Clip closure to prevent adverse events after EMR of proximal large nonpedunculated colorectal polyps: meta-analysis of individual patient data from randomized controlled trials

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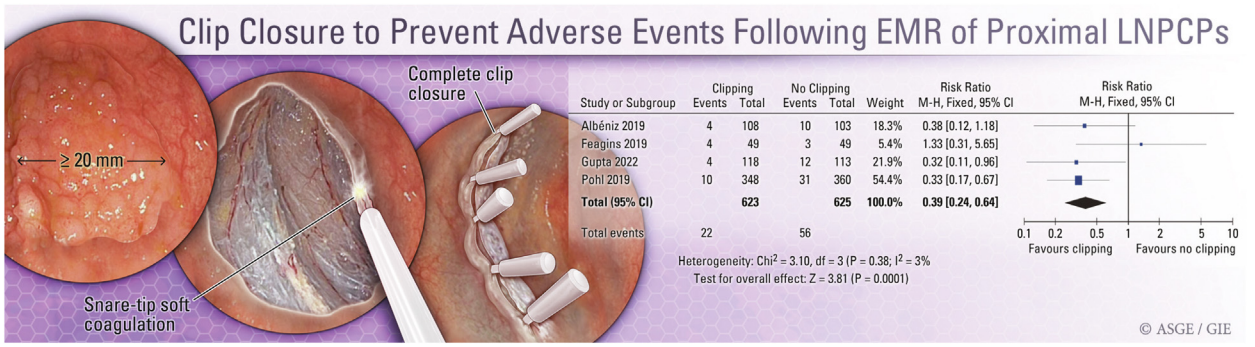
GRAPHICAL ABSTRACT



Background and Aims: After EMR, prophylactic clipping is often performed to prevent clinically significant post-EMR bleeding (CSPEB) and other adverse events (AEs). Prior evidence syntheses have lacked sufficient power to assess clipping in relevant subgroups or in nonbleeding AEs. We performed a meta-analysis of individual patient data (IPD) from randomized trials assessing the efficacy of clipping to prevent AEs after EMR of proximal large nonpedunculated colorectal polyps (LNPCPs) ≥20 mm.

Methods: We searched EMBASE, MEDLINE, Cochrane Central Registry of Controlled Trials, and PubMed from inception to May 19, 2021. Two reviewers screened citations in duplicate. Corresponding authors of eligible studies were invited to contribute IPD. A random-effects 1-stage model was specified for estimating pooled effects, adjusting for patient sex and age and for lesion location and size, whereas a fixed-effects model was used for traditional meta-analyses.

Results: From 3145 citations, 4 trials were included, representing 1248 patients with proximal LNPCPs. The overall rate of CSPEB was 3.5% and 9.0% in clipped and unclipped patients, respectively. IPD were available for 1150 patients, in which prophylactic clipping prevented CSPEB with an odds ratio (OR) of .31 (95% confidence interval [CI], .17-.54). Clipping was not associated with perforation or abdominal pain, with ORs of .78 (95% CI, .17-3.54) and .67 (95% CI, .20-2.22), respectively.

Conclusions: Prophylactic clipping is efficacious in preventing CSPEB after EMR of proximal LNPCPs. Therefore, clip closure should be considered a standard component of EMR of LNPCPs in the proximal colon. (Gastrointest Endosc 2022;96:721-31.)

(footnotes appear on last page of article)

EMR is efficacious in the management of large (≥20 mm) nonpedunculated colorectal polyps (LNPCPs),[1] with a superior cost and safety profile compared with surgical resection.[2-4] Although recent advances have undoubtedly helped mitigate the risk of both technical failure and adverse events (AEs) associated with this technique,[5,6] the performance of EMR is nevertheless associated with significant AEs. Among these, the most common is clinically significant post-EMR bleeding (CSPEB), occurring in over 7% of EMR cases performed for LNPCPs[1,7-9] and frequently resulting in unplanned healthcare utilization (UHU) with subsequent transfusion, endoscopic re-evaluation, and/or radiologic intervention.[7,10] Other AEs associated with EMR include perforation and postpolypectomy syndrome (PPS), each occurring in approximately 1% to 2% of cases.[1,11-13]

Several patient- and lesion-related parameters have been shown to independently increase the risk of AEs after EMR, including CSPEB and perforation. These include larger lesion size, with especially high risk for lesions ≥40 mm,[9,14-16] and proximal location within the colon.[7-9,16-18] Higher rates of CSPEB have also been associated with the use of antiplatelet and anticoagulant agents, even when these agents are appropriately managed periprocedurally,[15,19] as has the occurrence of intraprocedural bleeding.[20,22]

Several methods have been studied that strive to mitigate the risk of delayed AEs such as CSPEB and delayed perforation. Among the most investigated are endoscopic clips, which can be used prophylactically to close post-EMR defects (Fig. 1). Prior evidence syntheses have assessed both the efficacy and effectiveness of prophylactic clip closure on postpolypectomy defects of all sizes and locations in the colon, with conflicting results between observational studies and randomized trials.[21-23] It is, however, clear that low-risk lesions (eg, small lesions in the left side of the colon) do not benefit from routine prophylactic clip closure. No reviews to date have focused exclusively on EMR performed on LNPCPs in the proximal colon, which is known to carry the highest risk of CSPEB. This is primarily because few well-designed studies have specifically assessed this population in depth, instead assessing fairly heterogeneous populations of patients, polypectomy techniques, and polyp characteristics. Furthermore, existing reviews have lacked sufficient power to assess the efficacy of clipping within clinically relevant subgroups or in the prevention of nonbleeding events. Given the recent publication of several seminal studies assessing the efficacy of clipping in patients having undergone EMR on proximal LNPCPs,[18,24-26] we performed a systematic review and individual patient data (IPD) meta-analysis assessing the efficacy of prophylactic clipping in the prevention of all AEs after EMR of proximal LNPCPs.

METHODS

Overview

We performed a systematic review and meta-analysis complying with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting standards[27] and an IPD meta-analysis according to contemporary guidance including the PRISMA-IPD reporting standards.[28,29] Our review was registered with International Prospective Register of Systematic Reviews (registration no. CRD42021252934). Our primary objective was to assess the efficacy of prophylactic endoscopic clipping in preventing CSPEB after EMR of proximal LNPCPs. Our secondary objective was to assess the efficacy of prophylactic endoscopic clipping in preventing any AEs after EMR of proximal LNPCPs. Further secondary objectives were to determine whether the efficacy of prophylactic clipping on AEs differs among clinically relevant study-, patient-, and lesion-related subgroups.

Search strategy and study selection

An electronic search was performed of MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials, and PubMed, with the full search provided in Supplementary Tables 1-3, available online at wwwgiejournal.org. The search was executed from inception of the databases until May 19, 2021. Our search terms were also applied to clinical trials registries, and experts from the field were consulted to advise on ongoing studies. Two reviewers (N.F., L.F.) performed title and abstract screens of identified entries in parallel to identify potentially eligible citations. Any conflicts were resolved by consensus.

Eligibility criteria

A study was included in the final analysis if it met all following inclusion criteria: it was a randomized controlled trial (RCT), included adult patients undergoing colonoscopy with EMR of LNPCPs ≥20 mm in the proximal colon (defined as a location in or more proximal to the mid-transverse colon), compared patients having received attempted prophylactic clip closure versus no clip closure, and reported on ≥1 of the following post-EMR AEs: CSPEB, perforation, PPS, abdominal pain, or fever. A study was excluded if it lacked a control group, the control group underwent another form of prophylaxis or hemostasis (as opposed to an absence of attempted clip closure), or it reported on clip closure after endoscopic submucosal dissection.

Data extraction and study quality

After determination of the inclusion of eligible studies, all corresponding and/or senior authors from those studies were invited to join the core study team as coauthors and were asked to contribute any original source trial data (including IPD) in a deidentified and unabridged format. All

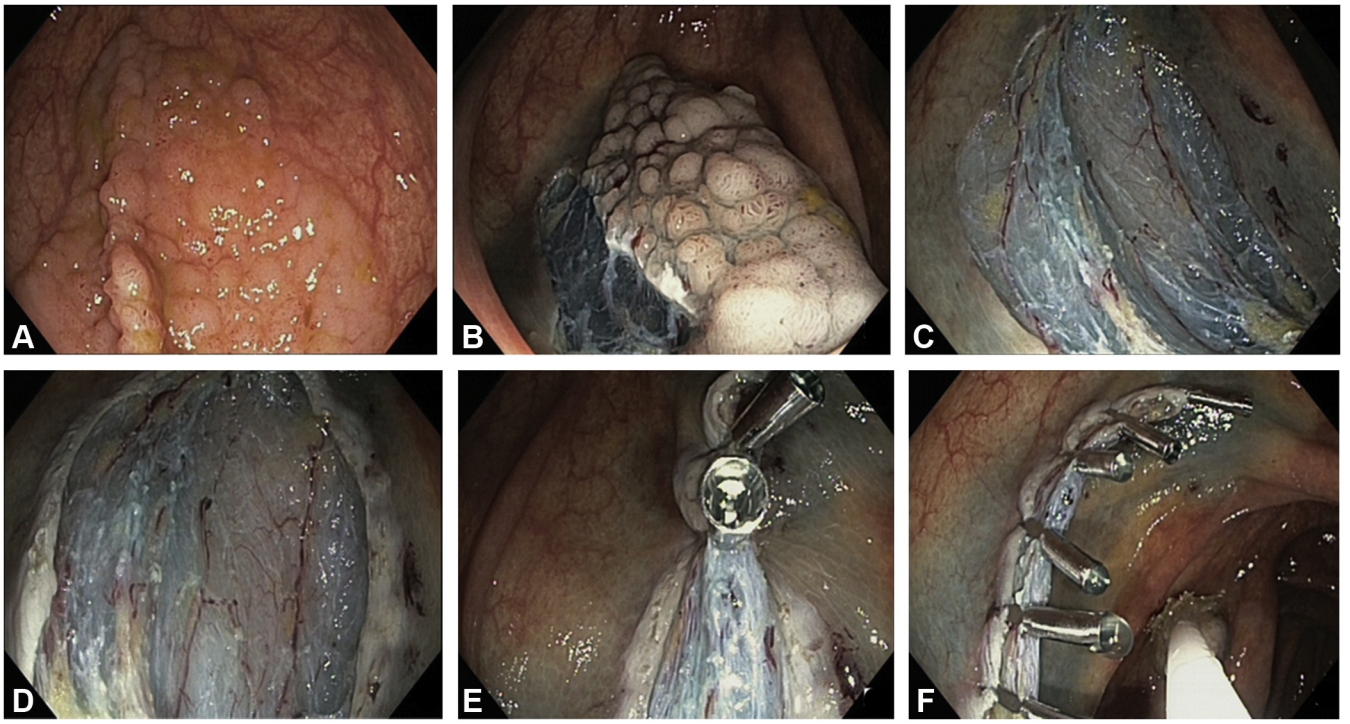


Figure 1. Clip closure after EMR of a large nonpedunculated colorectal polyp (LNPCP). **A,** LNPCP before EMR. **B,** LNPCP during EMR. **C,** Post-EMR defect. **D,** Snare-tip soft coagulation to the post-EMR defect margin. **E,** Clip closure. **F,** Complete clip closure of the post-EMR defect and retrieval of the specimen.

available IPD with originally collected study variables from the source trials were then collated. A comprehensive data extraction form was designed to extract data from all included studies for all outcomes and all subgroups (described below). Two reviewers (N.F., L.F.) performed data extraction and assessments of bias in parallel. Study quality was assessed using the Cochrane Risk of Bias Tool for randomized trials, v2,[30] and overall assessments of the certainty of the evidence base were performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[31] Inter-reviewer discrepancies in risk of bias assessments were resolved by consensus.

Outcomes

The primary outcome was CSPEB, defined as hematochezia or melena resulting in hospitalization, repeat endoscopic, surgical or radiologic intervention, or a drop in hemoglobin of ≥2 g occurring within 14 days of EMR.[32,33] Secondary outcomes were perforation or PPS within 14 days as well as abdominal pain or fever resulting in UHU within 14 days.

Statistical analysis

Crude rates were calculated for all outcomes in clipping and nonclipping groups by considering the numbers of events and total cases reported according to intention-to-treat approaches in each study. The efficacy of prophylactic clip closure (compared with no clip closure) was estimated using an odds ratio (OR) calculated from IPD from RCTs. A random-effects 1-stage model was specified for estimating pooled effects, adjusting for participants' sex, age, and antiplatelet and anticoagulation status in addition to lesion location and size.[34] For traditional meta-analyses, the efficacy of prophylactic clip closure (compared with no clip closure) was estimated using relative risk (RR) calculated from pooled data from RCTs and was presented in forest plots with 95% confidence intervals (CIs). A fixed-effects model was used to perform meta-analyses in anticipation of the ability to conclude a similar effect of clipping across studies.[30] The I^2 statistic was used to calculate and report heterogeneity. Publication bias was assessed by visual inspection of funnel plots as well as statistical interpretation of Begg and Egger tests.[35,36] Univariable meta-regression was also performed. Analyses were performed using Review Manager 5.4 (Cochrane Collaboration, London, UK) and STATA version 16.1 (StataCorp, College Station, Tex, USA).

Subgroup and sensitivity analyses

Subgroup analyses were performed to determine whether the efficacy of clip closure varied within clinically relevant subgroups identified a priori, including women versus men, those age ≥65 versus <65 years, patients on anticoagulant medications versus not, patients on antiplatelet medications versus not, patients with an American Society of Anesthesiologists score of I to II versus III to IV,[37] lesions ≥40 mm versus <40 mm, lesions with full versus partial versus attempted but failed clip closure, lesions in the cecum versus lesions in the ascending colon or hepatic flexure

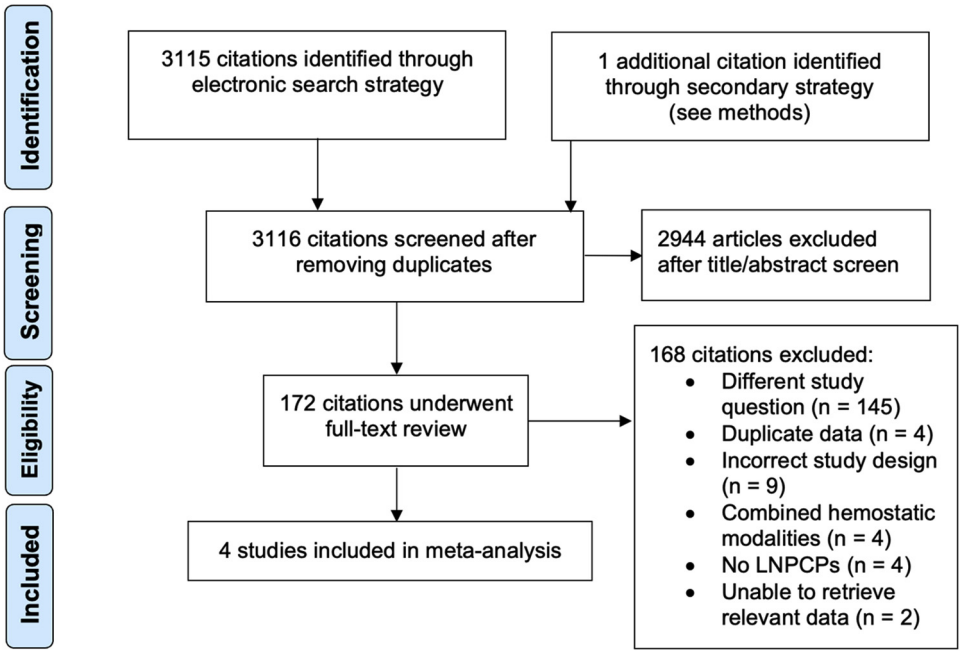


Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram summarizing identification, screening, eligibility, and final inclusion for meta-analysis. *LNPCP*, Large nonpedunculated colorectal polyp.

versus lesions in the transverse colon, lesions resected en bloc versus in a piecemeal fashion, resections during which intraprocedural bleeding was observed versus not, and serrated versus traditional adenomatous polyps as determined by expert histologic review. Meta-regression was also carried out to determine whether any of these variables were associated with the efficacy of clipping.

RESULTS

Study selection

A PRISMA flow diagram of the search results and study selection process is provided in Figure 2. The electronic search identified 3145 citations, with an additional citation identified through the secondary methods listed. Four studies were ultimately included in the meta-analysis after applying eligibility criteria.

Characteristics and quality of included studies

Baseline characteristics of the included studies are summarized in Table 1. Of 1248 EMRs included in the meta-analysis from randomized trials, 623 had prophylactic clip closure and 625 were left unclipped after resection. IPD for 1150 patients were available from 3 of the 4 included studies. Three of the 4 included studies were multicentered. The studies were well-distributed geographically, representing North America, Europe, and Oceania. The quality of all included studies were moderate to high overall according to the Cochrane Risk of Bias Tool for randomized trials, v2.[30] Study quality is summarized in Table 1, with full assessments provided in the Supplementary Tables.

AE rates

Overall and subgroup-specific AE rates are summarized in Table 2. The overall rate of CSPEB was 6.3%, with a rate of 3.5% in the clipped group and 9.0% in the unclipped group. Patients on antiplatelet medications experienced significantly higher CSPEB rates than those not on such medications (9.6% vs 4.8%, $P = .003$). Further subanalyses revealed similar mean lesion sizes of 32.6 mm, 32.9 mm, and 32.2 mm in the cecum, ascending colon or hepatic flexure, and transverse colon, respectively ($P = .80$); despite this, CSPEB occurred significantly more frequently in the cecum (9.1%) compared with the ascending colon or hepatic flexure (6.1%) or transverse colon (1.0%; $P = .001$. Even with a lesion size cutoff of ≥30 mm, bleeding rates in the cecum and ascending colon (9.7% and 7.5%) were significantly higher than in the transverse colon (.0%, $P = .008$). Full clip closure of proximal LNPCPs resulted in significantly lower bleeding rates compared with no attempted closure (2.6% vs 9.0%, $P < .001$); similarly, partial clip closure also resulted in significantly lower bleeding compared with no attempted clip closure (1.7% vs 9.0%, $P = .001$). Overall rates of perforation, PPS, fever, or abdominal pain requiring UHU were .6%, .7%, .3%, and 1.4%, respectively. Cases in which intraprocedural bleeding was observed resulted in significantly higher rates of both CSPEB (9.4% vs 5.7%, $P = .04$) and perforation (2.1% vs .3%, $P = .002$).

Efficacy of prophylactic clip closure on AEs

From IPD, prophylactic clipping prevented CSPEB with an OR of .31 (95% CI, .17-.54). From traditional meta-

TABLE 1. Summary of methodologic and patient- and lesion-related parameters in studies included in the meta-analysis

Author	Year	Country	Centers	Patients with proximal LNPCPs (clipped, unclipped)	Bleeding events (clipped, unclipped)	Median/mean no. of clips used per LNPCP (in clipping arm)	Risk of bias per Cochrane Risk of Bias Tool v2
Albéniz[24]	2019	Spain	Multiple	211 (108, 103)	14 (4, 10)	6.0	Some concerns
Feagins[25]	2019	USA	Multiple	98 (49, 49)	7 (4, 3)	1.5	Some concerns
Pohl[18]	2019	USA	Multiple	708 (348, 360)	41 (10, 31)	4.0	Low
Gupta[26]	2022	Australia	Single	231 (118, 113)	16 (4, 12)	5.0	Low
	Female patients	Patients aged ≥65 y	LNPCPs ≥40 mm	LNPCPs with full defect closure, of those attempted	LNPCPs in the cecum	LNPCPs resected en bloc	Procedures with intraprocedural bleeding observed
% (n/N)							
Albéniz[24]	32.7 (69/211)	76.3 (161/211)	47.4 (100/211)	57.4 (62/108)	28.4 (60/211)	12.3 (26/211)	16.6 (35/211)
Feagins[25]	4.1 (4/98)	59.2 (58/98)	7.1 (7/98)	55.1 (27/49)	38.8 (19/49)	53.1 (26/49)	18.4 (9/49)
Pohl[18]	41.2 (292/708)	57.6 (408/708)	20.8 (147/708)	76.7 (267/348)	31.2 (221/708)	9.7 (69/708)	14.3 (101/708)
Gupta[26]	45.0 (104/231)	70.1 (162/231)	42.9 (99/231)	58.5 (69/118)	41.6 (96/231)	7.4 (17/231)	19.9 (46/231)

LNPCP, Large nonpedunculated colorectal polyp.

analysis, prophylactic clip closure was also efficacious in preventing CSPEB, with an RR of .39 (95% CI, .24-.64) from meta-analysis of 4 studies representing 1248 proximal LNPCPs. Heterogeneity for this analysis was low at 3%, as demonstrated in the forest plot in Figure 3. In terms of absolute effects, this estimate suggests that prophylactic clip closure would result in 55 fewer cases of CSPEB per 1000 patients treated (corresponding to a number needed to treat of 18). Clipping was no more or less efficacious in the prevention of CSPEB in any clinically relevant subgroup, with these findings summarized in Table 3 for both IPD and traditional meta-analyses. The certainty of the overall estimate of efficacy based on the evidence base was high as per the GRADE framework,[31] as presented in Table 4. There was no visual or statistical evidence of publication bias (Supplementary Tables 1-3).

From IPD, clipping was not associated with perforation or abdominal pain, with ORs of .78 (95% CI, .17-3.54) and .67 (95% CI, .20-2.22), respectively. From traditional meta-analyses, clip closure also did not affect the incidences of perforation, PPS, or abdominal pain requiring UHU, with RRs of .76 (95% CI, .17-3.38), 1.26 (95% CI, .34-4.70), and 1.09 (95% CI, .42-2.78), respectively, although these analyses were limited by low event rates. The effect of clipping on these events is summarized in the forest plots in Figure 3. The certainty of these estimates based on the evidence base was low to very low as per the GRADE framework,[31] as presented in Table 4.

DISCUSSION

Our study including 4 contemporaneous and homogenous RCTs provides high-level evidence that CSPEB is prevented by clip closure of the defect after EMR of LNPCPs ≥20 mm in the proximal colon, both from IPD and using traditional meta-analysis approaches. The clinical benefits are readily tangible, with a number needed to treat of only 18 and an excellent safety profile.

CSPEB stems from the use of electrocautery during polyp transection. It is therefore rarely encountered during cold-snare polypectomy, which is now heralded as the endoscopic resection method of choice for nonpedunculated polyps <10 mm. Because EMR continues to be the cornerstone resection technique for polyps >20 mm,[38] CSPEB primarily remains a relevant AE in this subset of patients; however, early data for the efficacy and safety of cold-snare polypectomy in such lesions appear to be promising,[39] which could eventually obviate the need for prophylactic clipping. Multiple independent studies have demonstrated that the risk of CSPEB with electrocautery is greatest within the proximal colon.[7-9,16-18] Until now, meta-analyses assessing delayed bleeding have included the distal colon,[22] polyps <10 mm in size,[23] techniques such as endoscopic submucosal dissection,[22] and observational studies.[21] Therefore, unlike our study, they lacked the homogeneity and power required to evaluate the efficacy of clip closure in preventing CSPEB after EMR of LNPCPs in the proximal colon. Equally importantly, none of the prior analyses on this topic has been given access to unabridged primary trial data and therefore lacks the granularity to prove with authority that prophylactic clip closure should be standard of care after EMR of LNPCPs in the proximal colon, as contemporary guidelines from the American Society for Gastrointestinal Endoscopy recommend.

Our study is the first to specifically assess the pooled effect of clipping on the risk of delayed bleeding posed by

TABLE 2. Pooled risks of adverse events in relevant subgroups from included studies (clipped and unclipped groups)

Subgroup	Clinically significant post-EMR bleeding	Perforation	Postpolypectomy syndrome	Fever	Abdominal pain
Overall cohort	6.3 (78/1248)	.6 (7/1248)	.7 (7/1017)	.3 (1/309)	1.4 (17/1248)
Female patients	5.5 (26/469)	.9 (4/469)	1.6 (6/365)	1.4 (1/73)	1.3 (6/469)
Male patients	6.7 (52/779)	.4 (3/779)	.2 (1/652)	.0 (0/236)	1.4 (11/779)
	$P = .42$	$P = .28$	$P = .01$	$P = .07$	$P = .85$
Patients aged <65 y	5.4 (25/459)	.9 (4/459)	.8 (3/390)	.0 (0/90)	.9 (4/459)
Patients aged ≥65 y	6.7 (53/789)	.4 (3/789)	.6 (4/627)	.5 (1/219)	1.6 (13/789)
	$P = .37$	$P = .26$	$P = .81$	$P = .52$	$P = .25$
Patients not on anticoagulants *or* antiplatelets	4.8 (43/894)	.7 (6/894)	.6 (4/726)	.4 (1/226)	1.3 (12/894)
Patients on anticoagulants *only*	8.0 (9/112)	.9 (1/112)	.0 (0/88)	.0 (0/57)	1.8 (2/112)
	$P = .15$	$P = .79$	$P =$ NA	$P =$ NA	$P = .71$
Patients not on anticoagulants *or* antiplatelets	4.8 (43/894)	.7 (6/894)	.6 (4/726)	.4 (1/226)	1.3 (12/894)
Patients on antiplatelets *only*	9.6 (27/282)	.0 (0/282)	1.2 (3/243)	.0 (0/76)	1.4 (4/282)
	$P = .003$	$P =$ NA	$P = .28$	$P =$ NA	$P = .92$
Patients with American Society of Anesthesiologists score I or II	6.5 (44/679)	.3 (2/679)	.6 (3/542)	1.0 (1/101)	1.5 (10/679)
Patients with American Society of Anesthesiologists score III or IV	6.2 (26/421)	.7 (3/421)	.8 (3/377)	.0 (0/110)	1.2 (5/421)
	$P = .84$	$P = .32$	$P = .65$	$P = .30$	$P = .69$
Lesions <40 mm	6.1 (55/895)	.4 (4/895)	.7 (5/763)	.0 (0/202)	.6 (5/895)
Lesions ≥40 mm	6.5 (23/353)	.8 (3/353)	.8 (2/254)	.9 (1/107)	3.4 (12/353)
	$P = .81$	$P = .39$	$P = .83$	$P = .17$	$P < .001$
Lesions with full clip closure	2.6 (11/425)	.7 (3/425)	.6 (2/356)	.0 (0/89)	.9 (4/425)
Lesions with partial clip closure	1.7 (2/118)	.0 (0/118)	.0 (0/98)	.0 (0/32)	1.7 (2/118)
Lesions with attempted (but failed) clip closure	5.6 (1/18)	.0 (0/18)	10.0 (1/10)	.0 (0/5)	11.1 (2/18)
Lesions with no attempted clip closure	9.0 (56/625)	.6 (4/625)	.8 (4/512)	.7 (1/152)	1.3 (8/625)
	$P < .001$	$P = .82$	$P = .01$	$P = .84$	$P = .004$
Lesions in transverse colon*	1.0 (2/195)	.0 (0/195)	.0 (0/177)	.0 (0/54)	1.5 (3/195)
Lesions in ascending colon or hepatic flexure	6.1 (40/657)	.5 (3/657)	.6 (3/540)	.6 (1/176)	1.1 (7/657)
Lesions in cecum	9.1 (36/396)	1.0 (4/396)	1.3 (4/300)	.0 (0/79)	1.8 (7/396)
	$P = .001$	$P = .26$	$P = .20$	$P = .68$	$P = .62$
Lesions resected en bloc	6.5 (9/138)	.7 (1/138)	2.5 (3/121)	.0 (0/52)	.7 (1/138)
Lesions resected piecemeal	6.2 (69/1108)	.5 (6/1108)	.4 (4/894)	.4 (1/255)	1.4 (16/1108)
	$P = .89$	$P = .79$	$P = .01$	$P = .65$	$P = .49$
No intraprocedural bleeding observed	5.7 (60/1057)	.3 (3/1057)	.8 (7/872)	.4 (1/265)	.9 (9/1057)
Intraprocedural bleeding observed	9.4 (18/191)	2.1 (4/191)	.0 (0/145)	.0 (0/44)	4.2 (8/191)
	$P = .04$	$P = .002$	$P = .28$	$P = .68$	$P < .001$
Traditional adenoma (no high-grade dysplasia)	6.6 (55/837)	.7 (6/837)	.5 (3/625)	.8 (1/124)	1.8 (15/837)
Serrated lesion†	4.0 (8/200)	.5 (1/200)	1.1 (2/181)	.0 (0/7)	.0 (0/200)
Lesion with high-grade dysplasia or carcinoma	6.6 (9/136)	.7 (1/136)	1.5 (2/136)	.0 (0/59)	1.5 (2/136)
	$P = .38$	$P = .94$	$P = .39$	$P = .77$	$P = .16$

Values are % (n/N).
NA, Not assessable because of low event rates.
*Only lesions in the mid- to proximal segment of the transverse colon were considered.
†Sessile serrated adenomas/polyps and traditional serrated adenomas included.

traditional patient- and lesion-related factors. Importantly, CSPEB was reduced in the absence of these risk factors as much as with these risk factors. Therefore, after EMR of LNPCPs in the proximal colon, clip closure should be performed irrespective of a patient's risk profile. Furthermore, it is important to note that although prophylactic clipping does not reduce the risk of nonbleeding AEs, the benefits to CSPEB reduction do not come at the cost of an increased incidence in other AEs. Prior meta-analyses assessing prophylactic bleeding after EMR have not addressed nonbleeding AEs and have not fully assessed the effect of clipping on CSPEB according to clinically relevant subgroups.[21-23]

Importantly, our results suggest that prophylactically clipping lesions in the transverse colon is much less efficacious in the prevention of CSPEB compared with lesions in the ascending colon or cecum. This is in large part because of a much lower baseline risk of CSPEB after EMR of transverse colonic lesions, which we showed to be 1.0% (compared with 6.1% in the ascending colon and 9.1% in the cecum, $P = .001$). In clinical research, the transverse colon is commonly considered as part of the proximal

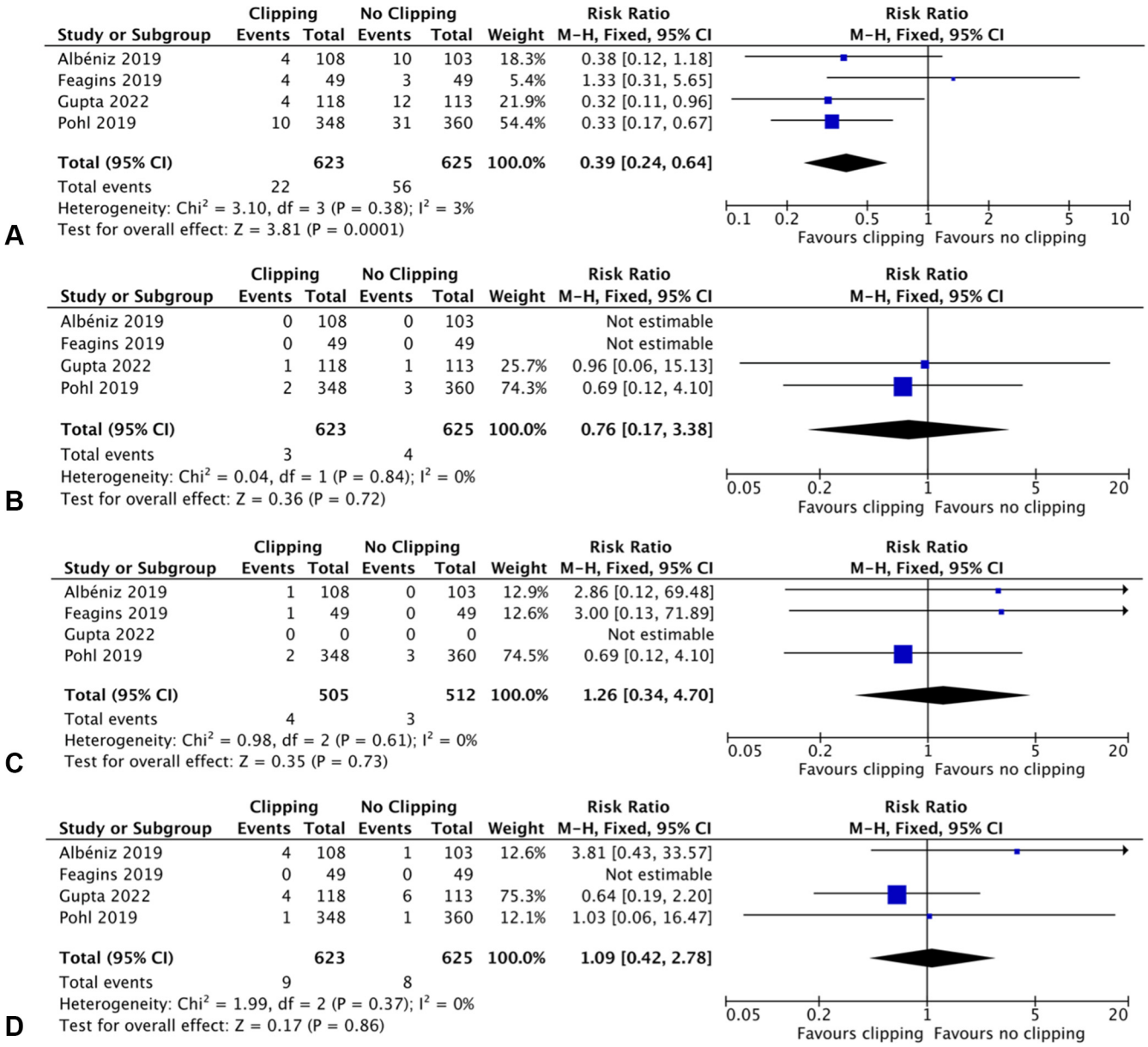


Figure 3. Forest plot demonstrating the relative risk of (**A**) clinically significant post-EMR bleeding, (**B**) perforation, (**C**) postpolypectomy syndrome, and (**D**) abdominal pain requiring unplanned healthcare utilization with clip closure versus no clipping. *CI*, Confidence interval.

colon, but our data clearly show that as it relates to CSPEB, the transverse colon should be considered as a separate entity. Our results demonstrate the futility of clipping lesions in the transverse colon, albeit with important caveats. In some patients, the distinction between the proximal transverse colon, hepatic flexure, and ascending colon is not as evident as in others. In such patients, if one is unsure about the precise location of a lesion within the colon, it is likely prudent to still attempt prophylactic clip closure. If it is clear based on anatomic landmarks that a lesion is in the transverse colon (especially in the mid- or distal transverse colon), clipping is likely of limited benefit. Our results also confirm that this approach holds true irrespective of lesion size.

It is important to note that even partial clip closure was effective in reducing CSPEB in a similar fashion as with full clip closure, with RRs of .23 (95% CI, .07-.73) versus .25 (95% CI, .14-.47) when no clipping was used as the reference. This may represent a counterintuitive finding to some. We postulate that partial closure may still achieve a reduction in the shear or stretch forces exerted on exposed and/or potentially injured submucosal vessels within the post-EMR defect and therefore ultimately result in decreased bleeding. Furthermore, in cases where full defect closure is not feasible because of lesion shape, location, and/or size, partial clipping could conceivably preferentially target 1 or more areas within the defect deemed at highest

TABLE 3. Summary of efficacy of clipping (vs no clipping) in the prevention of clinically significant post-EMR bleeding per clinically relevant subgroup

	Individual patient data meta-analysis		Traditional meta-analysis		
Subgroup	**Pooled odds ratio (95% CI)**	***P* value for interaction**	**Pooled relative risk (95% CI)**	**Heterogeneity (I^2) (%)**	***P* value for meta regression**
Patients aged <65 y	.27 (.10-.74)	.82	.37 (.16-.86)	0	.79
Patients aged ≥65 y	.31 (.16-.61)		.42 (.24-.73)	0	
Female patients	.24 (.09-.65)	.59	.34 (.15-.78)	0	.91
Male patients	.33 (.17-.66)		.42 (.24-.75)	35	
Patients not on anticoagulants *or* antiplatelets	.26 (.11-.60)	.73	.41 (.22-.78)	23	.94
Patients on anticoagulants *only*	.19 (.04-.90)		.35 (.09, 1.40)	0	
Patients not on anticoagulants *or* antiplatelets	.26 (.11-.60)	.53	.41 (.22-.78)	23	.85
Patients on antiplatelets *only*	.37 (.16-.88)		.46 (.22-1.00)	0	
Patients with American Society of Anesthesiologists score I or II	.41 (.21-.79)	.20	.42 (.23-.79)	0	.35
Patients with American Society of Anesthesiologists score III or IV	.16 (.05-.49)		.22 (.08-.58)	0	
Lesions <40 mm	.29 (.14-.58)	.84	.42 (.24-.72)	39	.94
Lesions ≥40 mm	.33 (.13-.85)		.35 (.15-.85)	59	
Lesions with full clip closure	.08 (.01-.54)	.51	.25 (.14-.47)	29	.08
Lesions with partial clip closure	.19 (.04-.97)		.23 (.07-.73)	15	
Lesions with attempted (but failed) clip closure	NA		1.16 (.35, 3.85)	0	
Lesions in transverse colon*	.92 (.06, 14.98)	.28	NA	N/A	.48
Lesions in ascending colon or hepatic flexure	.24 (.10-.55)		.35 (.18-.71)	19	
Lesions in cecum	.35 (.16-.77)		.45 (.22-.89)	47	
Lesions resected en bloc	.16 (.02-1.42)	.58	.38 (.09-1.51)	0	.90
Lesions resected piecemeal	.32 (.18-.57)		.40 (.24-.67)	0	
No intraprocedural bleeding observed	.28 (.15-.53)	.55	.38 (.22-.65)	44	.53
Intraprocedural bleeding observed	.42 (.13-1.37)		.55 (.21-1.48)	0	
Traditional adenoma	.26 (.13-.51)	.36	.33 (.18-.59)	0	.32
Serrated lesion†	.20 (.02-1.67)		.32 (.07-1.42)	0	
Lesion with high-grade dysplasia or carcinoma	.58 (.16-2.13)		.75 (.21-2.69)	0	

CI, Confidence interval; *NA*, not assessable because of low event rates; *N/A*, not applicable.
*Only lesions in the mid- to proximal segment of the transverse colon were considered.
†Sessile serrated adenomas/polyps and traditional serrated adenomas included.

risk to the endoscopist. Although further study is required to elucidate the benefits and cost-effectiveness of partial versus complete clipping, based on our results, it is reasonable to attempt prophylactic clip closure of all proximal LNPCP defects.

None of the included studies reported on the cost-effectiveness of clip closure. However, a recent study demonstrated an economical advantage of clipping post-EMR defects within the proximal colon.[40] We believe that the economic benefit may be greatest within the cecum, which in our study carried a greater than 9-fold risk of CSPEB compared with a location in the transverse colon and an approximately 1.5-fold risk compared with other locations in the proximal colon, consistent with prior evidence.[41] Although further studies are required to evaluate cost-effectiveness, we acknowledge that widespread generalizability of such studies is likely to be limited because of variations in regional costs associated with clip acquisition, management practices after CSPEB, and in the economic models used for analysis. Similarly, although we were unable to quantify the risk of polyp recurrence in this meta-analysis, in their study, Gupta et al[26] demonstrated that clip closure did not affect recurrence at first surveillance colonoscopy 6 months after EMR. Other knowledge gaps relating to our work also require future study. At the present time, the optimal spacing between applied prophylactic clips is unknown, and future studies should aim to address this gap. Furthermore, precisely what defines partial clip closure is not currently clear. Undoubtedly, there are different types of partial closure,

TABLE 4. Grading of Recommendations Assessment, Development and Evaluation[31] summary of findings for studies assessing the effect of prophylactic clipping vs no clipping after EMR of proximal large nonpedunculated colorectal polyp

Certainty assessment							No. of events/ patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Clipped group	Unclipped group	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Clinically significant post-EMR bleeding												
4	RCT	No concerns	No concerns	No concerns	No concerns	No concerns	22/623 (3.5%)	56/625 (9.0%)	RR .39 (.24-.64)	55 fewer per 1000 (from 68 fewer to 32 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Perforation												
4	RCT	No concerns	No concerns	No concerns	Very serious concerns	No concerns	3/623 (.5%)	4/625 (.6%)	RR .76 (.17 to 3.38)	2 fewer per 1000 (from 5 fewer to 15 more)	⨁⨁◯◯ LOW	IMPORTANT
Postpolypectomy syndrome												
3	RCT	Some concerns	No concerns	No concerns	Very serious concerns	No concerns	4/505 (.8%)	3/512 (.6%)	RR 1.26 (.34-4.70)	2 more per 1000 (from 4 fewer to 22 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Fever requiring unplanned healthcare utilization												
2	RCT	Some concerns	No concerns	No concerns	Very serious concerns	No concerns	0/157 (.0%)	1/152 (.7%)	RR .32 (.01-7.72)	4 fewer per 1000 (from 7 fewer to 44 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Abdominal pain requiring unplanned healthcare utilization												
4	RCT	No concerns	No concerns	No concerns	Very serious concerns	No concerns	9/623 (1.4%)	8/625 (1.3%)	RR 1.09 (.42-2.78)	1 more per 1000 (from 7 fewer to 23 more)	⨁⨁◯◯ LOW	IMPORTANT

CI, Confidence interval; *RCT*, randomized controlled trial; *RR*, relative risk.

and these arguably should not be treated as 1 group; as examples, buttressing the corner or edge of a defect versus closing the center of a defect while targeting a central vessel are 2 completely distinct techniques and should likely be treated as such.

The main strength of our study lies in our methodologic approach that used unabridged original trial data, which provided data granularity not typically seen with meta-analyses. As such, we had increased power to address specific clinically relevant subgroups. Commonly, meta-analyses of interventions are performed by methodologists or other authors with no clinical or technical expertise in the procedure(s) being performed. In our study, the authors are expert endoscopists who not only perform the procedures in question, but also designed the seminal trials that comprise the evidence base. Other strengths of our study include the low degree of heterogeneity, which, among other factors, resulted in a high certainty in the overall estimate of efficacy of clip closure in preventing CSEPB.[31] Furthermore, by including contemporary and homogenous RCTs, we present high-level evidence in support of clip closure of proximal LNPCPs.

Our study is not without limitations. The results obtained could potentially be difficult to replicate in nonacademic centers, because these trials were performed mostly in tertiary care centers with expert endoscopists trained in EMR. Thus, caution should be applied when generalizing our results to nonacademic settings or in settings where untrained endoscopists are performing EMR. Although our pooled data are based on intention-to-treat analyses, further large-scale observational studies are still needed to determine the effectiveness of this in real-world practice. Additionally, 2 studies initially meeting eligibility criteria on screening were not included in our analyses because of an inability to acquire relevant subgroup data.[41,42] Although the

inclusion of these 2 studies could conceivably have slightly altered the point estimates in our results, they would not have changed the overall significance, given that 1 study would have added at most 14 lesions[41] and the other clearly demonstrated a benefit of clipping overall.[42] Finally, our study is specific to EMR and excludes the impact of prophylactic clip closure after endoscopic submucosal dissection; therefore, our results should not be applied to the practice of endoscopic submucosal dissection, which is associated with a considerably higher-risk profile.[11] Nonetheless, EMR is likely to remain a cornerstone technique in the management of LNPCPs.

In conclusion, our meta-analysis of IPD from homogeneous RCTs demonstrates clear efficacy of clip closure in preventing CSPEB after EMR of LNPCPs in the proximal colon regardless of baseline patient- or procedure-related factors. Furthermore, clip closure is not significantly associated with increases of any other AEs. Given these findings, clip closure should be adopted as the standard of care for EMR of proximal LNPCPs. Formal cost-effectiveness analyses should be performed to incorporate the most recent synthesized evidence that we present into future healthcare decision models.

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Abbreviations: AE, adverse event; CI, confidence interval; CSPEB, clinically significant post-EMR bleeding; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IPD, individual patient data; LNPCP, large nonpedunculated colorectal polyp; OR, odds ratio; PPS, postpolypectomy syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial; RR, relative risk; UHU, unplanned healthcare utilization.

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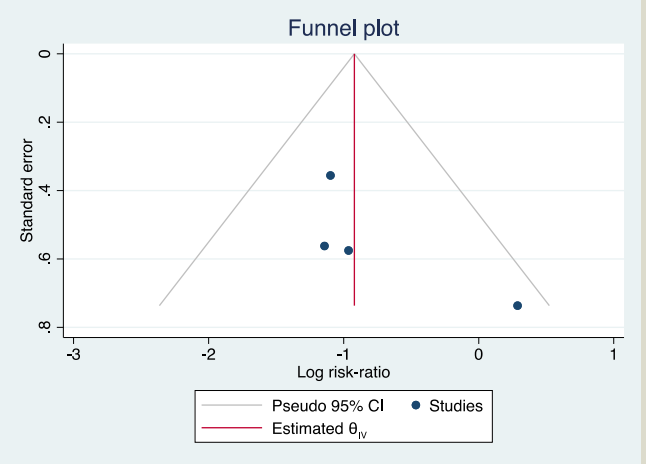
SUPPLEMENTARY TABLE 1. Unabridged electronic search strategy

EBM Reviews - Cochrane Central Register of Controlled Trials <April 2021>
Embase <1974 to 2021 May 19>
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to May 19, 2021>
1 exp Endoscopy/ 1048975
2 polypect*.tw. 16006
3 mucosal resect*.tw. 10139
4 exp Prophylactic Surgical Procedures/ 1265
5 prophylac*.tw. 224288
6 clip*.tw. 78939
7 hemoclip*.tw. 1884
8 endoclip*.tw. 1606
9 postpolypec*.tw. 1022
10 exp Postoperative Complications/ 1310127
11 delay*.tw. 1219155
12 post-polypec*.tw. 1457
13 exp Hemorrhage/ 1307972
14 bleed*.tw. 616005
15 exp Intestinal Perforation/ 41192
16 perforat*.tw. 215180
17 complicat*.tw. 2907619
18 adverse*.tw. 1667261
19 1 or 2 or 3 1059426
20 4 or 5 or 6 or 7 or 8 305125
21 9 or 10 or 11 or 12 2478859
22 13 or 14 or 15 or 16 or 17 or 18 5636528
23 19 and 20 and 21 and 22 3891
24 remove duplicates from 23 3145

SUPPLEMENTARY TABLE 2. Summary of risk of bias assessments for each included study according to Cochrane ROB 2 tool

				Missing data	Outcome measurement	Reported result		
Author	**Year**	**Randomization**	**Deviations**				**Other bias**	**Overall bias risk**
Albeniz	2019	low	low	low	some concerns	low	low	some concerns
Feagins	2019	low	low	low	some concerns	low	low	some concerns
Pohl	2019	low	low	low	low	low	low	low
Gupta	2021	low	low	low	low	low	low	low

SUPPLEMENTARY TABLE 3. Funnel plots and results of Begg's and Egger's tests for primary outcome



meta bias, begg
Effect-size label: Log Risk-Ratio
Effect size: _meta_es
Std. Err.: _meta_se
Begg's test for small-study effects
Kendall's score = 6.00
SE of score = 2.944
z = 1.70
Prob > |z| = 0.0894
meta bias, egger
Effect-size label: Log Risk-Ratio
Effect size: _meta_es
Std. Err.: _meta_se
Regression-based Egger test for small-study effects
Random-effects model
Method: REML
H0: beta1 = 0; no small-study effects
beta1 = 2.31
SE of beta1 = 1.851
z = 1.25
Prob > |z| = 0.2115