use of water-jet scope, and active bleeding. In the left-side colon group, adjustment for potential confounders included the 5 factors of age ≥70 years, sex, history of colonic diverticular hemorrhage, extravasation on CT, and use of water-jet scope. In the early colonoscopy group, adjustment for potential confounders included the seven factors of age ≥70 years, sex, heart rate ≥100 bpm, use of anticoagulant, extravasation on CT, use of endoscopic distal attachment cap, and use of water-jet scope. In the elective colonoscopy group, adjustment for potential confounders included the 6 factors of age ≥70 years, sex, hemoglobin <12 g/dl, modified Charlson Comorbidity Index ≥2, use of water-jet scope, and active bleeding. Most of the potential confounders were shown to be significant in univariate analysis ($p < 0.05$).

Abbreviations: AOR, adjusted odd ratio; CI, confidence interval; Inf, infinity; IVR, interventional radiology; OR, odds ratio; SRH, stigmata of recent hemorrhage.

[a]Early rebleeding is defined as rebleeding within 30 days of initial hemostasis.

[b]Late rebleeding is defined as rebleeding within 1 year of initial hemostasis.

In relation to SRH location, our large-scale study revealed direct clipping offered better outcomes for right-sided CDB, but not for left-sided CDB. Compared with right-side colon, left-side colon has a narrower lumen and stronger flexion,[25] which reduces scope maneuverability and visualization[26] and, in turn, can make it difficult to perform direct clipping precisely. This likely increased the risk of rebleeding with direct clipping and resulted in no significant difference between the two clipping methods for left-side colon. In contrast, right-side colon generally has a wider lumen and gentler flexion,[25] which may allow for stable scope maneuverability and precise direct clipping. We speculate that this is the reason for the significant difference in rebleeding rate between direct and indirect clipping in right-sided colon in this study. Recent studies in Western populations have reported colonic diverticula not only in left-side colon but also in right-side colon to some extent, with right-sided colonic diverticula present in 38% of US patients[27] and in 35.4% of Italian patients.[28] Thus, we believe that it is important in Western populations to understand the difference in the effectiveness of endoscopic treatment according to left-right differences.

Our results suggest that physicians select the treatment strategy for CDB according to the type and location of SRH. Moreover, direct clipping with improved visibility and stable maneuverability of the endoscope—for example, using a water-jet scope and distal attachment cap—may reduce the early rebleeding rate.

Intriguingly, we found that for early colonoscopy, but not elective colonoscopy, direct clipping reduced early and late rebleeding rates compared with indirect clipping. This was probably because our endoscopists who actively perform early colonoscopy have high technical skills and thus performed direct clipping precisely.

The American College of Gastroenterology guidelines[7] state that dilute epinephrine can be injected in or around the diverticulum with active bleeding to slow the bleeding, improve visibility, and facilitate clip placement, and several studies have shown the effectiveness of epinephrine injection for CDB.[2,4,8,29–31] However, none of these studies evaluated the effectiveness of clipping alone versus clipping with HSE for CDB. Our study is the first to show that clipping with HSE compared to clipping alone did not reduce early rebleeding,

regardless of using a direct or indirect method. This suggests that HSE injection does not contribute to hemostasis for CDB.

This study has some limitations. This was a retrospective study. Moreover, unmeasured confounders cannot be completely ruled out, although we tried to mitigate this by performing not only a multivariate logistic regression analysis, but also PSM, to verify the influence of direct clipping on early and late rebleeding. We cannot draw any firm conclusions in this study about the effectiveness of early colonoscopy for endoscopic clipping of CDB. At present, randomized controlled trials and observational studies have shown that early colonoscopy does not reduce rebleeding,[32] but another observational study has shown a higher identification rate of SRH.[33] Future prospective studies are needed to examine whether effective endoscopic treatment (e.g., direct clipping) can reduce rebleeding when SRH is identified during early colonoscopy. The strengths of this study include a large number of cases (n = 1041) and few missing values in data collection.[17,18] Moreover, we were able to collect detailed information on, for example, endoscopic findings (e.g., type and location of SRH) and extravasation on CT as well as long-term follow-up data, which have not been analyzed in previous studies.In conclusion, our large nationwide study highlights the use of direct clipping for CDB treatment whenever possible. Differences in bleeding pattern and colonic location can also be considered when deciding which clipping options to use. This study expands the knowledge of the efficacy of clip therapy for CDB that is used worldwide, and provides the possibility of treatment options based on endoscopic findings. This treatment strategy would contribute to improving poor patient outcomes.

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CONFLICT OF INTERESTS

All authors declare that there is no conflict of interest.

ETHICS APPROVAL STATEMENT

The ethics committees and institutional review boards of all 49 participating hospitals approved conducting this study with the opt-out method (Table S1).

AUTHOR CONTRIBUTIONS

Takaaki Kishino mainly wrote the manuscript. Naoyoshi Nagata was the principal investigator of this study and mainly edited the original manuscript. Takaaki Kishino and Naoyoshi Nagata designed and conducted the study and interpreted the data. Takaaki Kishino and Naoyoshi Nagata performed the statistical analysis. Katsumasa Kobayashi, Atsushi Yamauchi, Atsuo Yamada, Jun Omori, Takashi Ikeya, Taiki Aoyama, Naoyuki Tominaga, Yoshinori Sato, Naoki Ishii, Tsunaki Sawada, Masaki Murata, Akinari Takao, Kazuhiro Mizukami, Ken Kinjo, Shunji Fujimori, Takahiro Uotani, Minoru Fujita, Hiroki Sato, Sho Suzuki, Toshiaki Narasaka, Junnosuke Hayasaka, Tomohiro Funabiki, Yuzuru Kinjo, Akira Mizuki, Shu Kiyotoki, Tatsuya Mikami, Ryosuke Gushima, Hiroyuki Fujii, Yuta Fuyuno, Naohiko Gunji, Yosuke Toya, Kazuyuki Narimatsu, Noriaki Manabe, Koji Nagaike, Tetsu Kinjo, Yorinobu Sumida, Sadahiro Funakoshi, Kana Kawagishi, Tamotsu Matsuhashi, Yuga Komaki, Kuniko Miki, Kazuhiro Watanabe and Mitsuru Kaise designed the study, decided on and established the definitions of survey items, and interpreted the data.

INFORMED CONSENT

The authors retrospectively analyzed data from January 2010 to December 2019. Thus, a waiver of consent for this study was approved. All efforts were made to ensure confidentiality of the data.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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