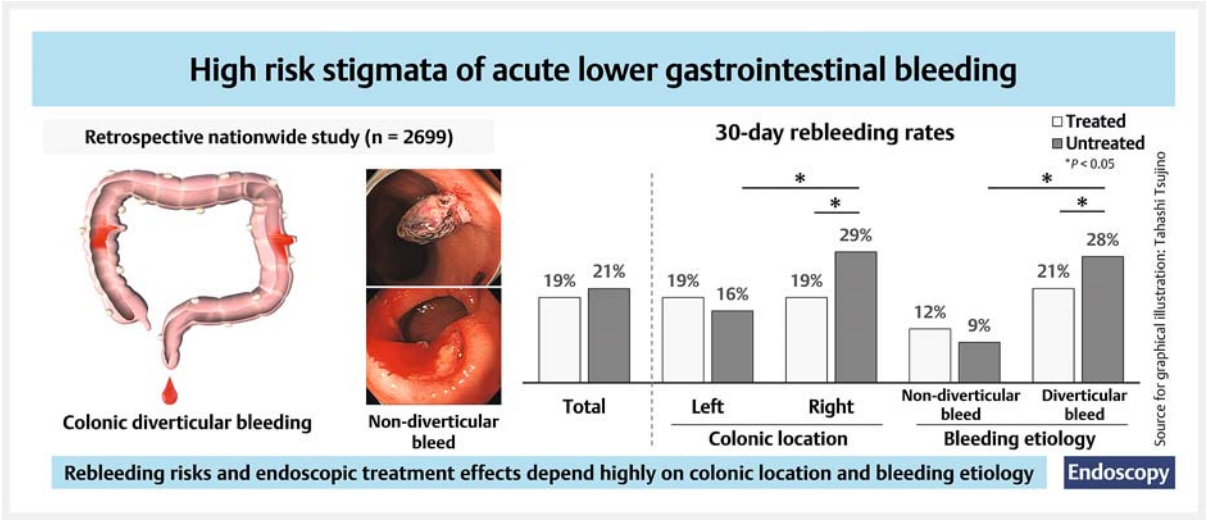
High risk stigmata and treatment strategy for acute lower gastrointestinal bleeding: a nationwide study in Japan

GRAPHICAL ABSTRACT



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ABSTRACT

Background The rebleeding risks and outcomes of endoscopic treatment for acute lower gastrointestinal bleeding (ALGIB) may differ depending on the bleeding location, type, and etiology of stigmata of recent hemorrhage (SRH) but have yet to be fully investigated. We aimed to identify high risk endoscopic SRH and to propose an optimal endoscopic treatment strategy.

Methods We retrospectively analyzed 2699 ALGIB patients with SRH at 49 hospitals (CODE BLUE-J Study), of whom 88.6 % received endoscopic treatment.

Results 30-day rebleeding rates of untreated SRH significantly differed among locations (left colon 15.5 % vs. right colon 28.6 %) and etiologies (diverticular bleeding 27.5 % vs. others [e. g. ulcerative lesions or angioectasia] 8.9 %), but not among bleeding types. Endoscopic treatment reduced the overall rebleeding rate (adjusted odds ratio [AOR] 0.69; 95 %CI 0.49–0.98), and the treatment effect was significant in right-colon SRH (AOR 0.46; 95 %CI 0.29–0.72) but not in left-colon SRH. The effect was observed in both active and nonactive types, but was not statistically significant. Moreover, the effect was significant for diverticular bleeding (AOR 0.60; 95 %CI 0.41–0.88) but not for other diseases. When focusing on treatment type, the effectiveness was not significantly different between clipping and other modalities for most SRH, whereas ligation was significantly more effective than clipping in right-colon diverticular bleeding.

Conclusions A population-level endoscopy dataset allowed us to identify high risk endoscopic SRH and propose a simple endoscopic treatment strategy for ALGIB. Unlike upper gastrointestinal bleeding, the rebleeding risks for ALGIB depend on colonic location, bleeding etiology, and treatment modality.

Introduction

The most serious complication of acute lower gastrointestinal bleeding (ALGIB) is the high rate of early rebleeding (11 %–26 %) [1–3], which occurs due to the lack of specific medication therapy, such as the proton pump inhibitors that are available for acute upper gastrointestinal bleeding [4, 5]. Importantly, only endoscopic treatment has convincing evidence for reducing early rebleeding in ALGIB [1–3]. However, the optimal strategy for endoscopic treatment of ALGIB has not been standardized [1–3]. The management of acute upper gastrointestinal bleeding was established based on the Forrest classification, the natural history (i. e. potential rebleeding risk), and the treatment effect according to bleeding type [4–6].

In ALGIB, endoscopic treatment may be indicated for stigmata of recent hemorrhage (SRH) on colonoscopy [1–3]; however, optimal management may differ depending on the situation. We hypothesized that common SRH factors such as location (left/right colon), type (active/nonactive bleeding), and etiology (diverticular bleeding/others) could be considered in ALGIB management. In particular, disease location is noteworthy, as it critically affects the natural history and treatment effect of several colonic diseases and states such as advanced cancers, post-polypectomy, and colitis, and consequently changes their management [7–9]; however, whether the treatment effect for ALGIB depends on the colonic location has yet to be fully investigated.

Evidence on the natural history, endoscopic treatment effect, and optimal treatment choice based on SRH factors would be helpful, as current management relies highly on the endoscopist's experience. For example, a Western guideline stated that clipping is recommended, particularly for bleeding in the right colon, as clipping is generally easier to perform than band ligation [1]; however, the statement lacked evidence of effectiveness and safety. We endeavored to propose standardized criteria for determining whether treatment was highly needed and whether selecting endoscopic treatment among various methods [1–3] was highly recommended in such cases.

To address these issues, we performed a comprehensive analysis using a population-level endoscopy dataset. We previously reported fundamental data on the treatment effects in patients with colonic diverticular bleeding (CDB) [10–12]. The current study expanded our research to include all patients with ALGIB and focused on proposing an SRH factor-based treatment strategy. Specifically, we aimed to examine the potential rebleeding risk, endoscopic treatment need, and importance of treatment choice based on SRH location, type, and etiology.

Methods

Study design, setting, and participants

This retrospective study was approved by the ethics committees of all 49 participating institutions throughout Japan (see **Table 1 s** in the online-only Supplementary material) and was carried out using the opt-out method. Data from patients with outpatient-onset acute hematochezia analyzed in this study were extracted from the CODE BLUE-J Study (COlonic DivErticular Bleeding Leaders Update Evidence from a multicenter Japanese Study) [13, 14]. As shown in **Fig. 1 s**, among patients needing emergency hospitalization for acute hematochezia between January 2010 and December 2019 in the original cohort (n = 10 342), we excluded those with the following: patients who did not undergo colonoscopy (n = 1278); those without SRH on colonoscopy (n = 6350); or those with SRH who underwent only barium impaction as treatment (n = 1). After exclusion, we analyzed 2699 ALGIB patients with SRH on colonoscopy to evaluate the endoscopic treatment effect based on SRH location, type, and etiology (Study 1).

In addition, we extracted 2301 patients treated endoscopically based on the presence of SRH to evaluate the effects of the endoscopic treatment types (Study 2). During this process, we excluded those with the following characteristics: no endoscopic treatment on colonoscopy (n = 308), combined treatments with two endoscopic techniques (n = 51), or endoscopic treatment types that were performed in fewer than 20 patients (n = 39). We excluded those who underwent combined treatments with two endoscopic techniques because the effectiveness of each technique could not be evaluated.

Variables

All variables were collected from the electronic endoscopy database and electronic medical records of each participating institution by dedicated researchers or gastroenterologists. Data on baseline characteristics included age, sex, lifestyle factors, performance status, vital signs, presenting symptoms, laboratory data, past history and comorbidities, medications, endoscopic factors (timing, preparation, and devices), SRH factors (location, type, and etiology), endoscopic treatment (treated or untreated), and endoscopic treatment type. Comorbidities were used to calculate the modified Charlson Comorbidity Index, which consists of 19 items from the original index [15] and two additional factors (hypertension and hyperlipidemia).

All SRHs were classified according to location (left or right colon), type (active or nonactive bleeding), and etiology (diverticular bleeding or others) (▶ **Fig. 1**, **Fig. 1 s**). The left colon was defined as the descending and sigmoid colon and the rectum, and the right colon was defined as the remaining colon locations. Nonactive bleeding included a nonbleeding visible vessel or adherent clot [3, 16]. Consistent with a previous report [16], some SRH cases did not receive endoscopic treatments for various reasons, including concerns about adverse event risks, technical access issues, loss of SRH visualization during the procedure, and severe active bleeding.

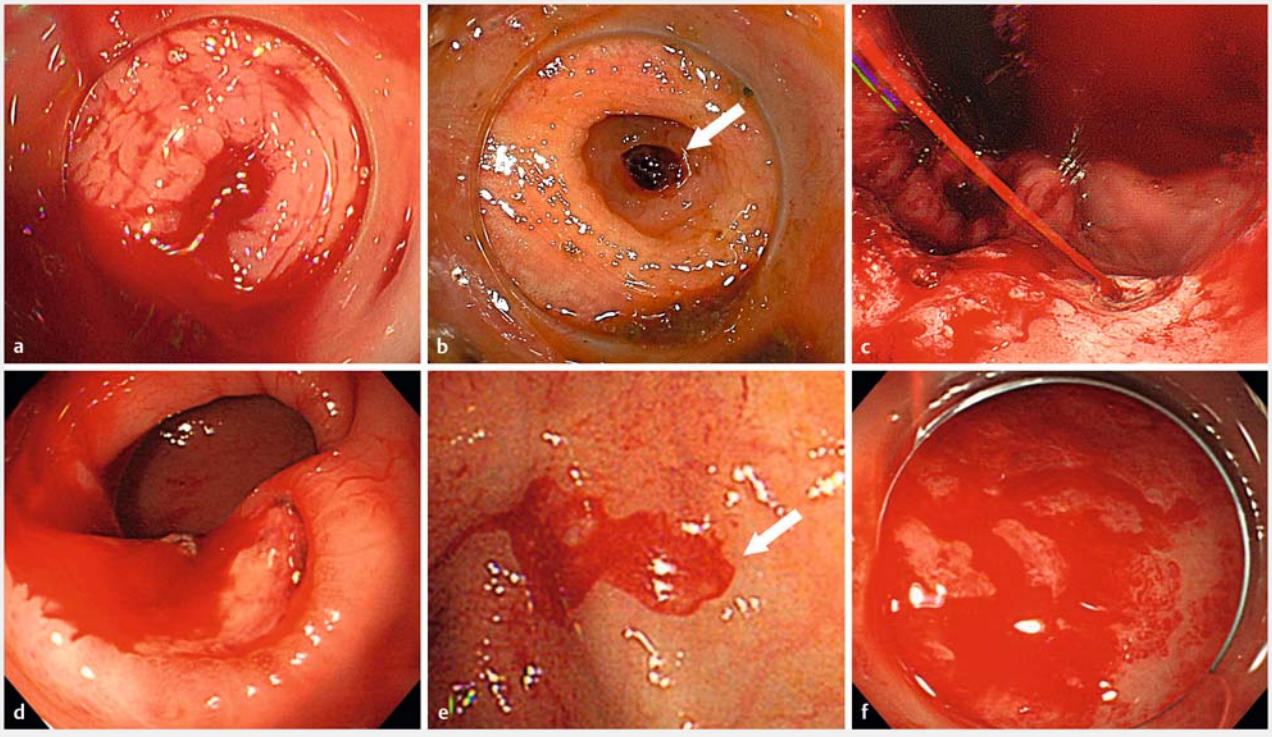
Five types of endoscopic treatment were included, and these were performed at the discretion of the attending physician: ligation (snare and band), clipping (direct and indirect), and coagulation. Clipping is the most commonly used technique for ALGIB worldwide due to its effectiveness, simplicity, low cost, and minimal tissue damage [1–3, 17]. Direct clipping is the direct placement of endoclips at a bleeding point in a diverticulum, whereas indirect clipping is indirect placement of endoclips at a diverticulum in a zipper-like manner. Ligation is becoming more widely performed for CDB [1–3], and coagulation is commonly used for SRH other than CDB [1, 2].

Clinical outcomes

The main outcome measure was rebleeding within 30 days of colonoscopy. Rebleeding was defined as a significant amount of fresh blood loss or passage of wine-colored stools after colonoscopy [13, 18]. The secondary outcome measure was post-treatment adverse events such as perforation and diverticulitis. These events were diagnosed based on symptoms, such as abdominal pain and fever, computed tomography findings, and blood test results. Mortality was not included as an outcome because mortality rates have been reported to be very low in ALGIB (<4 %), and more than half of the deaths were not related to bleeding [13, 19].

Statistical analysis

First, we examined the associations between baseline characteristics and 30-day rebleeding in untreated SRH (n = 308) to evaluate potential rebleeding risks based on natural history, using logistic regression models.



▶ **Fig. 1** Stigmata of recent hemorrhage of various bleeding etiologies. **a** Active diverticular bleeding. **b** Nonactive diverticular bleeding (nonbleeding visible vessel). **c** Ulcerative lesion. **d** Post-polypectomy bleeding. **e** Angioectasia. **f** Radiation proctitis.

Second, endoscopic treatment effects were assessed using the whole cohort (n = 2699) by comparing the rebleeding rates of treated and untreated SRH. Logistic regression models were used, and the multivariable analysis (adjusted odds ratio [AOR] and 95 %CI) was adjusted for age, sex, and 16 other factors, including patient characteristics, endoscopic factors, and SRH factors that had the potential to be clinically important variables. Two types of sensitivity analyses were performed to confirm the robustness of the results not strongly dependent on model selection methods or variables. First, multivariable analyses using covariates according to the three selection criteria were conducted. The pretreatment, common cause, and disjunctive cause criteria based on directed acyclic graphs were used to select covariates [20]. In this analysis, adjusted relative risks were calculated using log-binomial models in addition to AORs. Sensitivity analysis was also performed using propensity score matching to balance the baseline characteristics. To estimate the propensity score, we included the baseline characteristics that were significant ($P < 0.05$) in the univariable analysis between patients with treated and untreated SRH. We performed a one-to-one matching analysis using the nearest neighbor method within a caliper of 0.2 of the SD of the logit of the propensity score without replacement. In addition, the interactions between endoscopic treatment and the three SRH factors (location, type, etiology) were assessed to evaluate the impact of these factors on 30-day rebleeding. Furthermore, to stratify the treatment need, 30-day rebleeding rates between treated and untreated SRH cases were separately compared according to SRH location, type, and etiology (i. e. left colon nonactive bleeding, left colon active bleeding, right colon nonactive bleeding, and right colon active bleeding, each for diverticular bleeding and other etiologies).

Third, we focused on different effects according to the endoscopic treatment type using patients with treated SRH (n = 2301). Logistic regression models were used, and the multivariable analysis was adjusted for age, sex, and 15 other factors, including patient characteristics, endoscopic factors, and SRH factors that had the potential to be clinically important variables. The interactions for 30-day rebleeding among the treatment types and the three SRH factors were also assessed. Moreover, 30-day rebleeding rates among multiple endoscopic treatments were separately compared in every eight categories according to the three SRH factors to explore a suitable treatment type for each situation. In this subgroup analysis, we used the propensity score as a covariate rather than performing a regression adjustment with all of the covariates (i. e. traditional covariate adjustment), as around 10 rebleeding events per confounder were needed [21]. This propensity score method was standardized for covariate adjustment [22]. The abovementioned clinically important variables were integrated as covariates by calculating propensity scores. Thus, the multivariable analysis was adjusted for age, sex, and propensity score-based covariates.

Finally, post-treatment adverse event rates were compared based on the three SRH factors and treatment types using Fisher's exact test.

Statistical significance was set at $P < 0.05$. All statistical analyses were performed using STATA version 16 (StataCorp, College Station, Texas, USA).

Results

Study 1

Patient characteristics

Among 2699 SRH cases, 41.0 % were in the left colon, 54.1 % had active bleeding, 74.2 % were diverticular SRH, and 88.6 % were endoscopically treated (▶ **Table 1**). Among the eight categories based on the three SRH factors, right-colon active CDB was the most common (n = 763), followed by right-colon nonactive CDB (n = 619) (**Table 2 s**).

▶ **Table 1** Baseline characteristics of patients with stigmata of recent hemorrhage on colonoscopy (n = 2699).

Variable	Value, n (%)
Age ≥ 70 years	1648 (61.1)
Male sex	1825 (67.6)
Current drinker	1145 (50.0)
Current smoker	416 (17.4)
Performance status ≥ 2	324 (12.1)
Systolic blood pressure ≤ 100 mmHg	327 (12.4)
Pulse rate ≥ 100 bpm	533 (20.3)
Abdominal pain	162 (6.0)
Diarrhea	102 (3.8)
Loss of consciousness	171 (6.4)
Laboratory data	
▪ Hemoglobin < 12 g/dL	1508 (55.9)
▪ White blood cell > 10 000 /μL	367 (13.6)
▪ Platelets < 15×10^4 /μL	441 (16.3)
▪ Albumin < 3.0 g/dL	235 (9.2)
▪ Creatinine > 1.5 mg/dL	320 (12.0)
History of colorectal surgery	163 (6.0)
History of colonic diverticular bleeding	794 (29.5)
Modified Charlson Comorbidity Index ≥ 2	1572 (58.2)
Medication	
▪ NSAIDs	286 (10.6)
▪ Antiplatelet	810 (30.0)
▪ Anticoagulant	446 (16.5)
▪ Corticosteroid	143 (5.3)
Endoscopic factors	
▪ Early colonoscopy[1]	2173 (80.5)
▪ Bowel preparation[2]	2178 (80.7)

▶ **Table 1** (Continuation)

Variable	Value, n (%)
▪ Use of a distal attachment	2252 (83.4)
▪ Use of a waterjet scope	2373 (87.9)
Stigmata of recent hemorrhage	
▪ Location, left / right colon	1106 (41.0) / 1593 (59.0)
▪ Type, active / nonactive bleeding[3]	1459 (54.1)/1240 (45.9)
▪ Etiology, diverticular bleeding / other diseases[4]	2004 (74.2)/695 (25.8)
Endoscopic treatment	
▪ Treated[5]/untreated	2391 (88.6)/308 (11.4)

NSAIDs, nonsteroidal anti-inflammatory drugs.
[1] Early colonoscopy was defined as that performed within 24 hours of admission.
[2] Use of polyethylene glycol solution and/or glycerin enemas.
[3] Nonbleeding visible vessel (n = 501) and an adherent clot (n = 739).
[4] Post-polypectomy bleeding (n = 309), ulcerative lesions (n = 141), angioectasia (n = 55), radiation proctitis (n = 33), colitis (n = 29), and miscellaneous (n = 128).
[5] Duplicated: clipping (n = 1466), ligation (n = 763), coagulation (n = 162), hypertonic saline-epinephrine injection (n = 41), polypectomy (n = 7), and unknown (n = 3).

Natural history of untreated SRH

The 30-day rebleeding rates of untreated SRH (n = 308) significantly differed among locations (left 15.5 % vs. right 28.6 %; OR 0.46; 95 %CI 0.26–0.80; $P = 0.006$) and etiologies (diverticular bleeding 27.5 % vs. others 8.9 %; OR 3.88; 95 %CI 1.84–8.22; $P < 0.001$), but not among bleeding types (active 27.7 % vs. nonactive 19.1 %; OR 1.62; 95 %CI 0.90–2.91; $P = 0.105$) (▶ **Fig. 2a**, **Table 3s**).

Endoscopic treatment effects (treated SRH vs. untreated SRH)

Endoscopic treatment reduced the overall 30-day rebleeding rate (AOR 0.69; 95 %CI 0.49–0.98) (▶ **Fig. 2b**). The effect was significant in right-colon SRH (AOR 0.46; 95 %CI 0.29–0.72) but not in left-colon SRH (AOR 1.17; 95 %CI 0.66–2.08). Quantitative interactions for rebleeding were observed between endoscopic treatment and SRH locations ($P = 0.007$ for interaction). The treatment effect was observed in both the active and nonactive types, but was not statistically significant (active type AOR 0.59; 95 %CI 0.34–1.02; nonactive type AOR 0.75; 95 %CI 0.47–1.20). Moreover, the effect was significant in CDB cases (AOR 0.60; 95 %CI 0.41–0.88) but not in non-CDB cases (AOR 1.30; 95 %CI 0.52–3.13). These results remained unchanged in the sensitivity analysis using covariates based on three selection criteria (**Table 4s, Table 5s**) and in another sensitivity analysis that utilized propensity score matching (**Table 6s, Fig. 2s**).

In the right-colon active CDB category, the 30-day rebleeding rate of treated SRH (23.2 %) was significantly lower than that of untreated SRH (56.7 %) (AOR 0.23; 95 %CI 0.11–0.48) (▶ **Fig. 3**). In the right colon nonactive CDB category, the rebleeding rate of treated SRH (16.2 %) was significantly lower than that of untreated SRH (25.0 %) (AOR 0.58; 95 %CI 0.33–1.00). However, a statistically significant treatment effect was not observed for the other SRH cases.

Study 2

Comparison of endoscopic treatment effects among treatment types

Among 2301 endoscopically treated SRH, 61.7 % were treated with clipping. Overall, other treatments were significantly more effective than clipping for reducing 30-day rebleeding (AOR 0.50; 95 %CI 0.40–0.61) (▶ **Fig. 4a**). Quantitative interactions for rebleeding were observed among the treatment types and all SRH factors ($P < 0.05$), indicating that other treatments were more effective than clipping in the right colon, in the active type, and in diverticular bleeding. In the subgroup analyses of right-colon CDB, the rebleeding rates significantly differed among the treatment types (ligation, direct clipping, or indirect clipping) and depended on the SRH type (▶ **Fig. 4b**). However, the treatment effect was not significantly different among the treatment types in other SRH cases.

Post-treatment adverse events

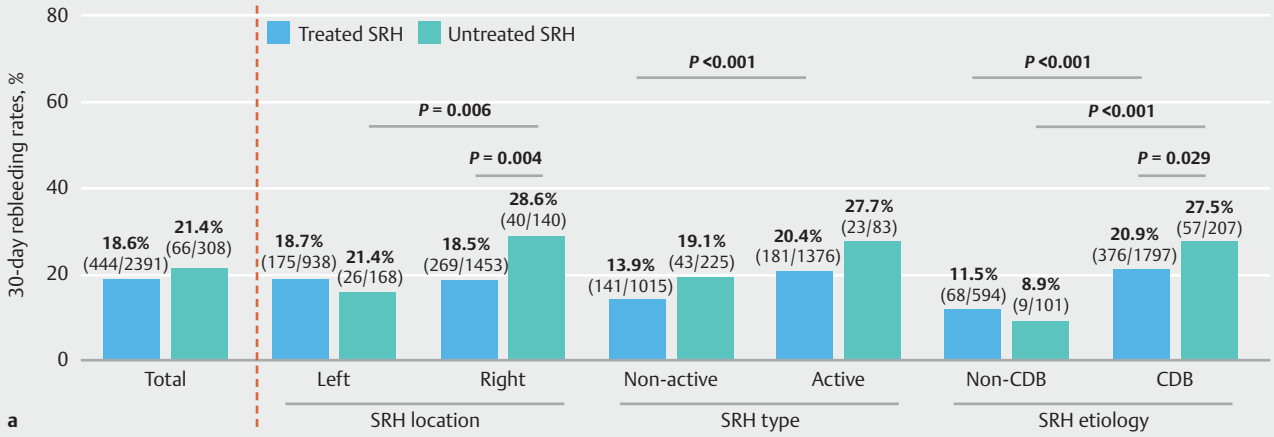
Perforation occurred in 0.09 % (2/2301) of all patients, and diverticulitis occurred in 0.23 % (4/1771) of patients with CDB. All perforations occurred after band ligation for left colon diverticular bleeding. Diverticulitis was observed after snare and band ligation and indirect clipping but was not observed after direct clipping. Post-treatment adverse event rates were not significantly different according to SRH location, type, etiology, and treatment type (▶ **Fig. 5**).

Proposal of an SRH factor-based treatment strategy for ALGIB

Based on the above-mentioned results, an optimal treatment strategy for ALGIB was proposed (**Fig. 3s**). Potential rebleeding risks, endoscopic treatment requirements, and necessity of treatment choice were stratified based on SRH location, type, and etiology.

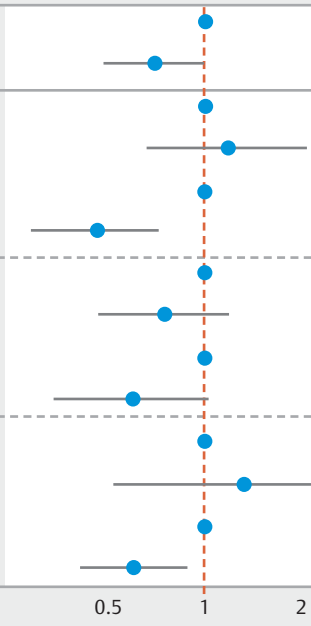
Discussion

Comprehensive analysis using our nationwide ALGIB endoscopy dataset could help determine the optimal treatment strategy for ALGIB based on SRH location, type, and etiology. First, we found that the 30-day rebleeding rates of untreated SRH (i. e. natural history) were high in the right colon and with the etiology of diverticular bleeding (▶ **Fig. 2a**), suggesting that these factors are important when considering indications for endoscopic treatments. Second, endoscopic treatments reduced the overall rebleeding rates, and the effect was statistically significant in right-colon CDB, irrespective of SRH type, but not in other SRH (▶ **Fig. 3**), suggesting that right-colon CDB was a strong indication for treatment compared with other SRH.



a

SRH factors	Endoscopic treatment	30-day rebleeding rate	Adjusted Odds ratio † (95% CI)	*P* for interaction
Total	Untreated	21.4%	Ref	
	Treated	18.6%	0.69 (0.49–0.98)	
Left colon	Untreated	15.5%	Ref	0.007*
	Treated	18.7%	1.17 (0.66–2.08)	
Right colon	Untreated	28.6%	Ref	
	Treated	18.5%	0.46 (0.29–0.72)	
Non active bleeding	Untreated	19.1%	Ref	0.579**
	Treated	13.9%	0.75 (0.47–1.20)	
Active bleeding	Untreated	27.7%	Ref	
	Treated	20.4%	0.59 (0.34–1.02)	
Non-CDB	Untreated	8.9%	Ref	0.311***
	Treated	11.5%	1.17 (0.66–2.08)	
CDB	Untreated	27.5%	Ref	
	Treated	20.9%	0.60 (0.41–0.88)	

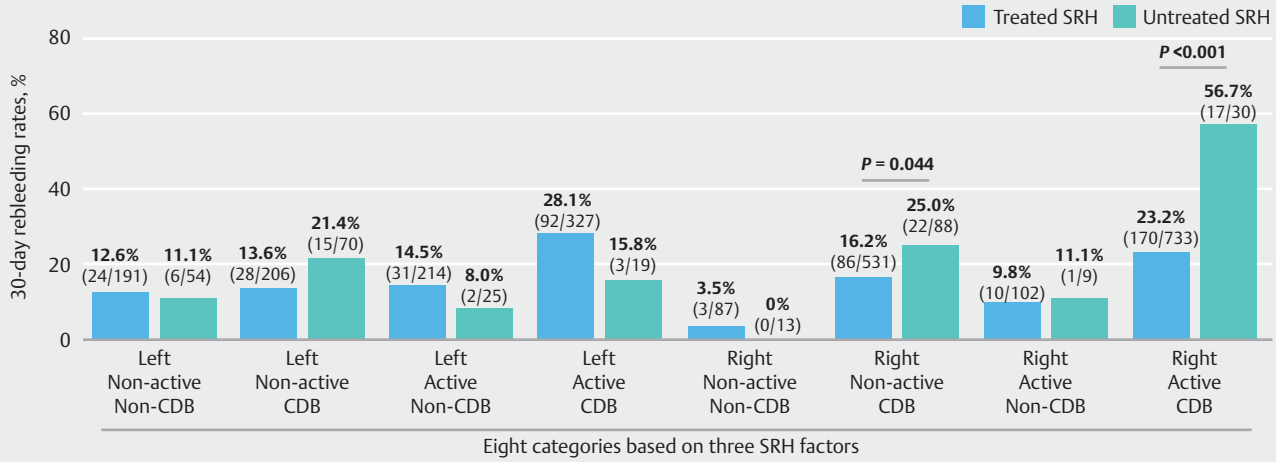


b

▶ **Fig. 2** 30-day rebleeding rates based on bleeding location, type, and etiology (n = 2,699). **a** 30-day rebleeding rates based on three stigmata of recent hemorrhage (SRH) factors. **b** Interaction analysis for 30-day rebleeding among the endoscopic treatments and SRH factors. The left colon was defined as the descending and sigmoid colon and the rectum, and the right colon was defined as the other locations. [1]Adjusted for age, sex, and the following 16 factors that had the potential to be clinically important variables: current drinker, systolic blood pressure ≤ 100 mmHg at admission, pulse rate ≥ 100 bpm at admission, abdominal pain, hemoglobin < 12 g/dL, white blood cell count > 10 000/μL, antiplatelet use, anticoagulant use, corticosteroid use, history of colonic diverticular bleeding, bowel preparation, use of a distal attachment, use of a waterjet scope, and SRH factors (location, type, and etiology). [2]Interaction for 30-day rebleeding among treatment and SRH location. [3]Interaction for 30-day rebleeding among treatment and SRH type. [4]Interaction for 30-day rebleeding among treatments and SRH etiology. CDB, colonic diverticular bleeding.

Third, regarding treatment types, the effectiveness was not significantly different between clipping and other treatments in most SRH, whereas ligation was significantly more effective than clipping in right-colon CDB (▶ **Fig. 4**). Moreover, the post-treatment adverse event rates were not significantly different among the three SRH factors and treatment types (▶ **Fig. 5**). Based on the findings, we proposed criteria for high risk endoscopic SRH and an optimal treatment strategy using three SRH factors (**Fig. 3 s**).

To our knowledge, the current study is the first to propose an SRH factor-based treatment strategy for ALGIB. The indication for endoscopic treatment relies heavily on bleeding locations and etiologies, which is different from the treatment indications for acute upper gastrointestinal bleeding according to the Forrest classification [4, 5]. Based on our results, endo-



▶ **Fig. 3** 30-day rebleeding rates according to eight categories based on bleeding location, type, and etiology (n = 2699). SRH, stigmata of recent hemorrhage; CDB, colonic diverticular bleeding.

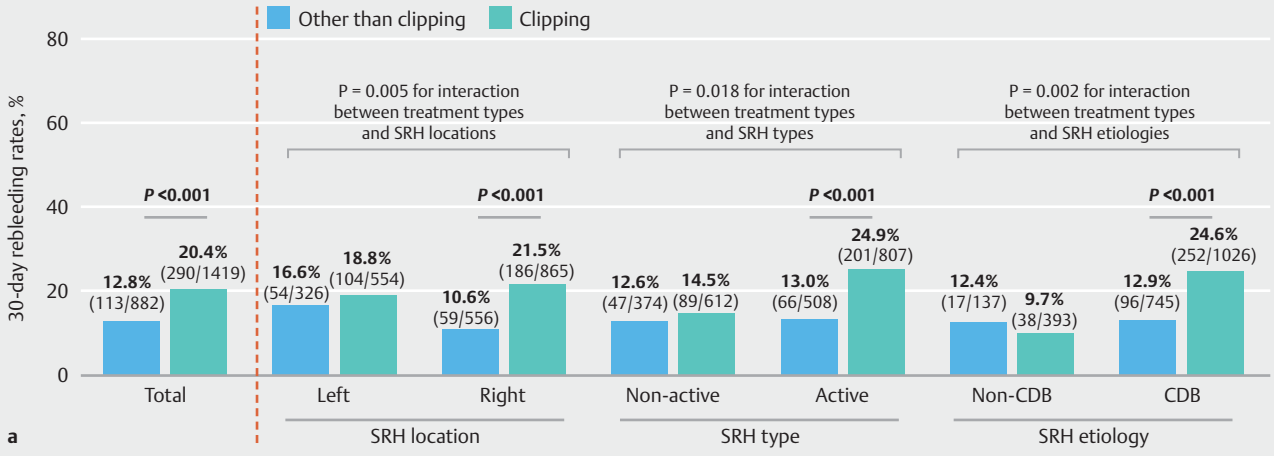
scopic treatments are strongly recommended for right-colon CDB, irrespective of SRH type, as these cases have high rebleeding risks and benefit from treatment. In contrast, left-colon bleeding is expected to stop spontaneously; thus, the need for endoscopic treatment is moderate, irrespective of the SRH type and etiology. Moreover, treatment choice is useful for right-colon CDB; ligation is recommended. The finding that ligation is occasionally indicated for right-colon SRH from the aspect of effectiveness may update the experience-based statement in the US guideline, which recommends clipping [1]. Interestingly, it also seems reasonable to select direct clipping instead of ligation for right-colon "nonactive" diverticular bleeding, if available. The management of right-colon CDB is important not only in Eastern countries but also in Western countries, given that a recent report from the West showed that a right-colon diverticulum was found in 38 % of all diverticulosis cases [23]. For left colon SRH, any treatment type is acceptable. Endoscopists can select treatment types for CDB based on the superior effectiveness of band ligation over clipping, and on the complications after band ligation (perforation 0.31 %; diverticulitis 0.16 %) and after clipping (diverticulitis 0.19 %) [3, 10]. It should be noted that perforation requiring surgery occurred in 1.8 % (2/112) of patients after band ligation for left-colon active diverticular bleeding.

Notably, the optimal treatment strategy was essentially different between the right and left colon, information that is completely lacking in recent Western and Eastern ALGIB guidelines [2, 3]. This difference was supported by recent reports that the right colon is an established risk factor for post-polypectomy bleeding, as well as that prophylactic clipping after polypectomy is effective in reducing bleeding in the right colon but not in the left colon [8]. A few hypotheses could be proposed regarding the differences in the natural history and endoscopic treatment effects among SRH locations. First, the right colon wall might be thinner and have high intraluminal pressures, which would increase the vulnerability of the vessels to damage and bleeding [24]. Moreover, the visualization and scope maneuverability may be poor in the left colon, as the left colon has stronger flexion and a narrower lumen than the right colon [25, 26].

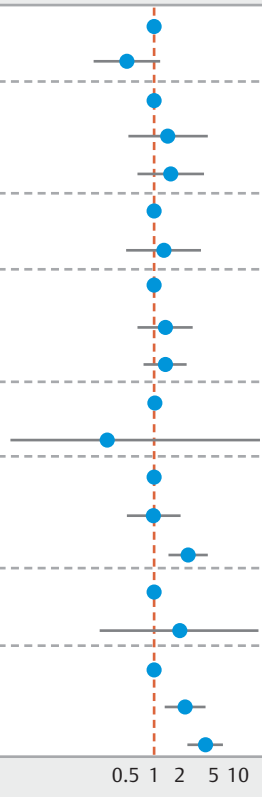
To date, the effectiveness of endoscopic treatments for SRH cases other than CDB has mostly been reported in single-center noncomparative studies (e. g. ≤ 73 cases with rectal ulcers and ≤ 29 cases with colonic angioectasia) [27, 28]. Of note, our data first revealed no significant difference in treatment effect between clipping and coagulation for non-CDB cases, regardless of the SRH location and type. The rebleeding rates between clipping and coagulation were not significantly different among all subgroups of post-polypectomy bleeding, ulcerative lesions, angioectasia, or radiation proctitis (data not shown). A previous report on rectal ulcers showed no significant difference in the effectiveness among various endoscopic treatments [27], which supports our finding.

This study has several limitations. First, the retrospective design of the study and the area limited to Japan might cause selection and institutional biases. Further studies outside of Japan are warranted to validate our findings. Second, the effectiveness of hypertonic saline-epinephrine injection could not be evaluated because of the small sample size (n = 41) and low statistical power. Moreover, our database lacked cost-effectiveness information, which could contribute to determining the optimal treatment strategy. On the other hand, our detailed endoscopic data of approximately 2700 cases enabled us to analyze the natural history of ALGIB and the treatment effect based on SRH factors, which has not been investigated previously, and to confirm the importance of endoscopic treatment by developing standardized criteria.

In conclusion, the criteria for high risk endoscopic SRH were identified, and a simple endoscopic treatment strategy for ALGIB was proposed for the first time based on our population-level endoscopy dataset. Unlike in acute upper gastrointestinal bleeding (in which the treatment effects are determined using

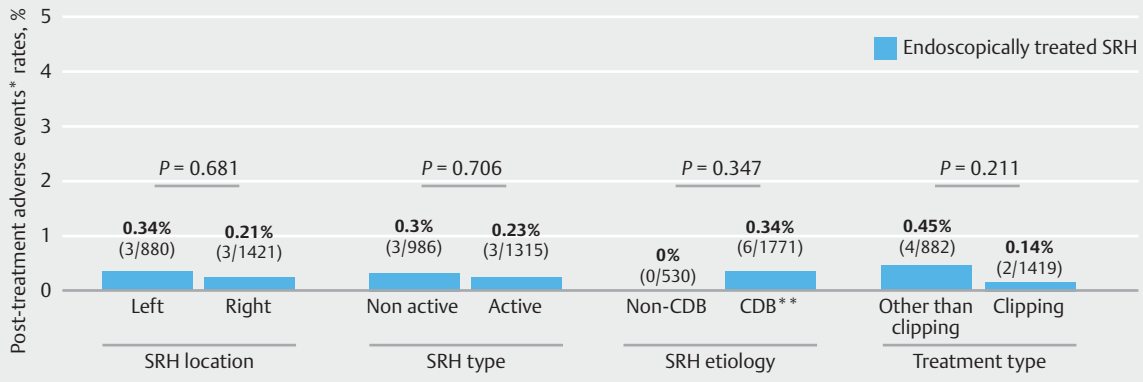


Eight categories based on three fctors	Treatment type	30-day rebleeding rate	Adjusted Odds ratio † (95% CI)	*P* value
Total non-active non-CDB	Coagulation	20.0% (10/50)	Ref	
(n = 174)	Clipping	10.5% (13/124)	0.47 (0.19–1.15)	0.099
Left non-active CDB	Ligation	10.9% (10/92)	Ref	
(n = 205)	Direct clipping	15.4% (6/39)	1.49 (0.50–4.43)	0.473
	Indirect clipping	16.2% (12/74)	1.59 (0.64–3.91)	0.315
Left active non-CDB	Coagulation	10.3% (6/58)	Ref	
(n = 181)	Clipping	13.0% (16/123)	1.39 (0.52–3.73)	0.514
Left active CDB	Ligation	22.2% (28/126)	Ref	
(n = 320)	Direct clipping	31.7% (19/60)	1.68 (0.83–3.43)	0.150
	Indirect clipping	28.4% (38/134)	1.53 (0.86–2.72)	0.151
Right non-active non-CDB	Coagulation	0% (0/9)	Ref	
(n = 82)	Clipping	2.7% (2/73)	0.30 (0.02–∞)*	1.000
Right non-active CDB	Ligation	12.1% (27/223)	Ref	
(n = 525)	Direct clipping	10.5% (13/124)	0.92 (0.45–1.88)	0.828
	Indirect clipping	24.2% (43/178)	2.71 (1.53–4.81)	0.001
Right active non-CDB	Coagulation	5.0% (1/20)	Ref	
(n = 93)	Clipping	9.6% (7/73)	2.02 (0.23–17.4)	0.524
Right active CDB	Ligation	10.2% (31/304)	Ref	
(n = 721)	Direct clipping	22.3% (29/130)	2.58 (1.49–4.46)	0.001
	Indirect clipping	32.1% (92/287)	4.20 (2.69–6.55)	<0.001



b

▶ **Fig. 4** Comparison of the 30-day rebleeding rates among treatment types in endoscopically treated patients (n = 2301). **a** 30-day rebleeding rates based on three stigmata of recent hemorrhage factors and treatment types. **b** 30-day rebleeding rates after each endoscopic treatment. Note. In addition to clipping, ligation and coagulation were performed. Ligations included the snare and band ligation methods. [1]Twelve variables that had the potential to be clinically important variables were integrated as covariates by calculating the propensity score, as around 10 rebleeding events per confounder were needed [21], including performance status, systolic blood pressure ≤ 100 mmHg at admission, pulse rate ≥ 100 bpm at admission, loss of consciousness, antiplatelet use, anticoagulant use, corticosteroid use, past history of colonic diverticular bleeding (CDB), early colonoscopy, bowel preparation, use of a distal attachment, and use of a waterjet scope. Thus, the multivariable analysis was adjusted for age, sex, and propensity score-based covariates. Multivariable analysis was not performed for left colon nonactive CDB cases and for any category of diseases other than CDB due to few rebleeding events. [2]Analyzed using exact logistic regression analysis. SRH, stigmata of recent hemorrhage.



▶ **Fig. 5** Post-treatment adverse event rates based on bleeding location, type, and etiology, and treatment type (n = 2301). [1]Perforation or diverticulitis. [2]Left active colonic diverticular bleeding (CDB): perforation occurred in 1.8 % (2/112) after band ligation. Diverticulitis occurred in 0.7 % (1/134) of cases after indirect clipping. Right nonactive CDB: diverticulitis occurred in 2.8 % (1/36) of patients after snare ligation, 0.5 % (1/187) after band ligation, and 0.6 % (1/178) after indirect clipping. SRH, stigmata of recent hemorrhage.

the Forrest classification according to bleeding types), the endoscopic treatment effects of ALGIB depend highly on colonic location and bleeding etiology, and these factors can be considered as indications for ALGIB treatment. Moreover, selecting a suitable endoscopic treatment type based on bleeding type may be desirable for right-colon CDB compared with other SRH. Our findings could contribute to standardizing the indications and strategies for endoscopic treatment of ALGIB.

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Competing interest

The authors declare that they have no conflict of interest.

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