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Early rebleeding rate following endoscopic treatment of colonic diverticular bleeding: a systematic review and meta-analysis

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Abstract

Background Various endoscopic treatment options are available for managing colonic diverticular bleeding (CDB). We conducted a systematic review and meta-analysis to assess the effectiveness of these endoscopic interventions in achieving hemostasis in patients with CDB, focusing on early rebleeding rate (ERR) within 30 days.

Methods A systematic literature search of the PubMed and Cochrane Library databases was performed for articles published between January 2008 and December 2023. Studies evaluating endoscopic clipping, with or without epinephrine injection, endoscopic band ligation (EBL) and endoscopic snare ligation (EDSL) in the treatment of CDB were included. The primary outcome was the overall pooled ERR following successful hemostasis. Secondary outcomes addressed ERRs associated with various hemostatic endoscopic techniques, and pooled ERRs for both direct and indirect clipping methods. Results are presented as pooled rates and odds ratio (OR) with 95% confidence intervals (CI).

Results Sixteen studies were included, comprising 1435 patients with definite CDB of whom 1273 received endoscopic hemostatic treatment. Overall pooled ERR was 14.73% (95%CI 9.33-20.14%). Pooled ERRs were 9.83% (95%CI 7.41-12.26%) in the EBL/EDSL group and 22.32% (95%CI 12.48-32.16%) in the endoscopic clipping group (P=0.02). A subgroup analysis of the clipping group showed a significant difference between the pooled ERRs favoring direct clipping: 12.04% (95%CI 3.06-21.02%) vs. 27.74% (95%CI 18.34-37.14%), P=0.02. The measured effect favors direct over indirect clipping in reducing early rebleeding episodes: OR 0.45, 95%CI 0.24-0.85; P=0.01.

Conclusion In the management of patients presenting with CDB, EBL/EDSL and direct clipping showed significantly lower ERRs compared to indirect clipping.

Keywords Colonic diverticular bleeding, endoscopy, hemostasis, treatment

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Introduction

Colonic diverticular bleeding (CDB) is the most common cause of lower gastrointestinal bleeding (LGIB), accounting for 20-50% of cases worldwide [1]. The prevalence varies in the literature according to the colonic location of diverticular disease. Multicenter studies described a prevalence of CDB of 13% among LGIB in the United Kingdom vs. 63% in Japan, where right-sided diverticulosis, known to be at higher risk of bleeding, is more common [2]. Moreover, the reported incidence varies depending on the modality used for diagnosis [3]. In the absence of consensus about the diagnostic approach to CDB, physicians in Asian countries such as Japan resort more frequently to an endoscopic diagnosis for definite CDB than do those in the United Kingdom, for example (80% vs. 26%, respectively) [4]. Well-established risk factors for CDB include age older than 70 years, use of antithrombotics and nonsteroidal anti-inflammatory drugs (NSAIDs), and atherosclerosis [5]. The vast majority of CDB cases resolve

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*Dr. Delaleeuwe and Dr. Aoun share co-first authorship

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spontaneously; however, some patients require intervention to achieve hemostasis [6]. Studies have shown endoscopic management to be less invasive, with a lower complication rate than transcatheter arterial embolization (TAE) or surgery [7]. Endoscopic treatment modalities, including endoscopic clipping (EC), with or without epinephrine injection, endoscopic band ligation (EBL) and endoscopic snare ligation (EDSL), have been shown to prevent early rebleeding occurrence (within 30 days), notably in the presence of stigmata of recent hemorrhage (SRH) [6]. No randomized control trials comparing the efficacy of the different endoscopic treatments have been published to date [8].

This systematic review aims to describe the overall pooled early rebleeding rate (ERR) among patients with definite CDB treated endoscopically. In addition, ERR was compared in relation to the different endoscopic techniques used, including indirect and direct clipping, among others.

Materials and methods

Protocol and registration

This review's protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024499363.

Eligibility criteria

A search was conducted based on the PICO model, as follows:

- P: Adults presenting with CDB;
- I: Endoscopic techniques applied for hemostasis, including EC, EBL and EDSL, epinephrine injection;
- C: Not applicable;
- O: ERR after successful endoscopic hemostasis of CDB.

Studies published in the English language as full text, between the years 2008 and 2023, clinical trials, observational prospective studies, retrospective cohort studies and case series with more than 10 patients were included.

Patients under 18 years of age, *ex vivo* or animal models, LGIB of other etiology, and cases associated with diverticulitis, as well as clinical guidelines, systematic reviews and case reports, were excluded.

Information sources and search strategy

A systematic literature search of the PubMed and Cochrane Library (Cochrane Central Register of Controlled Trials) databases was performed in January 2024. Dedicated search terms were produced: ("Colonic Disease"[Mesh] OR "Colon"[Mesh] OR colon*[TIAB]) AND (diverticul*[TIAB] OR "Diverticulum"[Mesh]) AND ("Hemorrhage"[Mesh] OR hemorrhag*[TIAB] OR bleed*[TIAB]) AND ("Endoscopy, gastrointestinal"[Mesh] OR colonoscop*[TIAB] OR "Hemostasis, endoscopic"[MeSH Terms] OR "Endoscopic Hemostasis"[Text Word] OR clip* [TIAB] OR band*[TIAB] OR Epinephr*[TIAB] OR Snare[TIAB]) AND (2008:2023[pdat]).

Two investigators (ID, JA) independently assessed the potential relevance of the retrieved articles based on title and abstract. Subsequently, the full text of the selected articles was reviewed in the same manner to decide whether they were eligible for inclusion in the study. All references of selected articles were reviewed carefully for additional inclusions. In case of disagreement, the articles were included or not included after a joint discussion with senior investigators (PG, PE). This systematic review was performed according to the updated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines from 2020 (Supplementary Table 1) [9].

Data collection and analysis

All eligible studies were assessed with the extraction of the following data: name of first author, year of study publication, country of publication, study design, endoscopic treatment modality used, number of patients enrolled, patients' characteristics (sex, age, comorbidities, use of oral antithrombotics/NSAIDs, past history of diverticular bleeding), bowel preparation, location of CDB, SRH (defined as active bleeding, visible vessel or adherent clot), ERR (defined as any bleeding episode occurring during the first 30 days after initial endoscopic treatment), need for surgery or TAE, adverse events (perforation, diverticulitis).

Outcome measures

The primary outcome was to describe the pooled overall ERRs after successful endoscopic hemostasis of CDB. Secondary outcomes included a comparison of the ERR according to the different endoscopic modalities used for treatment. In addition, the pooled ERRs were calculated for the direct and indirect clipping methods. Direct clipping involves capturing the culprit vessel directly, whereas indirect clipping is defined as closing the diverticular orifice in a zipper-like manner [10].

Quality assessment and risk of bias

Quality assessment was carried out independently by 2 authors (ID, JA) using the National Heart, Lung, and Blood Institute (NHLBI) tool [11].

Statistical analysis

Data analysis was performed using the statistical software Review Manager (RevMan 5.3.5, Copenhagen, Denmark,

the Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Outcomes were compared using the random-effects model (DerSimonian and Laird method). Heterogeneity among studies was measured using the I^2, with lower values representing lower levels of heterogeneity. In case of significant heterogeneity (P<0.1), a predefined sensitivity analysis was performed by repeating the analysis excluding 1 study at a time to assess the potential excessive influence of a single study on the overall significance. Forest plots were created for the visual display of results. Publication bias was assessed by visual inspection of the funnel plots for symmetry. Results are presented as pooled rates with 95% confidence intervals (CI), or as odds ratios (OR) with 95%CI. Finally, we used both overlapping CI inspection and the test for subgroup differences provided by the statistical software to perform a per-endoscopic modality subgroup analysis for ERR.

Ethical approval

This study was a systematic review. Ethics approval or institutional review board approval was not necessary, as the study did not involve patient consent.

Results

Study selection

The initial search produced 550 potentially relevant articles, of which 3 duplicates were removed, leaving 547 articles to be assessed. After records had been screened based on title and abstract, the full texts of 51 articles were reviewed. During this process, a total of 26 articles were excluded for not meeting the inclusion criteria, 5 after a joint discussion with senior investigators (PE and PG). These articles were assessed for overlapping cohorts, defined as the same endoscopic technique applied over the same time course, in the same hospital, and 9 additional articles were excluded. No articles were added after review of the references of the selected articles, resulting in a total of 16 articles that were included in this systematic review. The search methodology, following the PRISMA guidelines, is illustrated in Fig. 1 [9].

Characteristics of included studies

A total of 1435 patients with definite CDB were included, from 2 prospective [12,13] and 14 retrospective observational studies [14-27], of whom 1273 patients were treated endoscopically. Five of the 16 studies were multicenter, performed in 2-11 medical centers [12,17,18,21,24]. Studies were published between the years 2012 and 2022. Ten studies evaluated 1 endoscopic technique: EC in 6 studies [14,17-19,24,27], of which 1 study evaluated the over-the-scope-clip [19], EBL in 3 studies [22,25,26], and EDSL in 1 study [12]. Six studies compared 2 of the previously mentioned techniques [13,15,16,20,21,23]. The retrieved articles were mostly from Japan, with only 1 study from the United States of America [18].

The majority of patients from the included studies were male (72%), and the patients' mean age ranged from 62-77 years. Fifteen articles reported the use of antithrombotics in patients with CDB (38%) [12-25,27], while 12 articles reported the use of NSAIDs (20%) [12-15,17-21,23,25,27]. Most patients (85%) underwent PEG bowel preparation before diagnostic endoscopy. The culprit bleeding diverticulum was identified in 98% of the patients, with missing data points in the remaining 2%. CDB was found in 68% of the cases in the right colon. SRH were described in almost all included studies (14 of 16), with a detection rate of active bleeding of 48% and 44% for visible vessel or adherent clot, while the remaining 8% had missing data. The characteristics of the included studies are summarized in Table 1.

Methodological quality and risk of bias

The overall quality of the included observational studies, according to the National Heart, Lung and Blood Institute quality assessment tool, was deemed good (Supplementary Table 2) [11]. Criteria including the research question, study population definition, exposure assessment prior to outcome measurement, sufficient timeframe to see an effect, exposure measures and assessment, outcome measures, and follow-up rate were clearly defined in all 16 included studies. The criterion of uniform eligibility was not met in 1 study [14]. The participation rate was less than 50% in 2 studies [14,18]. Sample size justification was described in the 2 included prospective studies [12,13]. In view of the fact that the exposure of interest, defined as endoscopic treatment modality, is a dichotomous variable, analysis of different levels of exposure was not applicable for the totality of the studies. Similarly, an assessment of repeated exposure was not pertinent in the totality of the studies, since endoscopic treatment was performed only once. Finally, the method of hemostasis was selected according to the physicians' judgment in the 2 prospective studies [12,13], while no blinding was possible in the other retrospective studies.

Primary endpoint – overall pooled ERR

Data from 16 studies, including 1273 endoscopically treated patients for definite CDB, showed an overall pooled ERR of 14.73% (95%CI 9.33-20.14%) (Fig. 2). Visual inspection of the funnel plot did not reveal any publication bias (Supplementary Fig. 1).

Secondary endpoints

A pooled ERR was calculated for the different endoscopic modalities, regrouping EDSL and EBL in

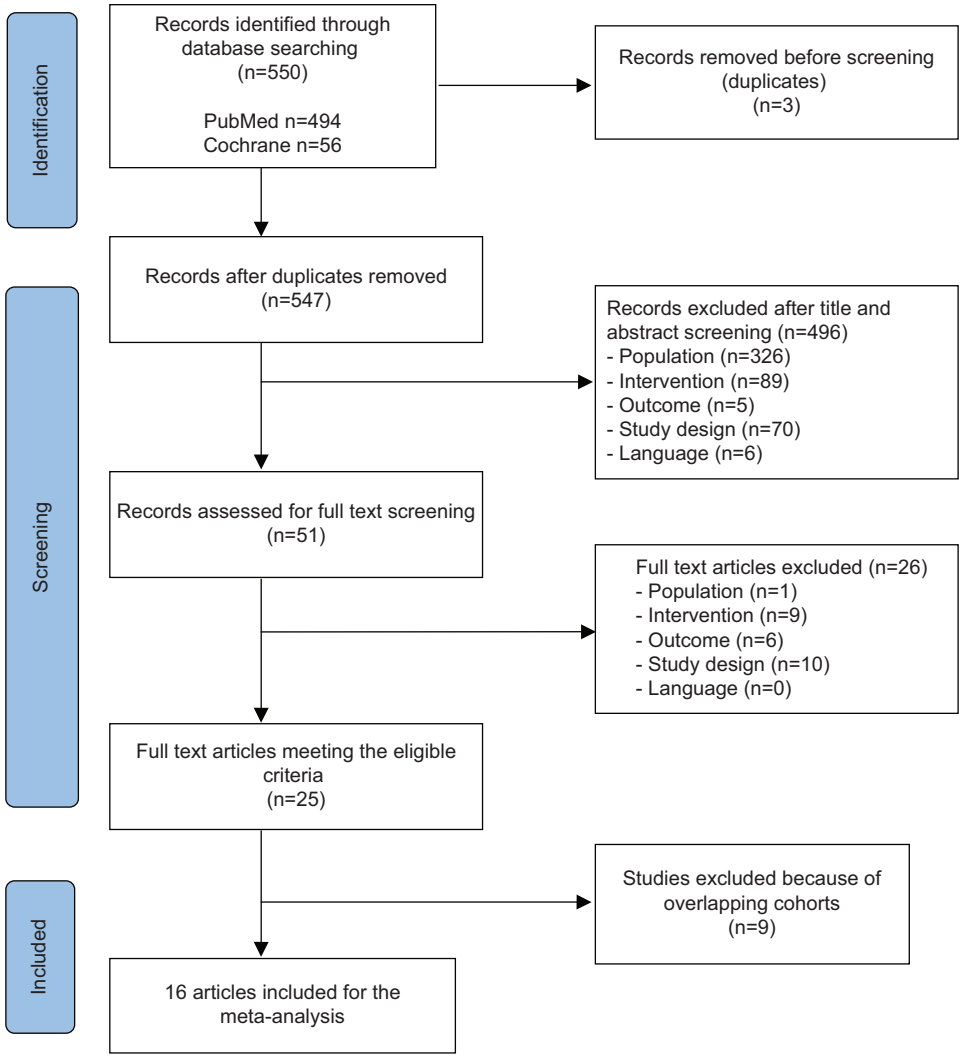


Figure 1 PRISMA flow diagram: flowchart of literature search

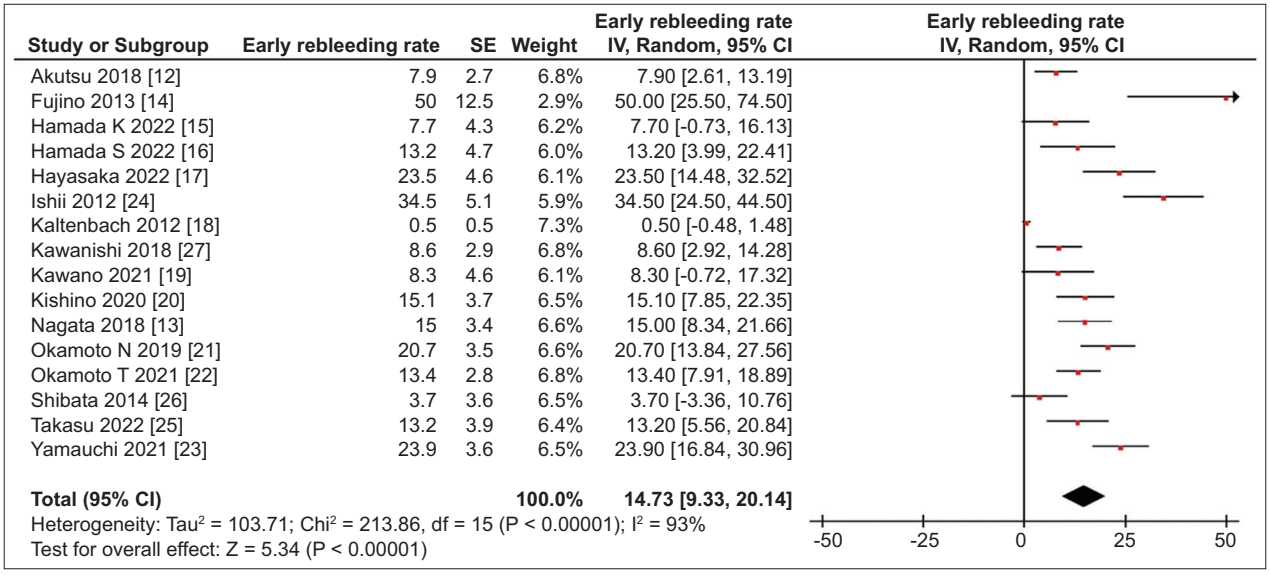


Figure 2 Overall early rebleeding rate
SE, standard error; CI, confidence interval

Table 1 Demographics of included patients

Authors [ref.]	Year	Study Design	Country	Patients with definite CDB (N)	Treatment modality	Male N (%)	Age (years)	Use of oral antithrombotics N (%)	Use of NSAIDs N (%)	Past history of CDB N (%)	PEG Bowel preparation N (%)	Location of CDB R (%)	L (%)	SRH AB N (%)	SRH VV/AC N (%)
Akutsu *et al* [12]	2018	Prospective multicenter (11)	Japan	123	EDSL	99 (80)	Mean 68±12	42 (34)	9 (7)	66 (54)	68 (55)	91 (74)	32 (26)	69 (56)	54 (44)
Fujino *et al* [14]	2013	Retrospective single-center	Japan	90	EC	60 (67)	Mean 65±15	26 (29)	18 (20)	28 (31)	74 (82)	50 (56)	37 (41)	16 (18)	NR
Hamada *et al* [15]	2022	Retrospective single-center	Japan	18	EBL	13 (72)	Median 77 (50-87)	10 (56)	0 (0)	2 (11)	14 (78)	8 (44)	10 (56)	16 (89)	2 (11)
Hamada *et al* [15]	2022	Retrospective single-center	Japan	21	EDSL	17 (81)	Median 72 (38-86)	12 (57)	3 (14)	8 (38)	18 (86)	15 (71)	6 (29)	19 (90)	2 (10)
Hamada *et al* [16]	2022	Retrospective single-center	Japan	35	Epi+EC	22 (63)	Mean 77±9	23 (66)	NR	NR	NR	20 (57)	15 (43)	35 (100)	0 (0)
Hamada *et al* [16]	2022	Retrospective single-center	Japan	18	EC	14 (78)	Mean 69±10	7 (39)	NR	NR	NR	16 (89)	2 (11)	18 (100)	0 (0)
Hayasaka *et al* [17]	2022	Retrospective multicenter (2)	Japan	85	EC	66 (78)	Median 72 (62-80)	20 (24)	30 (35)	28 (33)	68 (80)	59 (69)	26 (31)	59 (69)	26 (31)
Kaltenbach *et al* [18]	2012	Retrospective multicenter (2)	USA	64	EC	61 (95)	Mean 66±11	19 (30)	49 (77)	23 (36)	64 (100)	37 (58)	27 (42)	12 (19)	12 (19)
Kawano *et al* [19]	2021	Retrospective single-center	Japan	36	OTSC	25 (69)	Median 78 (61-97)	14 (39)	6 (17)	NR	19 (42)	24 (67)	12 (33)	21 (58)	15 (42)
Kishino *et al* [20]	2020	Retrospective single-center	Japan	31	EBL	15 (54)	Median 72 (67-87)	17 (55)	14 (45)	18 (58)	31 (100)	21 (68)	10 (32)	21 (68)	10 (32)
Kishino *et al* [20]	2020	Retrospective single-center	Japan	62	EC	36 (58)	Median 76 (66-83)	17 (27)	16 (26)	29 (47)	62 (100)	48 (77)	14 (23)	35 (56)	27 (44)
Nagata *et al* [13]	2018	Prospective single-center	Japan	61	EBL	36 (59)	Mean 71±13	37 (61)	13 (21)	32 (53)	61 (100)	36 (59)	25 (41)	26 (43)	35 (57)
Nagata *et al* [13]	2018	Prospective single-center	Japan	47	EC	29 (62)	Mean 72±9	22 (47)	11 (23)	23 (49)	47 (100)	34 (72)	13 (28)	25 (53)	22 (47)
Okamoto *et al* [21]	2019	Retrospective multicenter (7)	Japan	67	EBL	48 (72)	Median 72 (63-81)	26 (38)	2 (3)	0 (0)	67 (100)	45 (67)	22 (33)	NR	NR
Okamoto *et al* [21]	2019	Retrospective multicenter (7)	Japan	68	EC	30 (44)	Median 73 (64-86)	32 (47)	0 (0)	0 (0)	68 (100)	35 (51)	33 (49)	NR	NR
Okamoto *et al* [22]	2021	Retrospective single-center	Japan	153	EBL	118 (77)	Median 70 (53-85)	45 (29)	NR	NR	153 (100)	117 (76)	36 (24)	43 (28)	109 (72)

(*Contd...*)

Table 1 (*Continued*)

Authors [ref.]	Year	Study Design	Country	Patients with definite CDB (N)	Treatment modality	Male N (%)	Age (years)	Use of oral antithrombotics N (%)	Use of NSAIDs N (%)	Past history of CDB N (%)	PEG Bowel preparation N (%)	Location of CDB R (%)	L (%)	SRH AB N (%)	SRH VV/AC N (%)
Yamauchi *et al* [23]	2021	Retrospective single-center	Japan	45	EC	36 (80)	Median 75 (30-93)	25 (56)	4 (9)	NR	23 (51)	28 (62)	17 (38)	23 (51)	22 (49)
Yamauchi *et al* [23]	2021	Retrospective single-center	Japan	97	EBL	82 (85)	Median 75 (30-93)	55 (57)	10 (10)	NR	56 (58)	77 (79)	20 (21)	63 (65)	34 (35)
Ishii *et al* [24]	2012	Retrospective multicenter (2)	Japan	89	EC	61 (69)	Mean 63±14	25 (28)	NR	NR	89 (100)	63 (71)	26 (29)	41 (46)	48 (54)
Takasu *et al* [25]	2022	Retrospective single-center	Japan	79	EBL	62 (78)	Median 70 (57-84)	28 (35)	4 (5)	NR	64 (81)	59 (75)	20 (25)	31 (39)	48 (61)
Shibata *et al* [26]	2014	Retrospective single-center	Japan	53	EBL	34 (64)	Median 74 (43-88)	NR	NR	NR	37 (70)	19 (36)	8 (15)	13 (25)	14 (26)
Kawanishi *et al* [27]	2018	Retrospective single-center	Japan	93	EC	72 (77)	Median 66 (35-94)	25 (27)	23 (25)	NR	NR	69 (74)	24 (26)	38 (41)	55 (59)

CDB, colonic diverticular bleeding; NSAIDs, non-steroidal anti-inflammatory drugs; PEG, polyethylene glycol; R, right; L, left; SRH, stigmata of recent hemorrhage; AB, active bleeding; VV, visible vessel; AC, adherent clot

1 group [12,13,15,20-23,25,26] and EC in the other group [13-21,23,24,27]. The pooled ERRs were 9.83% (95%CI 7.41-12.26%) in the EBL/EDSL group, and 22.32% (95%CI 12.48-32.16%) in the EC group. The test for subgroup differences showed that ERR was significantly lower in the endoscopic ligation group compared to clipping (P=0.02) (Fig. 3). No publication bias was detected (Supplementary Fig. 2).

A subgroup analysis of 5 studies was performed, comparing direct vs. indirect clipping [13,16,17,20,23]. A total of 21 of 226 patients treated with direct clipping experienced early rebleeding, vs. 47 of 272 patients treated with indirect clipping. The pooled ERRs were 12.04% (95%CI 3.06-21.02%) vs. 27.74% (95%CI 18.34-37.14%) in the direct and indirect clipping groups, respectively. This difference was statistically significant (P=0.02; Fig. 4). The measured effect favors direct over indirect clipping as a means to reduce early rebleeding episodes (OR 0.45, 95%CI 0.24-0.85; P=0.01), with almost no heterogeneity (I^2=5%; Fig. 5). Visual inspection did not reveal any publication bias (Supplementary Fig. 3, 4).

Need for surgery or TAE

TAE was performed in 1 of the 655 patients treated with EBL [20], whereas a need for TAE or surgery was described in 26 of the 525 patients in the EC group [16-18,20,24].

Adverse events

In our study, few adverse events were noted. These included 5 cases of diverticulitis among 655 patients treated with EBL/EDSL [12,13,22]. Only 1 case of perforation was reported among the 618 patients in the EC group [16].

Discussion

In this systematic review and meta-analysis, we evaluated the ERR of definite CDB, both overall and according to the different endoscopic techniques used to achieve hemostasis. Analysis of data from 1273 patients with definite CDB in 16 individual studies showed an overall ERR of 14.73%, regardless of the endoscopic modality used for treatment. Moreover, our results showed a statistically significant advantage of EBL/EDSL over EC in terms of ERR. A subgroup analysis of the EC category (direct vs. indirect clipping) showed significantly lower ERRs for the direct clipping group, suggesting that indirect clipping might be contributing to the higher ERRs in the EC group compared to EBL/EDSL.

According to existing data in the literature, the different endoscopic techniques discussed above have both strengths and limitations. EBL and EDSL are the primary endoscopic ligation techniques studied for achieving hemostasis in CDB. Both methods are comparable as regards their technique for obliteration of the underlying bleeding vessel by mechanical

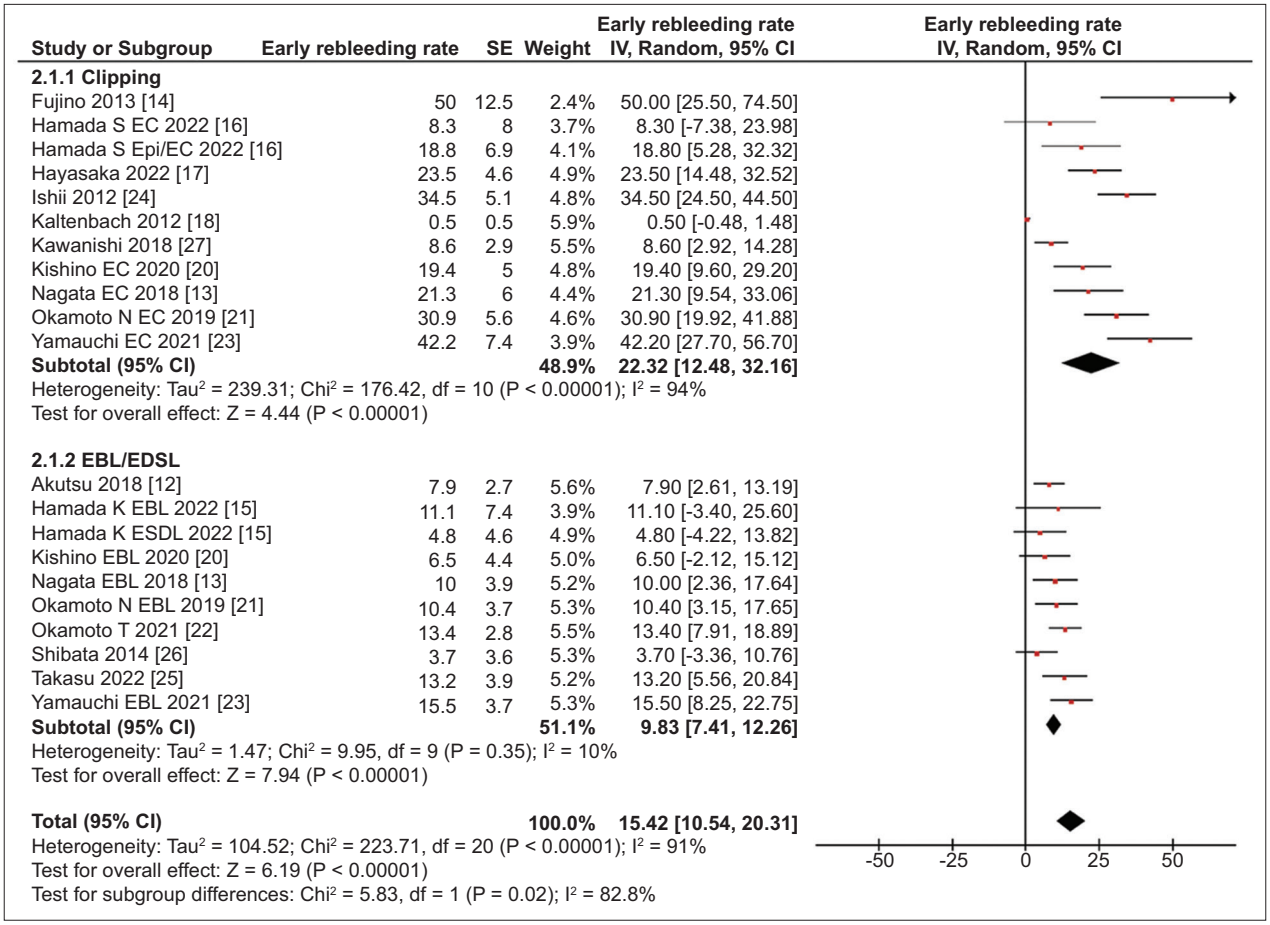


Figure 3 Early rebleeding rate per modality of endoscopic treatment
SE, standard error; CI, confidence interval

compression. EBL seems to be an effective technique to treat CDB, with a successful hemostasis rate of 99% and relatively low ERRs of 9% reported in the literature, comparable to the results found in our analysis (9.83%) [28]. However, the need for scope re-insertion makes this technique more time-consuming, making EBL a less attractive choice of therapy, particularly for right-sided CDB, or in elderly patients with comorbidities [3]. Moreover, with an O-ring attached to the endoscope tip, the field of view is narrowed, and finding the binding site is considered more difficult with EBL compared to other modalities [15].

Simple to execute, EDSL has the advantage of not needing a ligation device or re-insertion of the scope. Besides, the transparent hood used in EDSL keeps the field of view relatively wide [15]. However, EDSL remains a recent technique, insufficiently studied for the treatment of CDB. In this systematic review, only 2 studies used EDSL [12,15], compared to 8 studies using EBL as a hemostatic technique [13,15,20-23,25,26].

EBL and EDSL present similar efficacy in achieving hemostasis, as well as comparable ERRs at 30 days [15]. For the reasons mentioned above, we decided to combine the 2 techniques for the subgroup analysis. Further studies investigating EDSL in the treatment of CDB are needed to support the existing data in the literature.

On the other hand, EC is a commonly used treatment modality for CDB, given its simplicity and low invasiveness, providing a high technical success rate of 96% [28]. However, hemostasis may be difficult to achieve, particularly in patients with active bleeding or small diverticular orifices [28]. Clipping is largely classified into direct clipping, in which the culprit bleeding vessel is clipped directly, and indirect clipping, where the openings of the diverticula are closed. Inconsistent data are found in the literature comparing the ERRs of direct and indirect clipping. More specifically, Kobayashi *et al* and Nagata *et al* found no significant difference in the ERRs between the 2 methods [13,29], whereas Kishino *et al* showed a significantly lower ERR associated with direct clipping [10,20]. Our results align with the latter publications, showing significantly lower ERR with direct clipping compared to indirect clipping.

Although the larger over-the-scope-clip might be effective as a hemostatic method for CDB, large cohorts comparing it to the existing techniques are lacking [19]. Furthermore, as with EBL, the need for reinsertion leads to a longer examination duration, with the suction cap narrowing the field of view and making it more challenging to identify the bleeding diverticulum [19]. For the purposes of subgroup analysis, we

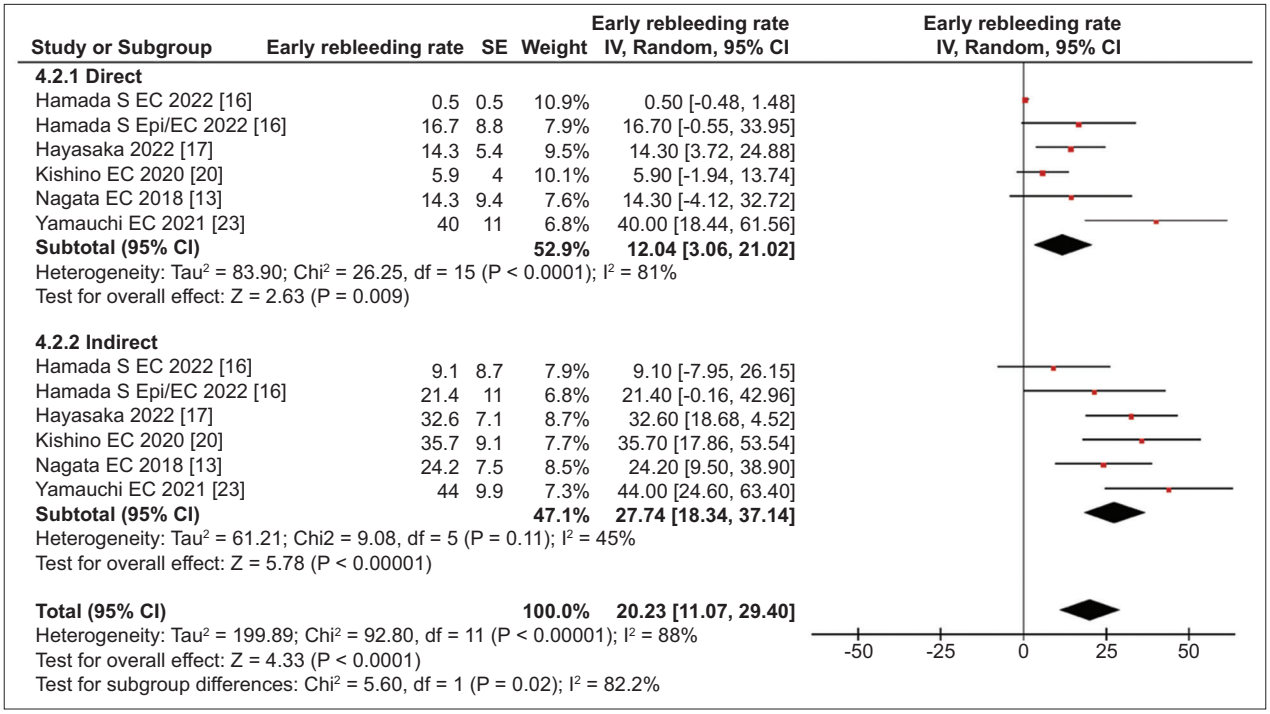


Figure 4 Early rebleeding rate per clipping type
SE, standard error; CI, confidence interval

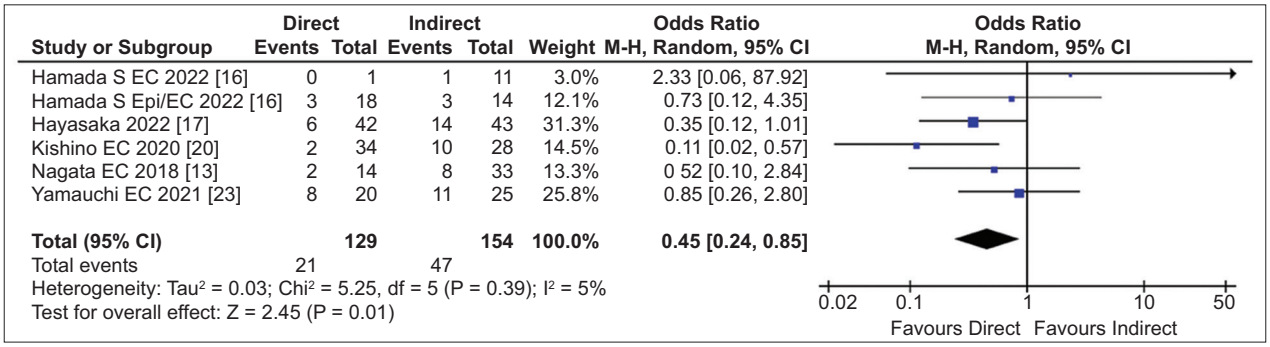


Figure 5 Probability of early rebleeding according to clipping type
SE, standard error; CI, confidence interval

opted to exclude the only study using the over-the-scope-clip for the treatment of CDB [19].

Right-sided diverticular disease (RSD) in Western countries is likely to be underestimated, with recent studies from Italy and France reporting a prevalence of RSD reaching 35% [30]. According to the literature, RSD increases the risk of CDB significantly, with more than two thirds of diverticular bleeding occurring proximal to the splenic flexure [31,32]. This has been attributed to the wider necks and domes of the right-sided diverticula, leaving a greater length of the *vasa recta* exposed to injury [32]. In our analysis, including predominantly Japanese patients, the culprit diverticulum responsible for the CDB was identified on the right side of the colon in 68% of the patients.

The strength of our analysis is the guarantee of reproducibility by using a predefined registered protocol. Although recently published large multicenter cohort studies [10,28,33] comparing the ERRs among the different endoscopic modalities were not included in our analysis because of overlapping cohorts, we evaluated data from 16 articles, including 1273 patients endoscopically treated for CDB, making it the largest systematic review and meta-analysis to date. In addition, previously published systematic reviews did not compare ERR according to clipping type.

We acknowledge some limitations in our study. High levels of heterogeneity were present among the different included studies. This may be attributed to the different sample sizes, population demographics, study designs and follow-up protocols used. Moreover, the included studies (except 1) were mostly from Japan, creating a sampling bias for the Asian

population, and limiting the generalizability of the results. Furthermore, EBL and EDSL were not analyzed separately.

To conclude, results from our analysis favor the superiority of EBL/EDSL and direct clipping over indirect clipping in the endoscopic management of CDB, since these modalities were associated with significantly lower rates of early rebleeding. It needs to be determined whether these data can be extrapolated to right-sided diverticular bleeding in Western countries.

Summary Box

What is already known:

- Most colonic diverticular bleeding (CDB) cases resolve spontaneously; some require intervention to achieve hemostasis
- Endoscopic treatment is an effective first-line treatment for CDB, with fewer complications than transarterial embolization or surgery
- In the absence of randomized controlled trials, there are inconsistent data regarding which endoscopic modality achieves the lowest early rebleeding rate (ERR)

What the new findings are:

- The overall pooled ERR after endoscopic treatment for CDB is 14.73%
- Endoscopic ligation techniques have significantly lower ERRs compared to endoscopic clipping (9.83% vs. 22.32%)
- Compared to direct clipping, indirect clipping shows a 55% higher risk of ERR, implying the need to favor direct over indirect clipping when possible

References

1. Adegboyega T, Rivadeneira D. Lower GI bleeding: an update on incidences and causes. *Clin Colon Rectal Surg* 2020;**33**:28-34.
2. Oakland K, Guy R, Uberoi R, et al. Acute lower GI bleeding in the UK: patient characteristics, interventions and outcomes in the first nationwide audit. *Gut* 2018;**67**:654-662.
3. Akutsu D, Narasaka T, Wakayama M, et al. Endoscopic detachable snare ligation: a new treatment method for colonic diverticular hemorrhage. *Endoscopy* 2015;**47**:1039-1042.
4. Oakland K, Chadwick G, East JE, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. *Gut* 2019;**68**:776-789.
5. Mizuki A, Tatemichi M, Nagata H. Management of diverticular hemorrhage: catching that culprit diverticulum red-handed! *Inflamm Intest Dis* 2018;**3**:100-106.
6. Yamada A, Niikura R, Yoshida S, et al. Endoscopic management of colonic diverticular bleeding. *Dig Endosc* 2015;**27**:720-725.
7. Cirocchi R, Grassi V, Cavaliere D, et al. New trends in acute management of colonic diverticular bleeding: a systematic review. *Medicine (Baltimore)* 2015;**94**:e1710.
8. Nagata N, Niikura R, Ishii N, et al. Cumulative evidence for reducing recurrence of colonic diverticular bleeding using endoscopic clipping versus band ligation: systematic review and meta-analysis. *J Gastroenterol Hepatol* 2021;**36**:1738-1743.
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71.
10. Kishino T, Nagata N, Kobayashi K, et al. Endoscopic direct clipping versus indirect clipping for colonic diverticular bleeding: A large multicenter cohort study. *United European Gastroenterol J* 2022;**10**:93-103.
11. National Heart, Lung, and Blood Institute (NHLBI). Study Quality Assessment Tools [Internet]. Bethesda (MD): NIH; [cited 2024 Apr 6]. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools [Accessed 3 January 2025].
12. Akutsu D, Narasaka T, Kobayashi K, et al. Newly developed endoscopic detachable snare ligation therapy for colonic diverticular hemorrhage: a multicenter phase II trial (with videos). *Gastrointest Endosc* 2018;**88**:370-377.
13. Nagata N, Ishii N, Kaise M, et al. Long-term recurrent bleeding risk after endoscopic therapy for definitive colonic diverticular bleeding: band ligation versus clipping. Gastrointest Endosc 2018;**88**:841-853.
14. Fujino Y, Inoue Y, Onodera M, et al. Risk factors for early re-bleeding and associated hospitalization in patients with colonic diverticular bleeding. *Colorectal Dis* 2013;**15**:982-986.
15. Hamada K, Kawano K, Nishida S, et al. Endoscopic detachable snare ligation therapy for colonic diverticular hemorrhage improves procedure time compared to endoscopic band ligation. *Turk J Gastroenterol* 2022;**33**:443-448.
16. Hamada S, Teramoto A, Zukeyama R, et al. Efficacy of combination therapy with epinephrine local injection and hemostatic clips on active diverticular bleeding. *J Clin Med* 2022;**11:** 5195.
17. Hayasaka J, Kikuchi D, Odagiri H, et al. Effectiveness of clipping for definitive colonic diverticular bleeding in preventing early recurrent bleeding. *Intern Med* 2022;**61**:451-460.
18. Kaltenbach T, Watson R, Shah J, et al. Colonoscopy with clipping is useful in the diagnosis and treatment of diverticular bleeding. *Clin Gastroenterol Hepatol* 2012;**10**:131-137.
19. Kawano K, Takenaka M, Kawano R, et al. Efficacy of over-the-scope clip method as a novel hemostatic therapy for colonic diverticular bleeding. *J Clin Med* 2021;**10**:2891.
20. Kishino T, Kanemasa K, Kitamura Y, Fukumoto K, Okamoto N, Shimokobe H. Usefulness of direct clipping for the bleeding source of colonic diverticular hemorrhage (with videos). *Endosc Int Open* 2020;**8**:E377-E385.
21. Okamoto N, Tominaga N, Sakata Y, et al. Lower rebleeding rate after endoscopic band ligation than endoscopic clipping of the same colonic diverticular hemorrhagic lesion: a historical multicenter trial in Saga, Japan. *Intern Med* 2019;**58**:633-638.
22. Okamoto T, Nakamura K, Yamamoto K, et al. Safety and effectiveness of endoscopic band ligation for colonic diverticular bleeding in elderly patients. *Digestion* 2021;**102**:760-766.
23. Yamauchi A, Kou T, Kishimoto T, et al. Risk factor analysis for early rebleeding after endoscopic treatment for colonic diverticular bleeding with stigmata of recent hemorrhage. *JGH Open* 2021;**5**:573-579.
24. Ishii N, Hirata N, Omata F, et al. Location in the ascending colon is a predictor of refractory colonic diverticular hemorrhage after endoscopic clipping. *Gastrointest Endosc* 2012;**76**:1175-1181.
25. Takasu A, Ikeya T, Shiratori Y. Comparison of conventional and new endoscopic band ligation devices for colonic diverticular bleeding. *Clin Endosc* 2022;**55**:408-416.
26. Shibata S, Shigeno T, Fujimori K, Kanai K, Yoshizawa K. Colonic diverticular hemorrhage: the hood method for detecting responsible diverticula and endoscopic band ligation for

hemostasis. *Endoscopy* 2014;**46**:66-69.
27. Kawanishi K, Kato J, Kakimoto T, et al. Risk of colonic diverticular rebleeding according to endoscopic appearance. *Endosc Int Open* 2018;**6**:E36-E42.
28. Kobayashi K, Nagata N, Furumoto Y, et al; CODE BLUE-J study collaborators. Effectiveness and adverse events of endoscopic clipping versus band ligation for colonic diverticular hemorrhage: a large-scale multicenter cohort study. *Endoscopy* 2022;**54**:735-744.
29. Kobayashi K, Furumoto Y, Akutsu D, et al. Endoscopic detachable snare ligation improves the treatment for colonic diverticular hemorrhage. *Digestion* 2020;**101**:208-216.
30. Turner GA, O'Grady MJ, Purcell RV, Frizelle FA. The epidemiology and etiology of right-sided colonic diverticulosis: a review. *Ann Coloproctol* 2021;**37**:196-203.
31. Imaeda H, Hibi T. The burden of diverticular disease and its complications: west versus east. *Inflamm Intest Dis* 2018;**3**:61-68.
32. Mohammed Ilyas MI, Szilagy EJ. Management of diverticular bleeding: evaluation, stabilization, intervention, and recurrence of bleeding and indications for resection after control of bleeding. *Clin Colon Rectal Surg* 2018;**31**:243-250.
33. Yamauchi A, Ishii N, Yamada A, et al. Outcomes and recurrent bleeding risks of detachable snare and band ligation for colonic diverticular bleeding: a multicenter retrospective cohort study. *Gastrointest Endosc* 2023;**98**:59-72.

Supplementary material

Supplementary Table 1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	p. 1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 5
Objectives	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	p. 5
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p. 7
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool (s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 8
Effect measures	12	Specify for each outcome the effect measure (s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p. 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 7-9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 8-9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice (s). If meta-analysis was performed, describe the model (s), method (s) to identify the presence and extent of statistical heterogeneity, and software package (s) used.	p. 8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 8-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 8-9

(*Contd...*)

Supplementary Table 1 (*Continued*)

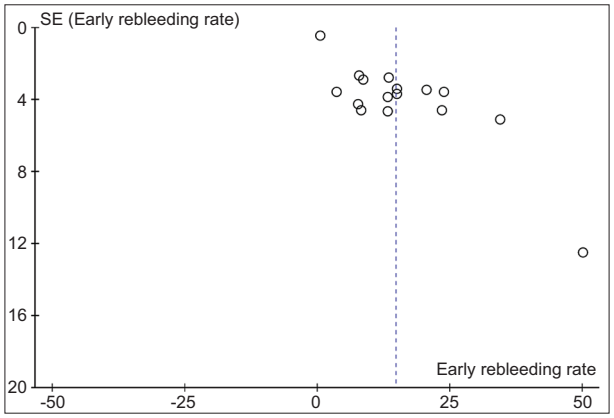
Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NR
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p. 8-9
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p. 9-10
Study characteristics	17	Cite each included study and present its characteristics.	p. 9-10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 10-11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NR
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p. 10-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p. 25-28
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NR
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NR
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NR
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p. 25-28
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p. 12-15
	23b	Discuss any limitations of the evidence included in the review.	p. 15
	23c	Discuss any limitations of the review processes used.	p. 15
	23d	Discuss implications of the results for practice, policy, and future research.	p. 15
		OTHER INFORMATION	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p. 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	NA
Competing interests	26	Declare any competing interests of review authors.	p. 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

NR, not reported; NA, not applicable

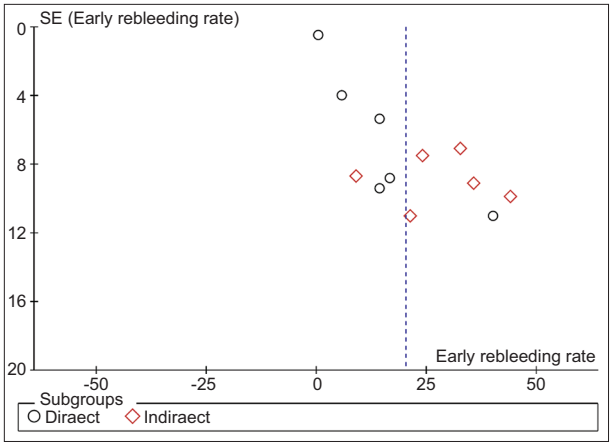
Supplementary Table 2 National Heart, Lung, Blood Institution risk of bias and quality assessment tool

Authors [ref.]	Research question	Study population	Participation rate >50%	Uniformity of eligibility criteria	Sample size justification	Exposure assessed prior to outcome measurement	Sufficient time frame to see effect	Different levels of the exposure of interest	Exposure measures and assessment	Repeated exposure assessment	Outcome measures	Blinding of outcome assessors	Follow-up rate	Statistical analysis
Akutsu *et al* [12]	1	1	1	1	1	1	1	NA	1	NA	1	0	1	1
Fujino *et al* [14]	1	1	0	0	0	1	1	NA	1	NA	1	NA	1	1
Hamada *et al* [15]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	1
Hamada *et al* [16]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	0
Hayasaka *et al* [17]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	1
Kaltenbach *et al* [18]	1	1	0	1	0	1	1	NA	1	NA	1	NA	1	0
Kawano *et al* [19]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	0
Kishino *et al* [20]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	1
Nagata *et al* [13]	1	1	1	1	1	1	1	NA	1	NA	1	0	1	1
Okamoto *et al* [21]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	1
Okamoto *et al* [22]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	1
Yamauchi *et al* [23]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	1
Ishii *et al* [24]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	0
Takasu *et al* [25]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	0
Shibata *et al* [26]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	0
Kawanishi *et al* [27]	1	1	1	1	0	1	1	NA	1	NA	1	NA	1	1

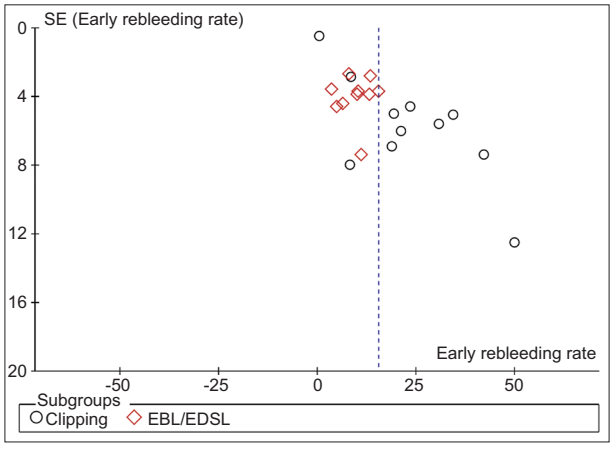
NA, not applicable



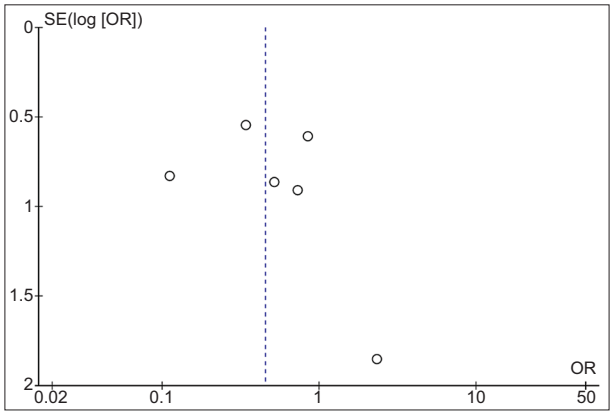
Supplementary Figure 1 Overall early rebleeding rate
SE, standard error



Supplementary Figure 3 Early rebleeding rate per clipping type
SE, standard error



Supplementary Figure 2 Early rebleeding rate per modality of endoscopic treatment
SE, standard error



Supplementary Figure 4 Probability of early rebleeding according to clipping type
SE, standard error; OR, odds ratio