Annals of Gastroenterology (2024) **37,** 682-694

Endoscopic dilation of small-intestine strictures in Crohn's disease by balloon-assisted enteroscopy: a systematic review and meta-analysis

Vishali Moond[a], Vikram Jeet Singh Gill[a], Sheza Malik[b], Ameya Kasture[c], Sandesh Parajuli[d], Suha Soni[e], Saurabh Chandan[f], Arkady Broder[g], Babu P. Mohan[h], Douglas Adler[i]

Saint Peter's University Hospital/Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA; Rochester General Hospital, Rochester, New York, USA; Shree Bhausaheb Hire Government Medical College, Dhule, Maharashtra, India; Reading Hospital, PA, USA; University of Texas, Houston - School of Public Health, Houston, Texas, USA; Creighton University School of Medicine, Omaha, USA; Saint Peter's University Hospital/Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA; Orlando Gastroenterology PA, USA; Center for Advanced Therapeutic Endoscopy, Centura Health, Porter Adventist Hospital, Denver, CO, USA

Abstract

Background Balloon-assisted enteroscopy (BAE) (both single- and double-balloon enteroscopy) has garnered attention in the treatment of small intestine strictures in patients with Crohn's disease (CD). This study aimed to evaluate the pooled clinical outcomes of BAE-mediated endoscopic dilation of small intestine strictures in patients with CD.

Methods We searched multiple databases for articles reporting outcomes following BAE for small intestinal strictures in patients with CD. Outcomes studied were pooled technical success, clinical success and adverse events. Standard meta-analysis methods were employed using the random-effects model, and heterogeneity was studied using I^2 statistics.

Results We analyzed 26 studies, 9 prospective and 17 retrospective, involving 1570 patients. The pooled technical success rate of double-balloon enteroscopy was 87.6% (95% confidence interval [CI] 82.1-91.5; I^2=53%) and the pooled therapeutic success rate was 69.7% (95%CI 61.6-76.7; I^2=71%). The pooled major complications per procedure were 5.5% (95%CI 3.5-8.4; I^2=57%); the risk of bleeding was 2.5% (95%CI 1.4-4.2; I^2=28%), and the risk of perforation was 2.7% (95%CI 1.6-4.5; I^2=3%). The pooled rate of recurrence after the first dilation was 42.3% (95%CI 16.9-72.5; I^2=59%), and the rate of repeat endoscopic balloon dilation was 23.9% (95%CI 14.1%-37.5%; I^2=85%), while the pooled rate of repeat surgery was 25.3% (95%CI 11.8%-46.0%; I^2=44%].

Conclusion BAE is a good first line approach for patients with CD-induced strictures in an attempt to treat symptoms and potentially avoid surgery.

Keywords Crohn's disease, endoscopic dilation, balloon-assisted enteroscopy, stricture

Ann Gastroenterol 2024; 37 (6): 682-694

Introduction

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD) characterized by sporadic areas of transmural inflammation within the gastrointestinal tract; it has an incidence of 3-20.2 per 100,000 person-years in North America [1,2]. According to the Montreal classification, CD can be divided into: (1) non-stricturing, non-penetrating disease; (2) penetrating; and (3) stricturing [3]. Throughout their illness, individuals with CD may exhibit 1 or more of these disease phenotypes; they frequently go from an inflammatory stage to a stricturing or penetrating stage [4], while approximately 20-40% of CD patients develop stricturing disease within 10 years of disease diagnosis [5-7].

Conflict of Interest: DGA: Consultant for Boston Scientific; all other authors declare no conflicts of interest.

Correspondence to: Douglas G. Adler, MD, FACG, FAGA, FASGE, Director, Center for Advanced Therapeutic Endoscopy, Centura Health, Porter Adventist Hospital, Denver, CO, USA,
e-mail: dougraham2001@gmail.com

Received 4 Junw 2024; accepted 31 July 2024;
published online 22 October 2024

DOI: https://doi.org/10.20524/aog.2024.0920

The most common area for stricture development is the ileocecal region, accounting for up to half of cases, which can be primary or anastomotic [5]. The treatment of CD strictures of the small bowel is challenging [8-10]. Medical treatment modalities are being used; however, the CREOLE trial demonstrated that nearly 40% of patients with symptomatic stenoses required either endoscopic balloon dilation (EBD) or surgery [11]. Surgical therapy includes bowel resection and strictureplasty, whereas endoscopic therapies include EBD and endoscopic stricturotomy. Given the high histological and clinical recurrence rates and complications associated with surgery, EBD has emerged as a valuable adjunct and alternative to surgery [8,10-12].

EBD is included in the current guideline recommendations for treating ileal CD strictures [11,13]. Most studies in the existing literature have assessed EBD for terminal ileal and ileocolic anastomotic strictures, which are reachable via standard colonoscopy; however, little is known about EBD for small bowel strictures, which can only be reached by balloon-assisted enteroscopy (BAE) [8,10,13,14].

Recently, various reports on EBD for small bowel strictures using BAE have emerged [15-18]. However, all of these reports have involved small cohorts, and the long-term efficacy was not sufficiently evaluated. Moreover, there is a need to update the adverse outcomes that are associated with these procedures [16,19-42]. The current literature reports a variety of clinical outcomes and complications in this patient cohort. This study aimed to evaluate the pooled clinical outcomes of BAE-mediated endoscopic dilation of small intestine strictures in patients with CD.

Materials and methods

Search strategy

We conducted a comprehensive search of several databases and conference proceedings, including PubMed, EMBASE, and Web of Science databases (earliest inception to December 2023). An experienced medical librarian using inputs from the study authors helped with the literature search to identify studies reporting BAE. The detailed literature search strategy is provided in Appendix A. Two authors (VM, VJSG) independently reviewed the titles and abstracts of studies identified in the primary search and excluded studies that did not address the research question, based on pre-specified exclusion and inclusion criteria. The full text of the remaining articles was reviewed to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus, and in discussion with a co-author (BPM). The bibliographic section of the selected articles, as well as the systematic and narrative articles on the topic, were manually searched for additional relevant articles.

We adhered to the Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist (checklists provided in supplementary materials: Appendices B and C, respectively) [44,45].

Study selection

In this meta-analysis, we included studies that evaluated patients with CD strictures endoscopically treated by BAE, irrespective of inpatient/outpatient setting and geography, as long as they provided data needed for the analysis. Eligible studies enrolled adult patients (age >18 years) with a confirmed diagnosis of CD, strictures of the small intestine (including jejunum and ileum) associated with CD, dilated via BAE using through-the-scope EBD. The following were our exclusion criteria: (1) studies presented as conference abstracts; (2) studies in the pediatric population (age <18 years); (3) studies not published in the English language; (4) case reports and small case series with less than 8 patients per study; and (5) the dilated stricture was located in a non-small-bowel location. In cases of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were included.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form by at least 2 authors (VM, VJSG), while 2 authors (SP, AK) did the quality scoring independently. The Newcastle-Ottawa scale for cohort studies was used to assess the quality of studies [46]. This quality score consists of 8 questions, the details of which are provided in Supplementary Table 1.

Outcomes assessed

The primary analysis of this study focused on calculating the pooled rate of technical success, clinical success, adverse events, rates of repeat dilation, rates of recurrence of strictures, and surgery required during the follow up with BAE. Pooled rates were calculated for commonly encountered adverse event subcategories with BAE: namely, perforation, bleeding, small

[a]Department of Internal Medicine, Saint Peter's University Hospital/ Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA (Vishali Moond, Vikram Jeet Singh Gill); [b]Department of Internal Medicine, Rochester General Hospital, Rochester, New York, USA (Sheza Malik); [c]Shree Bhausaheb Hire Government Medical College, Dhule, Maharashtra, India (Ameya Kasture); [d]Department of Internal Medicine, Reading Hospital, PA, USA (Sandesh Parajuli); [e]University of Texas, Houston - School of Public Health, Houston, Texas, USA (Suha Soni); [f]Division of Gastroenterology and Hepatology, Creighton University School of Medicine, Omaha, USA (Saurabh Chandan); [g]Department of Gastroenterology, Saint Peter's University Hospital/ Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA (Arkady Broder); [h]Orlando Gastroenterology PA, Orlando, USA (Babu P. Mohan); [i]Director, Center for Advanced Therapeutic Endoscopy, Centura Health, Porter Adventist Hospital, Denver, CO, USA (Douglas Adler)

bowel obstruction (SBO), localized peritonitis, pancreatitis, and hyperamylasemia associated with the procedure. Additionally, when possible, the adverse events were categorized based on the American Society for Gastrointestinal Endoscopy (ASGE) lexicon and pooled rates were determined for mild, moderate, severe, and fatal adverse events [47].

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates in each case, following the methods suggested by DerSimonian and Laird [48] and using the random-effects model. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis [49]. We assessed heterogeneity between study-specific estimates using the Cochran Q statistical test for heterogeneity, the 95% prediction interval (PI), which deals with the dispersion of the effects, and the I^2 statistics [50, 51], in which values of <30%, 30-60%, 61-75%, and >75% are suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [52]. Publication bias was ascertained, qualitatively, by visual inspection of the funnel plot, and quantitatively, by the Egger test. When publication bias was present, further statistics using the fail-Safe N and Duval and Tweedie's "Trim and Fill" tests were used to ascertain the impact of the bias [53]. Three levels of impact were reported based on the concordance between the reported results and the actual estimate if there was no bias. The impact was reported as minimal if both versions were estimated to be the same, modest if the effect size changed substantially but the final finding would remain the same, and severe if the basic final conclusion of the analysis was threatened by the bias [54]. All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, NJ).

Results

Search results and population characteristics

From a total of 2246 citations identified from databases (PubMed, EMBASE, Web of Science), 1996 records were screened after the removal of 250 duplicate records. Of these, 516 reports were assessed for eligibility. Reports were excluded for the following reasons: review articles and editorials (n=318), case reports and case series (n=54), studies not exclusive to Crohn's disease (n=66), possible cohort overlaps (n=15), studies not published as full manuscripts (n=19), and studies that did not meet the inclusion criteria (n=18). Therefore, a total of 26 BAE studies (with a total of 1576 patients) were included in the final analysis [16,19-43]. The schematic diagram of study selection is illustrated in Supplementary Fig. 1.

A total of 26 publications, including 9 prospective studies and 17 retrospective studies, were analyzed. Technical success was defined as the ability to successfully reach and dilate the target stricture. Clinical success was defined as the improvement or relief of symptoms of intestinal obstruction. Major adverse events were defined as perforation, bleeding, dilation-related surgery, small bowel obstruction (SBO), localized peritonitis, pancreatitis, and hyperamylasemia associated with the procedure. Secondary outcomes were defined as need for surgery, at the site of the dilated stricture only and not in other parts of the intestine. Detailed definitions, degree of adverse events and reintervention, were defined in accordance with the ASGE report.

Symptom recurrence was only assessed in subjects where clinical efficacy was achieved after endoscopic dilation, and follow-up time was defined as months from initial dilation to time of symptom recurrence; subjects were censored at the time of re-dilation, surgery or last follow-up visit if they had no recurrence of symptoms. For time to surgery, follow-up time was defined as months from the first dilation to time of surgery; patients were censored at the time of last follow-up visit if they did not have surgery. For first re-intervention, follow-up time was defined as the months from the first dilation to either first re-dilation or surgery; patients were censored at the time of last follow-up visit if they did not have a re-intervention.

Continuous outcomes reported as median with minimum and maximum limits, or with 95% confidence interval (CI) or interquartile range (IQR) were converted to mean values using the method suggested by Luo *et al*, and the corresponding standard deviation (SD) was calculated using the method suggested by Wan *et al*.

Characteristics and quality of included studies

The meta-analysis included 26 independent cohort studies with a total of 1570 patients [16,19-43], described in Table 1. None of the studies were population-based. All of the included studies reported clear information on the technical success, clinical success and adverse event rates, including the subcategory of the adverse events. None of the studies had patients lost to follow up. Eighteen studies were considered to be of high quality and 8 as medium quality. No studies were considered low quality. Supplementary Table 1 details the study quality assessment.

Meta-analysis outcomes

The study population was comprised of 47.7% males with a mean age of 44.7±15.42 years and a mean follow-up duration of 25±14 months. The mean age at diagnosis of CD was 28.85±11 years, and the mean duration of CD was 13.08±2.5 years, with the disease located mainly in the ileal region (37.69%). The median length of the strictures was 1.60±0.25 cm.

The pooled technical success rate of balloon assisted enteroscopy was 87.6% (95%CI 82.1-91.5; I^2= 53%) and the pooled therapeutic success rate was 69.7% (95%CI 61.6-76.7; I^2= 71%; Table 1, Fig. 1, 2). The pooled rate of major adverse

Table 1 Study and population characteristics

Study, year [ref.]	Study details	Total patients	CD patients with Strictures	Male/ Female	Mean duration of CD (with a known diagnosis of CD)	Median age at time of Diagnosis (years, IQR)	Mean age (years, SD)	No of dilatations	Median diameter of balloon (mm)	Disease location	Number of strictures	Length of strictures (cm)	DBE via Oral route
DeSpott *et al*, 2009 [16]	Prospective case series, Feb 2005 - Oct 2008, single, tertiary referral center, UK	11	11/11	4/7	24 (13-31)	NR	46.4 +/-7.8	18	15.4 (12-20)	NR	18	NR	5
Ding *et al*, 2015 [20]	Retrospective cohort, Jan 2007 - Feb 2009, single, tertiary referral center, UK	12	12/12	4/8	NR	NR	39 (20-59)	22	NR	NR	12	NR	5
Ferlitsch *et al*, 2006 [39]	Prospective cohort, November 1993 - February 2003, Austria	46	39/39	26/20	NR	22 (15±38)	34 (30±53)	73	20	Ileum only -13/39 (33.3%) Colon only- 5/39 (12.8%) Ileum and colon -29/39 (74.35) Including upper gastrointestinal tract- 3/39 (7.6%)	NR	20 (10±50)	NR
Fukumoto *et al*, 2007 [21]	Retrospective cohort, Sep 2000 - Dec 2005, multi-center, Japan	179	23/57	117/62	NR	NR	51 (1.4)	35	NR	NR	23	NR	NR
Goenka *et al*, 2020 [36]	Prospective cohort, Dec 2016 - Dec 2019, single center, India	158	14/158	94/64	NR	NR	55 (13–94)	4	NR	NR	NR	NR	114
Gill *et al*, 2014 [22]	Retrospective review, July 2004 to September 2012, single tertiary center, Australia	32	20/32	15/17	NR	NR	52.7±15.1	25	14 (10–18)	Distal Ileum 10/15 (66.6%), Jejunum 2/15 (13.3%), Prox to Neo TI 1/15 (6.7%), Surgical anastomotic in Distal small bowel 1/15 (6.7%), Stoma 1/15 (6.7%)	NR	NR	3

(*Contd...*)

Table 1 (*Continued*)

Study, year [ref.]	Study details	Total patients	CD patients with Strictures	Male/ Female	Mean duration of CD (with a known diagnosis of CD)	Median age at time of Diagnosis (years, IQR)	Mean age (years, SD)	No of dilatations	Median diameter of balloon (mm)	Disease location	Number of strictures	Length of strictures (cm)	DBE via Oral route
Halloran *et al*, 2013 [23]	Retrospective review, Jan 2004 to Nov 2012, single tertiary center, USA	21	21/21	13/8	NR	NR	44.8 (23-78)	40	12 (10-18)	NR	77	NR	18
Hirai *et al*, 2010 [24]	Retrospective review, April 2005 - September 2007, single tertiary center, Japan	25	25/25	20/5	12.3+/7.5 years	NR	36.0+/- 8.9	NR	NR	Jejunum 1/25 (4%) Ileum 21 (84%) Anastomosis 3 (12%)	NR	NR	NR
Hirai *et al*, 2014 [26]	Retrospective, April 2005- September 2012, single tertiary center, Japan	65	65/65	51/14	NR	NR	36.0±10.5	NR	12-18	Ileitis-40/65 (61.5%), Ileocolitis 25/65 (38.5%)	NR	<3 cm=49 , ≥3 cm=16	NR
Hirai *et al*, 2018 [40]	Prospective cohort, Aug 2011 - Oct 2013, multicenter, Japan	95	95/95	66/29	11.1±8.8 years	NR	38.5±10.4	NR	NR	Ileum 59/95 (62.1%) Ileocolon 36/95 (37.8%)	NR	>=3 cm at 82 locations [85.4%], ≥ 3 cm at only 9 locations [9.4%].	NR
Irani *et al*, 2012 [41]	Retrospective review, January 2007 - December 2011, single tertiary center, USA	13	4/13	11/2	NR	NR	60	16	NR	NR	17	5+/5.7 mm	4
Kim *et al*, 2016 [25]	Retrospective review, May 2012 - February 2015, single tertiary center, South Korea	8	8/8	-	NR	NR	NR	30	15	NR	30	NR	NR
Kita *et al*, 2007 [42]	Prospective cohort, September 2000 and October 2005, single tertiary center, Japan	250	NR		NR	NR	NR	NR	NR	NR	NR	NR	225

(*Contd...*)

Table 1 (*Continued*)

Study, year [ref.]	Study details	Total patients	CD patients with Strictures	Male/ Female	Mean duration of CD (with a known diagnosis of CD)	Median age at time of Diagnosis (years, IQR)	Mean age (years, SD)	No of dilatations	Median diameter of balloon (mm)	Disease location	Number of strictures	Length of strictures (cm)	DBE via Oral route
Kroner *et al*, 2016 [32]	Retrospective review, February 2009 - September 2013, single tertiary center, USA	71	15/71	29/42	NR	NR	62.7±15	NR	NR	NR	NR	NR	31
Milewski *et al*, 2013 [27]	Retrospective cohort, Jan 2005 - Oct 2012, single center, Poland	116	75/116		NR	NR	NR	NR	NR	NR	NR	NR	NR
Morishima *et al*, 2009 [28]	Retrospective cohort, June 2003 - Aug 2008, single center, Japan	20	20/20	19/1 (14/3)	NR	NR	35.4	NR	NR	NR	NR	NR	NR
Navaneethan *et al*, 2014 [29]	Prospective cohort, Jan 2005 - Jan 2012, single center, US	108	49/65	group A=16/6, group B=22/21	8 (1 – 14)	NR	group A=46 (39 – 64), group B=41 (32 – 54)	group A=25, group B=53	NR	Small-bowel 14/43 (32.6%) Ileo-colonic 26/43 (60.5%) Ileo-colonic and duodenum 3/43 (6.9%)	NR	NR	group A=13, group B=25
Ning *et al*, 2023 [37]	Retrospective cohort, November 2017-April 2023, multicenter, China	28	NR	23/5	NR	NR	31.5 (27.5-35)	NR	NR	Ileal disease 24/28 (85.7%), Colonic disease 0/28 (0%), Ileocolonic disease 4/28 (14.3%)	NR	1 (1-1.98)	NR
Nishida *et al*, 2017 [30]	Retrospective cohort, April 2016 - May 2015, single center, Japan	37	37/37	31/6	10.0 (5.5–14.0) years	24.7 (20.5–28.4)	35.0 (31.8–37.9)	72	12-15	Ileal 21/37 (56.8%) Colonic 0/37 (0%) Ileocolonic 16/37 (43.2%)	NR	NR	NR
Nishimura *et al*, 2011 [43]	Prospective, Sept 2000 - Jan 2010, single center, Japan	8	NR	6/2	NR	NR	64 (42-89)	12	12	Jejunum 2/12 (16.6%) ileum 5/12 (41.6%)	11	NR	NR

(*Contd...*)

Table 1 (*Continued*)

Study, year [ref.]	Study details	Total patients	CD patients with Strictures	Male/ Female	Mean duration of CD (with a known diagnosis of CD)	Median age at time of Diagnosis (years, IQR)	Mean age (years, SD)	No of dilatations	Median diameter of balloon (mm)	Disease location	Number of strictures	Length of strictures (cm)	DBE via Oral route
Ohmiya *et al*, 2009 [31]	Retrospective cohort, prospective study, June 2003 - July 2007, single-center, Japan	66	23/66	46/20	NR	NR	48.0 (17-85)	47	8-20	NR	NR	NR	34
Parakkal *et al*, 2013 [19]	Retrospective cohort, Jan 2001 - Dec 2013, single center, Japan	91	NR	45/46	NR	33 (9 – 57)	NR	125	NR	NR	69	1.5 (1 – 5)	57
Pohl *et al*, 2007 [33]	Prospective cohort, Sept 2003- May 2006, single center, Germany	19	NR	14/5	NR	NR	46	15	17	Jejunum 4/19 (21.1%), Ileum 15/19 (78.9%).	NR	3	NR
Sunada *et al*, 2016 [34]	Retrospective cohort, 2002-2014, single center, Japan	85	NR	26/59	NR	NR	36.5	473	12.4	NR	NR	NR	NR
Yamada *et al*, 2012 [35]	Retrospective cohort, June 2003 - August 2011, single center, Japan	46	46/46	38/8	NR	NR	NR	128	NR	NR	NR	< 5	NR
Yoshida *et al*, 2020 [38]	Prospective cohort, single Center, Japan	10	10/10	-	NR	NR	NR	9	NR	NR	NR	NR	NR

Study, year [ref.]	DBE via Rectal route	DBE via other routes	Technical success (CD)	Therapeutic success (CD)	Major complications per procedure	Major complications - Bleeding	Major complications - Perforation	Major complications others	Follow up	Symptomatic Recurrence During Follow up	Repeat Dilation	Surgery During Follow up
DeSpott *et al*, 2009 [16]	4	2	14/18 (81.8%)	8/9 (88.89%)	1/9 (11.11%)	NR	1/9 (11.11%)	NR	615 (60-1230) days	2/9 (22.22%)	2/9 (22.22%)	0
Ding *et al*, 2015 [20]	7	NR	22/22 (100%)	9/12 (75%)	1/12 (8.33%)	NR	1/12 (8.33%)	NR	1789 (1643-2592) days	7/12 (58.34%)	9/12 (75%)	3/12 (25%)
Ferlitsch *et al*, 2006 [39]	NR	NR	37/39 (95%)	38.46%	3/73 (4%)	1/73 (1.36%)	2/73 (2.7%)	NR	21 (3±98) months	24/39 (62%)	12/39 (31%)	11/39 (28%)

(*Contd...*)

Table 1 (*Continued*)

Study, year [ref.]	Study details	Total patients	CD patients with Strictures	Male/ Female	Mean duration of CD (with a known diagnosis of CD)	Median age at time of Diagnosis (years, IQR)	Mean age (years, SD)	No of dilatations	Median diameter of balloon (mm)	Disease location	Number of strictures	Length of strictures (cm)	DBE via Oral route
Fukumoto *et al*, 2007 [21]	NR	NR	35/35 (100%)	17/23 (73.91%)	0	0	0	NR	NR	6/23 (26.08%)	4/23 (17.39%)	2/23 (8.6%)	
Goenka *et al*, 2020 [36]	66	Bidirectional approach 22 (13.92%)	NR	4/4 (100%)	4/22 (18.18%)	3/22 (13.63%)	1/22 (4.5%)	2/22 (9%)	NR	NR	NR	NR	
Gill *et al*, 2014 [22]	26	3 stoma	15/15 (100%)	11/14 (78.57%)	2/25 (8%)	NR	2/25 (8%)	NR	16 (3–60) months	3/15 (20%)	1/15 (6.67%)	3/15 (20%)	
Halloran *et al*, 2013 [23]	22	0	36/40 (90.5%)	11/15 (76%)	1/40 (2.5%)	NR	1/40 (2.5%)	NR	289 (3-960, median 60) days	9/19 (47.36%)	4/19 (21.05%)	5/21 (24%)	
Hirai *et al*, 2010 [24]	NR	NR	18/25 (72%)	20/25 (80%)	2/25 (8%)	1/25 (4%)	NR	1/25 (4%)	11.4+/8.7 months	4/18 (22.22%)	4/18 (22.22%)	5/25 (20%)	
Hirai *et al*, 2014 [26]	NR	NR	52/65 (80%)	48/52 (92.3%)	12/65 (18.46%)	1/65 (1.5%)	1/65 (1.5%)	4/65 (6.1%)	41.8±24.9 months	28/53 (53%)	26/52 (50%)	17/65 (26%)	
Hirai *et al*, 2018 [40]	NR	NR	89/95 (93.68%)	66/95 (69.47%)	5/95 (5.26%)	3/95 (3.15%)	N/A	1/95 (1%)	2 years	NR	NR	1/95 (1.05%)	
Irani *et al*, 2012 [41]	8	Bidirectional approach 1	12/13 (92%)	10/13 (77%)	1/13 (7.69%)	NR	1/13 (7.69%)	NR	46 months	3/13 (23.07%)	2/13 (15.38%)	1/13 (7.69%)	
Kim *et al*, 2016 [25]	NR	NR	7/8 (87.5%)	29/30 (96.6%)	1/8 (12.5%)	NR	1/8 (12.5%)	NR	18 months	1/7 (14.38%)	1/7 (14.28%)	0	
Kita *et al*, 2007 [42]	194	0	55/71 (77.4%)	45/71 (63.38%)	NR	NR	NR	NR	NR	NR	NR	NR	
Kroner *et al*, 2016 [32]	53	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Milewski *et al*, 2013 [27]	NR	NR	NR	NR	0	0	0	0	NR	NR	NR	NR	
Morishima *et al*, 2009 [28]	NR	NR	33/35 (94.28%)	5/17 (29.41%)	NR	NR	NR	NR	345 days	12/17 (71%)	8/17 (47%)	4/17 (24%)	

(*Contd...*)

Table 1 (*Continued*)

Study, year [ref.]	Study details	Total patients	CD patients with Strictures	Male/ Female	Mean duration of CD (with a known diagnosis of CD)	Median age at time of Diagnosis (years, IQR)	Mean age (years, SD)	No of dilatations	Median diameter of balloon (mm)	Disease location	Number of strictures	Length of strictures (cm)	DBE via Oral route
Navaneethan *et al*, 2014 [29]	group A=12, group B=28	0	6/8 (75%)	5/8 (62.5%)	group A=0, group B=3/43 (6.9%)	2/43 (4.60%)	1/43 (2.30%)	0	8-10 months	NR	1/43 (2.30%)	1(group b)	
Ning *et al*, 2023 [37]	NR	NR	56/58 (96%)	21/28 (71.4%)	5/147 (3.4%)	3/147 (2.04%)	2/147 (1.36%)	NR	519.5 (306–728) days	9/28 (32.14%)	2/28 (7.14%)	7/28	
Nishida *et al*, 2017 [30]	NR	NR	NR	19/37 (51.35%)	3/112 (2.7%)	0	3/112 (2.70%)	NR	27.1 (1.6–59.3) months	18/37 (48.64%)	NR	18 (48.6%)	
Nishimura *et al*, 2011 [43]	NR	NR	4/7 (57.14%)	1/7 (14.28%)	0/7 (0%)	0	0	0	22 (16-88 months)	1/8 (12.50%)	1/8 (12.50%)	3/8 (37.5%)	
Ohmiya *et al*, 2009 [31]	91	NR	45/47 (95.74%)	11/16 (68.75%)	4/47 (8.5%)	0	1/47 (2.12%)	3/114 (2.6%)	16 (2-43) months	5/16 (31%)	2/16 (12.50%)	3/16 (19%)	
Parakkal *et al*, 2013 [19]	68	0	N/A	12/23 (52.17%)	3/91 (3.29%)	2/91 (2.19%)	1/91 (1.09%)	NR	435 (68 – 1002) days	-	14/91 (15.38%)	11/23 (48%)	
Pohl *et al*, 2007 [33]	NR	NR	8/10 (80%)	6/10 (60%)	0	0	0	0	10 (4-16) months	3/8 (37.5%)	NR	4/10 (40%)	
Sunada *et al*, 2016 [34]	NR	NR	N/A	74/85 (87.3%)	5/473 (1%)	1/473 (0.2%)	4/473 (0.8%)	NR	41.9 months	NR	64/85 (75.3%)	21/85 (24.7%)	
Yamada *et al*, 2012 [35]	NR	NR	N/A	37/46 (80%)	NR	NR	NR	NR	52 months	30/46 (64%)	NR	13/46 (28%)	
Yoshida *et al*, 2020 [38]	NR	NR	8/10 (80%)	5/10 (50%)	0	0	0	0	33.3 (4 to 96) months	7/10 (70%)	NR	2/10 (20%)	

CD, Crohn's disease; DBE, double-balloon enteroscopy; NR, not reported; IQR, interquartile range; SD, standard deviation; TI, terminal ileum

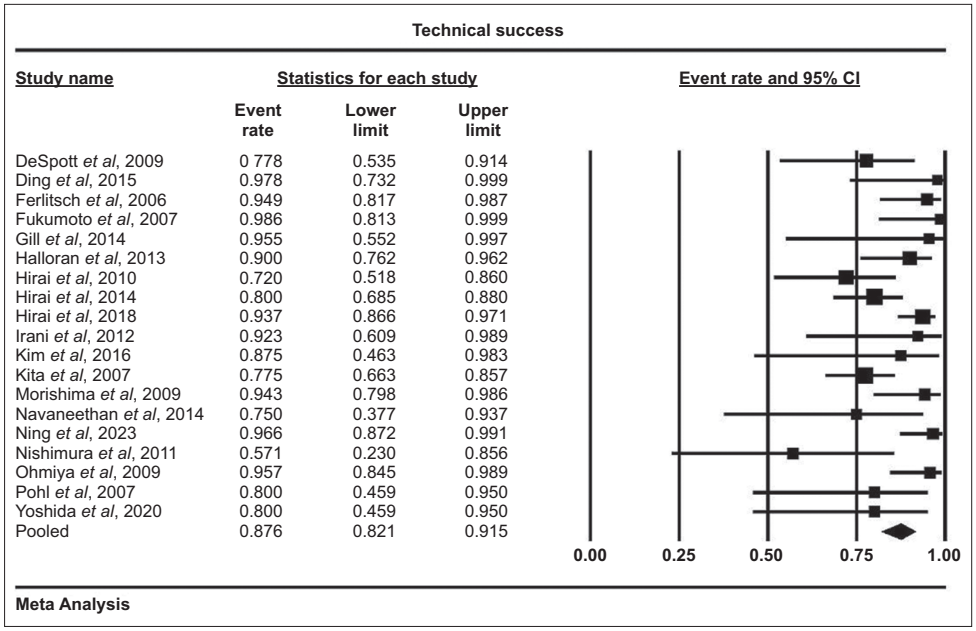


Figure 1 Forest plot, technical success of balloon-assisted endoscopy
CI, confidence interval

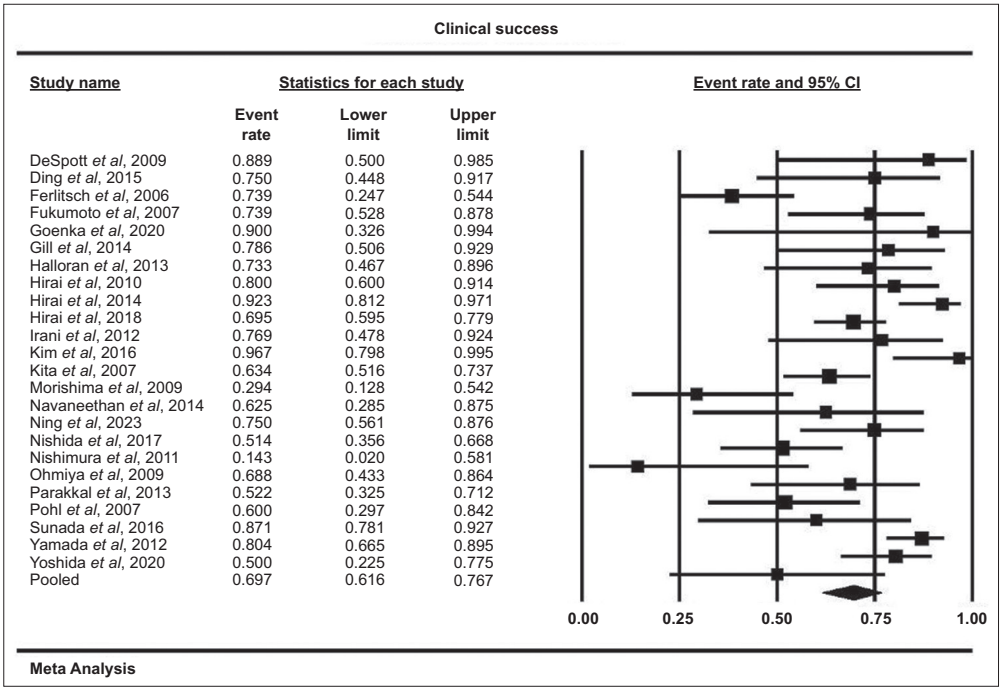


Figure 2 Forest plot, clinical success of balloon-assisted endoscopy
CI, confidence interval

events per procedure was 5.5% (95%CI 3.5-8.4; I^2=57%). The risk of bleeding was 2.5% (95%CI 1.4-4.2; I^2=28%), while the risk of perforation was 2.7% (95%CI 1.6-4.5; I^2=3%). Other overall adverse events, including SBO, localized peritonitis, pancreatitis, and hyperamylasemia associated with the procedure came to 4.2% (95%CI 1.1-1.44; I^2=11%). The results are summarized in Table 2 and the corresponding forest plots are illustrated in Supplementary Figs. 2-5. There were no reported deaths with BAE. The adverse events were further categorized according to the ASGE Lexicon criteria: the pooled mild adverse event rate associated with BAE was 2.3% (95%CI 1.5-3.4; I^2=0%), the moderate adverse event rate was 1.9% (95%CI 1.2-2.9; I^2=0%), and the severe adverse event rate was 2.9% (95%CI 1.8-4.7; I^2=0%), while the fatal adverse event rate

Table 2 Summary of pooled rates

Outcomes	Pooled rate, I^2 (proportions, mean difference); number of studies
Technical success	87.6% (82.1-91.5%); 53%; 19
Clinical success	69.7% (61.6-76.7%); 71%; 24
Major complications	5.5% (3.5-8.4%); 57%; 22
Bleeding	2.5% (1.4-4.2%); 28%; 16
Perforation	2.7% (1.6-4.5%); 3%; 20
Other complications	4.2% (1.1-1.44%); 11%; 5
ASGE Lexicon	
Mild	2.3% (1.5-3.4%); 0%; 26
Moderate	1.9% (1.2-2.9%); 0%; 26
Severe	2.9% (1.8-4.7%); 0%; 26
Fatal	1.2% (0.7-2.1%); 0%; 22

Publication bias, 2-tailed P-value <0.01

ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval

was 1.2% (95%CI 0.7-2.1; I^2=0%) The corresponding forest plots are illustrated in Supplementary Figs. 6-9.

The pooled rate of recurrence after the first dilation was 42.3% (95%CI 16.9-72.5; I^2=59%). The pooled rate of patients who required repeat endoscopic balloon dilation was 23.9% (95%CI 14.1-37.5%; I^2=85%), while the pooled rate of repeat surgery was 25.3% (95%CI 11.8-46.0%; I^2=44%). The corresponding forest plots are illustrated in Supplementary Figs. 10-12.

Validation of meta-analysis results

Sensitivity analysis

To assess whether any single study had a dominant effect on the meta-analysis, we excluded 1 study at a time and analyzed the effect on the main summary estimate. In this analysis, no single study significantly affected the outcome or the heterogeneity.

Heterogeneity

We assessed the dispersion of the calculated rates using the PI and I^2 percentage values. The PI gives an idea of the range of the dispersion and I^2 tells us what proportion of the dispersion is true rather than chance. Despite high I^2 values, the pooled rates of mean sessions of treatment, and mean pre- and post-treatment hemoglobin had narrow prediction intervals, suggesting minimal dispersion of effects. We observed moderate heterogeneity in the rates of technical success and major complications (I^2=53% and 57%, respectively). Low heterogeneity was noted for bleeding, perforation and other complication rates (I^2=28%, 3% and 11%, respectively). However, there was substantial heterogeneity in the clinical success rates (I^2=71%). No heterogeneity (I^2=0) was noted for ASGE Lexicon mild, moderate, severe and fatal adverse event rates.

Publication bias

On the basis of visual inspection of the funnel plots, as well as quantitative measurement that used the Egger regression test, there was evidence of publication bias. The funnel plot study scatter indicated the possibility of "small study effect" confounding. Further statistics using the fail-Safe N and Duval and Tweedie's "Trim and Fill" tests revealed the impact of the possible publication bias to be minimal, not changing the calculated estimate or the conclusion of this meta-analysis. The funnel plot is summarized in Supplementary Fig. 13.

Discussion

As there remains a lack of comprehensive reporting of the clinical outcomes and associated complications linked to BAE for small intestine strictures, we performed the first meta-analysis of good-quality studies consisting of the largest comparative cohort of studies to date reporting the overall pooled rates of the outcomes exclusively for BAE. In this meta-analysis of 26 studies involving 1570 patients, we analyzed the pooled technical success and therapeutic success of BAE for CD-related small intestine strictures, which were 87.6% and 69.7% respectively. The overall rate of major adverse events with BAE was found to be 5.5%. The overall low incidence of major adverse events at 5.5%, particularly perforation (2.7%) and bleeding (2.5%), reinforces the procedure's safety profile.

These findings confirm BAE as a highly effective modality for managing CD-related small intestine strictures. Our analysis shows that BAE for the treatment of CD-related small intestinal strictures can be performed safely, with a clinical success rate of just under 70%. Unlike prior research, where variations in reporting methods were prevalent, our analysis only encompassed studies with clear and consistent data presentation, with 18 of 26 (70%) studies being graded as high-quality [36,55,56].

A recent review performed by Bettenworth *et al*, which evaluated 18 clinical studies, reported the technical and short-term clinical efficacy of BAE in this same clinical context to be 94.9% and 82.3%, respectively [54]. However, the results of our study showed that both the technical success and the clinical success rates were much lower, which could be attributed to the different sample sizes in the 2 studies. In this same study, it was reported that 48.3% of patients experienced symptom recurrence during follow up, which was relatively higher than in our study, and 38.8% of the patients required re-dilation, which was also higher compared to our study. The overall adverse event rates were similar (5.5% vs. 5.3%).

The rates of mild, moderate, severe and fatal adverse events were reported to be 2.3%, 1.9%, 2.9% and 1.2%, respectively. The calculated pooled rate of adverse events was as follows: perforation 2.7%, bleeding 2.5%, and other complications, including SBO, localized peritonitis, pancreatitis, and hyperamylasemia associated with the procedure, were 4.2%. This is the first study to report these rates in the BAE population via meta-analysis.

The strengths of this analysis are as follows: systematic literature search with well-defined inclusion criteria, carefully excluding redundant studies, the inclusion of all high-quality

studies, detailed extraction of adverse events, their subcategories, technical success and clinical success information, rigorous evaluation of study quality, low to moderate heterogeneity, narrow range of prediction intervals, statistics to establish and/or refute the validity of the results of the analysis. Moreover, an absence of patient loss to follow up in the data retrieval process further bolsters the reliability of our conclusions. The findings of this study offer valuable insights into the efficacy and safety of BAE, reinforcing its role as a minimally invasive alternative to surgery for managing CD-related strictures and potentially guiding future clinical practices and research.

Our study had some limitations. There was an inherent heterogeneity between the different studies in our analysis. Our study relied heavily on prospective studies and retrospective studies, without any major randomized control trials. Despite these limitations, our study provides valuable information on the pooled success rates and adverse outcomes associated with BAE.

In conclusion, the technical and clinical success rates of BAE were 87.6% and 69.7%, respectively. The pooled rate of major adverse events was 5.5%. Our findings are particularly relevant in light of the current trend toward less invasive management of CD strictures, where BAE serves as a less invasive alternative to surgical intervention, which carries a higher risk profile and significant morbidity. The non-surgical approach of BAE, with its less intensive post-procedure recovery and preservation of bowel integrity, is a compelling option for patients and clinicians alike.

Summary Box

What is already known:

- Crohn's disease (CD) often leads to the formation of strictures in the small intestine, with a significant percentage of patients requiring intervention
- Balloon-assisted enteroscopy (BAE) has been used for endoscopic balloon dilation of small intestinal strictures in CD, offering a minimally invasive alternative to surgery
- Previous studies have reported varied success rates and complications associated with BAE, but data on long-term outcomes and safety are limited

What the new findings are:

- BAE has a high pooled technical success rate of 87.6% and a clinical success rate of 69.7% in the treatment of small bowel strictures in CD
- The pooled risk of major complications, including perforation and bleeding, is low, with perforation occurring in 2.7% and bleeding in 2.5% of cases
- The rate of symptom recurrence after initial dilation is 42.3%, with 23.9% of patients requiring repeat dilation and 25.3% ultimately undergoing surgery
- BAE offers a safe and effective first-line approach for managing small bowel strictures in CD

References

1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;**142**:46-54.
2. Gajendran M, Loganathan P, Catinella AP, Hashash JG. A comprehensive review and update on Crohn's disease. *Dis Mon* 2018;**64**:20-57.
3. Spekhorst LM, Visschedijk MC, Alberts R, et al; Dutch initiative on Crohn and Colitis. Performance of the Montreal classification for inflammatory bowel diseases. *World J Gastroenterol* 2014;**20**:15374-15381.
4. Feuerstein JD, Cheifetz AS. Crohn disease: epidemiology, diagnosis, and management. *Mayo Clin Proc* 2017;**92**:1088-1103.
5. Yano Y, Matsui T, Hirai F, et al. Cancer risk in Japanese Crohn's disease patients: investigation of the standardized incidence ratio. *J Gastroenterol Hepatol* 2013;**28**:1300-1305.
6. Yamamoto T, Watanabe T. Surgery for luminal Crohn's disease. *World J Gastroenterol* 2014;**20**:78-90.
7. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;**8**:244-250.
8. Bettenworth D, Gustavsson A, Atreja A, et al. A pooled analysis of efficacy, safety, and long-term outcome of endoscopic balloon dilation therapy for patients with stricturing Crohn's disease. *Inflamm Bowel Dis* 2017;**23**:133-142.
9. Rieder F, Bettenworth D, Ma C, et al. An expert consensus to standardise definitions, diagnosis and treatment targets for anti-fibrotic stricture therapies in Crohn's disease. *Aliment Pharmacol Ther* 2018;**48**:347-357.
10. Bettenworth D, Mücke MM, Lopez R, et al. Efficacy of endoscopic dilation of gastroduodenal Crohn's disease strictures: a systematic review and meta-analysis of individual patient data. *Clin Gastroenterol Hepatol* 2019;**17**:2514-2522.
11. Rieder F, Latella G, Magro F, et al. European Crohn's and Colitis Organisation topical review on prediction, diagnosis and management of fibrostenosing Crohn's disease. *J Crohns Colitis* 2016;**10**:873-885.
12. Erkelens GW, van Deventer SJ. Endoscopic treatment of strictures in Crohn's disease. *Best Pract Res Clin Gastroenterol* 2004;**18**:201-207.
13. Adamina M, Bonovas S, Raine T, et al. ECCO Guidelines on therapeutics in Crohn's disease: surgical treatment. *J Crohns Colitis* 2020;**14**:155-168.
14. Baniya R, Upadhaya S, Subedi SC, et al. Balloon enteroscopy versus spiral enteroscopy for small-bowel disorders: a systematic review and meta-analysis. *Gastrointest Endosc* 2017;**86**:997-1005.
15. Matsui T, Ikeda K, Tsuda S, et al. Long-term outcome of endoscopic balloon dilation in obstructive gastrointestinal Crohn's disease: a prospective long-term study. *Diagn Ther Endosc* 2000;**6**:67-75.
16. Despott EJ, Gupta A, Burling D, et al. Effective dilation of small-bowel strictures by double-balloon enteroscopy in patients with symptomatic Crohn's disease (with video). *Gastrointest Endosc* 2009;**70**:1030-1036.
17. Sabaté JM, Villarejo J, Bouhnik Y, et al. Hydrostatic balloon dilatation of Crohn's strictures. *Aliment Pharmacol Ther* 2003;**18**:409-413.
18. Hirai F, Beppu T, Sou S, Seki T, Yao K, Matsui T. Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. *Dig Endosc* 2010;**22**:200-204.
19. Deepak P, Quinn KP, Fletcher JG, et al. Utility and safety of balloon-assisted enteroscopy in small bowel Crohn's disease: single-center cohort experience: 667. *Am J Gastroenterol* 2016;**111**:S304.
20. Ding NS, Mohammad S, Hendy P, Humphries A, Hart A. P518 Five year outcomes of Crohn's small bowel strictures treated with double balloon enteroscopic dilatation. *J Crohn's Colitis* 2015;**9**

(suppl_1):S338-S339.
21. Fukumoto A, Tanaka S, Yamamoto H, et al. Diagnosis and treatment of small-bowel stricture by double balloon endoscopy. *Gastrointest Endosc* 2007;**66**:S108-S112.
22. Gill RS, Kaffes AJ. Small bowel stricture characterization and outcomes of dilatation by double-balloon enteroscopy: a single-centre experience. *Therap Adv Gastroenterol* 2014;**7**:108-114.
23. Halloran BP, Melmed GY, Jamil LH, Lo SK, Vasiliauskas E, Mann NK. Sa1649 double balloon enteroscopy-assisted stricture dilation delays surgery in patients with small bowel Crohn's disease. *Gastrointest Endosc* 2013;**77**:AB280.
24. Hirai F, Beppu T, Sou S, Seki T, Yao K, Matsui T. Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. *Dig Endosc* 2010;**22**:200-204.
25. Kim JS, Cho YS. P532. Effectiveness of balloon dilation using single balloon enteroscopy in multiple small bowel stricture. *J Crohns Colitis* 2016;**10**(Suppl 1):S371.
26. Hirai F, Beppu T, Takatsu N, et al. Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease. *Dig Endosc* 2014;**26**:545-551.
27. Milewski J, Zuk K, Nasierowska-Guttmejer A, Rydzewska G. Sa1648 Double balloon enteroscopy (DBE) in suspected small-bowel Crohn's disease - one center experience. *Gastrointest Endosc* 2013;**77**:AB279-AB280.
28. Morishima K, Ohmiya N, Nakamura M, et al. The evaluation of the postoperative Crohn's jejunoileitis and balloon dilation for the strictures by using double balloon enteroscopy (DBE). *Gastrointest Endosc* 2009;**69**:PAB198.
29. Navaneethan U, Vargo JJ, Menon KV, Sanaka MR, Tsai CJ. Impact of balloon-assisted enteroscopy on the diagnosis and management of suspected and established small-bowel Crohn's disease. *Endosc Int Open* 2014;**2**:E201-E206.
30. Nishida Y, Hosomi S, Yamagami H, et al. Analysis of the risk factors of surgery after endoscopic balloon dilation for small intestinal strictures in Crohn's disease using double-balloon endoscopy. *Intern Med* 2017;**56**:2245-2252.
31. Ohmiya N, Arakawa D, Nakamura M, et al. Small-bowel obstruction: diagnostic comparison between double-balloon endoscopy and fluoroscopic enteroclysis, and the outcome of enteroscopic treatment. *Gastrointest Endosc* 2009;**69**:84-93.
32. Kroner PT, Brahmbhatt BS, Bartel MJ, Stark ME, Lukens FJ. Yield of double-balloon enteroscopy in the diagnosis and treatment of small bowel strictures. *Dig Liver Dis* 2016;**48**:446-448.
33. Pohl J, May A, Nachbar L, Ell C. Diagnostic and therapeutic yield of push-and-pull enteroscopy for symptomatic small bowel Crohn's disease strictures. *Eur J Gastroenterol Hepatol* 2007;**19**:529-534.
34. Sunada K, Shinozaki S, Nagayama M, et al. Long-term outcomes in patients with small intestinal strictures secondary to Crohn's disease after double-balloon endoscopy-assisted balloon dilation. *Inflamm Bowel Dis* 2016;**22**:380-386.
35. Yamada K, Ohmiya N, Nagura A, et al. Sa1709 usefulness of endoscopic diagnosis of postoperative small-bowel lesions and balloon dilation for strictures in patients with Crohn's disease at double-balloon enteroscopy. *Gastrointest Endosc* 2012;**75**:AB251.
36. Goenka MK, Afzalpurkar S, Rai VK, et al. Single-balloon enteroscopy in management of small-bowel disorders. *Indian J Gastroenterol* 2020;**39**:550-556.
37. Ning SB, Yang H, Li B, et al. Balloon-assisted enteroscopy-based endoscopic stricturotomy for deep small bowel strictures from Crohn's disease: First cohort study of a novel approach. *Dig Liver Dis* 2023;**55**:1397-1402.
38. Yoshida A, Takatsuka K, Ueno F, Kobayashi K, Iwabuchi S. Therapeutic single-balloon enteroscopy for small intestinal stenosis may modify outcome of patients with Crohn's disease receiving infliximab: 1160. *Am J Gastroenterol* 2010;**105**:S421.
39. Ferlitsch A, Reinisch W, Püspök A, et al. Safety and efficacy of endoscopic balloon dilation for treatment of Crohn's disease strictures. *Endoscopy* 2006;**38**:483-487.
40. Hirai F, Andoh A, Ueno F, et al. Efficacy of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease: a nationwide, multi-centre, open-label, prospective cohort study. *J Crohns Colitis* 2018;**12**:394-401.
41. Irani S, Balmadrid B, Seven G, et al. Balloon dilation of benign small bowel strictures using double balloon enteroscopy: 5-year review from a single tertiary referral center. *Gastrointest Interv* 2012;**1**:74-78.
42. Kita H, Yamamoto H, Yano T, et al. Double balloon endoscopy in two hundred fifty cases for the diagnosis and treatment of small intestinal disorders. *Inflammopharmacology* 2007;**15**:74-77.
43. Nishida Y, Hosomi S, Yamagami H, et al. Analysis of the risk factors of surgery after endoscopic balloon dilation for small intestinal strictures in Crohn's disease using double-balloon endoscopy. *Intern Med* 2017;**56**:2245-2252.
44. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;**25**:603-605.
45. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008-2012.
46. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177-188.
47. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010;**71**:446-454.
48. Sutton AJ, Abrams KR, Jones DR. An illustrated guide to the methods of meta-analysis. *J Eval Clin Pract* 2001;**7**:135-148.
49. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-560.
50. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol* 2011;**64**:1294-1302.
51. Kanwal F, White D. "Systematic reviews and meta-analyses" in Clinical Gastroenterology and Hepatology. *Clin Gastroenterol Hepatol* 2012;**10**:1184-1186.
52. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009;**172**:137-159.
53. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;**342**:d549.
54. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;**337**:867-872.
55. Bettenworth D, Bokemeyer A, Kou L, et al. Systematic review with meta-analysis: efficacy of balloon-assisted enteroscopy for dilation of small bowel Crohn's disease strictures. *Aliment Pharmacol Ther* 2020;**52**:1104-1116.
56. Gill RS, Kaffes AJ. Small bowel stricture characterization and outcomes of dilatation by double-balloon enteroscopy: a single-centre experience. *Therap Adv Gastroenterol* 2014;**7**:108-114.

Supplementary material

Appendix A Literature search strategy

Searches ran on 12/11/2023

OVID

Database(s): Ovid MEDLINE(R) ALL (1946 to December 11, 2023), EBM Reviews - Cochrane Central Register of Controlled Trials December 2023, EBM Reviews - Cochrane Database of Systematic Reviews

#	Searches	Results
1	*Crohn's disease/or *endoscopic dilation/or small intestine strictures or *ED	246
2	*Single balloon enteroscopy/or *double balloon enteroscopy/or *BAE/or balloon-assisted enteroscopy.mp. or BAE.mp.	333
3	*BAE/or *balloon-assisted enteroscopy/or BAE.mp.	428
4	1 and 2 and 3	1007
5	Remove duplicates from 4	692

PubMed, 811 results (English only)

((crohn's disease [majr] AND endoscopic dilation [majr]) OR "BAE"[majr] OR balloon-assisted enteroscopy.[tiab]) OR "single balloon enteroscopy"[majr] OR "double balloon enteroscopy"[majr] small intestine strictures"[majr] AND ("endoscopic dilation"[majr] OR BAE [tiab] OR double balloon enteroscopy [tiab]) OR single balloon enteroscopy [tiab]) OR SBE [tiab] OR DBE [tiab] AND ("endoscopic balloon dilation"[majr] OR "balloon-assisted enteroscopy"[majr] OR BAE [tiab])

Scopus

1	TITLE-ABS-KEY (("crohn's disease" OR "CD" OR balloon assisted enteroscopy) AND ("endoscopic dilation" OR "BAE" OR "single balloon enteroscopy" OR "double balloon enteroscopy") AND ("BAE" OR "DBE" OR "SBE") AND (small intestine stricture))	383

Web of Science

1	("crohn's disease" OR "CD" OR balloon assisted enteroscopy) AND ("endoscopic dilation" OR "BAE" OR "single balloon enteroscopy" OR "double balloon enteroscopy") AND ("EUS-BD" OR "BAE" OR "DBE" OR "SBE") AND (small intestine stricture)	360

2246. total article references
250. duplicates found in EndNote
1996. total references in EndNote

Appendix B PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
		TITLE	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
		METHODS	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, 8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8, 9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
		RESULTS	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10

(*Contd...*)

Section/topic	#	Checklist item	Reported on page #
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1, Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, Supplementary Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11, forest plot figures, Table 3
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	10, 11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
		DISCUSSION	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12, 13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
		FUNDING	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6 (7): e1000097. doi: 10.1371/journal.pmed1000097
For more information, visit: www.prisma-statement.org

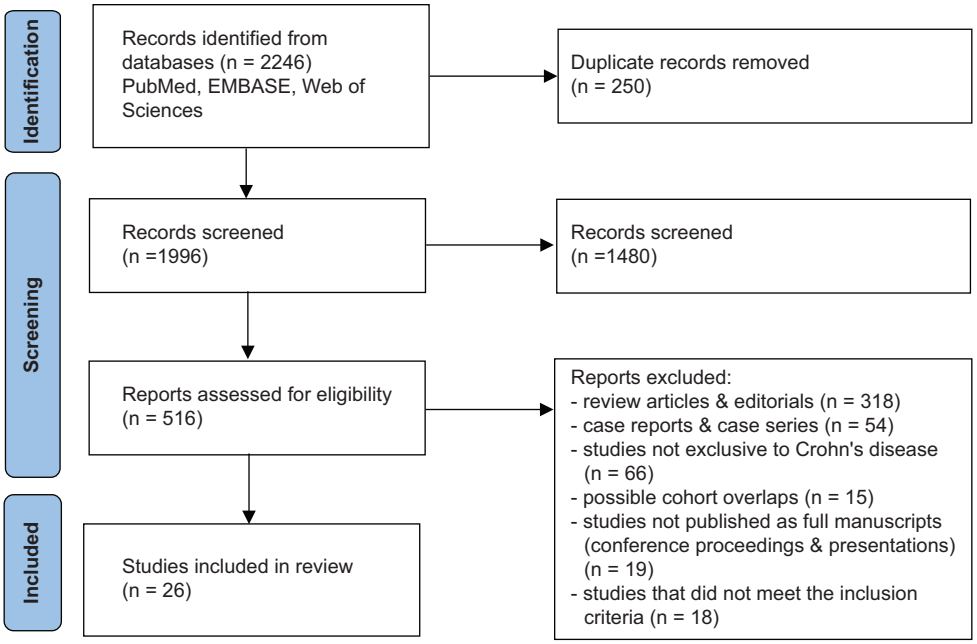
Appendix C MOOSE checklist

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

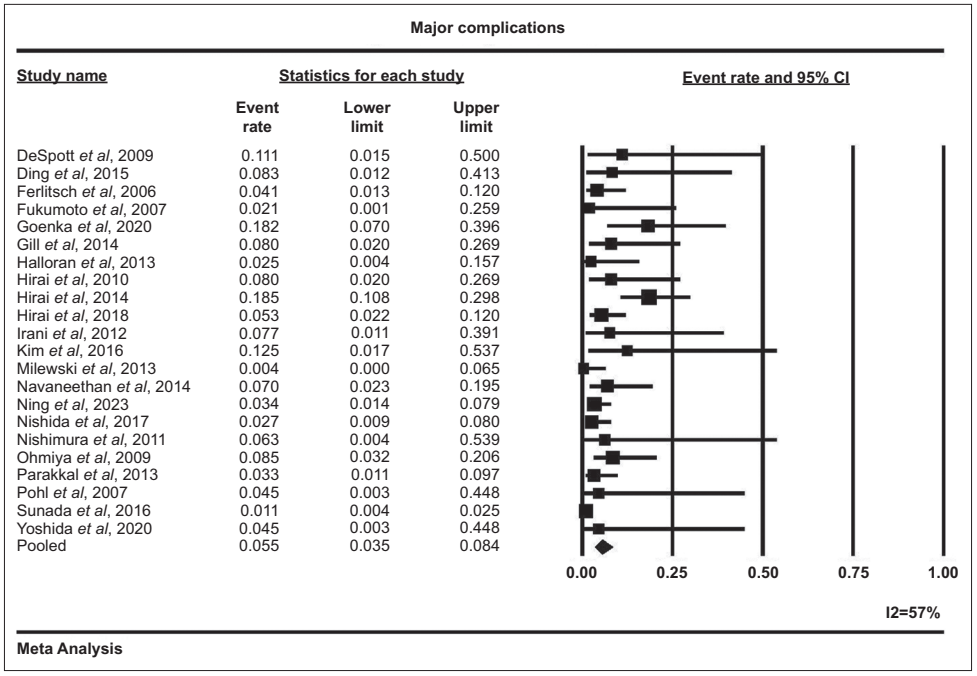
Item No	Recommendation	Reported on Page No
	Reporting of background should include	
1	Problem definition	6
2	Hypothesis statement	-na-
3	Description of study outcome (s)	7-8
4	Type of exposure or intervention used	7-8
5	Type of study designs used	7-8
6	Study population	7-8
	Reporting of search strategy should include	
7	Qualifications of searchers (eg, librarians and investigators)	7 Appendix-A
8	Search strategy, including time period included in the synthesis and key words	7, Appendix-A
9	Effort to include all available studies, including contact with authors	9
10	Databases and registries searched	Appendix-A
11	Search software used, name and version, including special features used (eg, explosion)	-na-
12	Use of hand searching (eg, reference lists of obtained articles)	7
13	List of citations located and those excluded, including justification	fig-1
14	Method of addressing articles published in languages other than English	8
15	Method of handling abstracts and unpublished studies	8
16	Description of any contact with authors	8
	Reporting of methods should include	
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	8
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	-NA-
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	8
22	Assessment of heterogeneity	8, 9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	9
24	Provision of appropriate tables and graphics	Provided
	Reporting of results should include	
25	Graphic summarizing individual study estimates and overall estimate	Figure 1,2 Suppl. Figures 1-13
26	Table giving descriptive information for each study included	Table 1, 2
27	Results of sensitivity testing (eg, subgroup analysis)	11
28	Indication of statistical uncertainty of findings	11

Supplementary Table 1 Study quality assessment

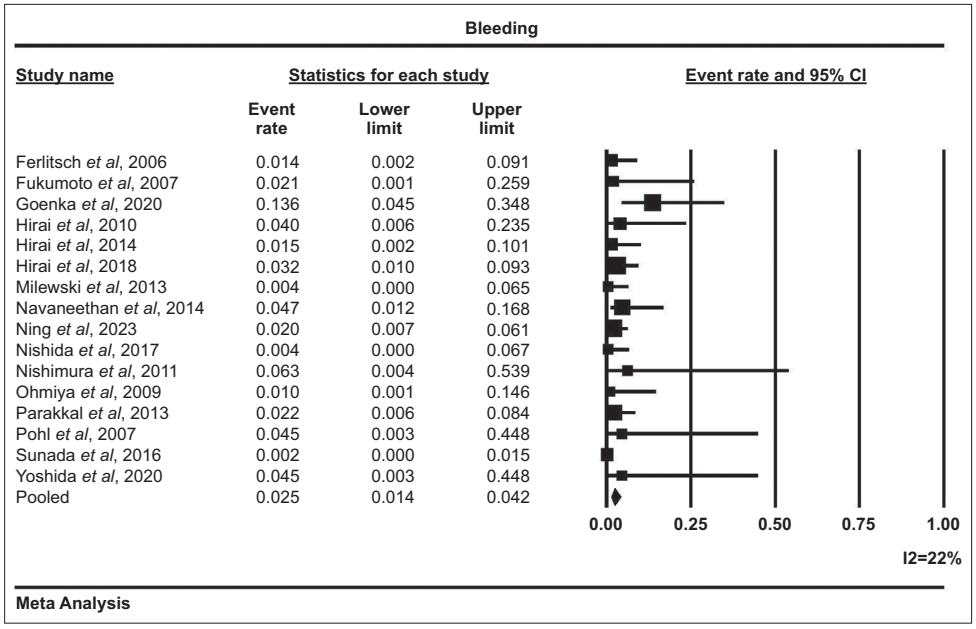
Study, year [ref.]	Selection				Comparability		Outcome		Score	Quality
	Representativeness of the average adult in community	Cohort size	Information on clinical outcomes	Outcome not present at start	Factors comparable between the groups	Adequate clinical assessment	Follow-up time	Adequacy of follow up	Max=8	High >6, medium 4 to 6, low <4
	Population based: 1; Multi-center: 0.5; Single-center: 0	>40 patients: 1; 39 to 20: 0.5; <20: 0	Information with clarity: 1; Information derived from percentage value: 0.5; unclear: 0	not present: 1; present: 0	yes: 1; no: 0	yes: 1; no: 0	yes: 1; not mentioned: 0	All patients followed-up: 1; >50% followed-up: 0.5; <50% followed-up OR not mentioned: 0		
DeSpott *et al*, 2009 [16]	1	0	1	1	1	1	1	1	7	High
Ding *et al*, 2015 [20]	0	0	1	1	1	1	1	1	6	High
Ferlitsch *et al*, 2006 [39]	0	1	1	1	1	1	1	1	6	High
Fukumoto *et al*, 2007 [21]	0.5	1	1	1	1	1	0	0	5.5	Medium
Goenka *et al*, 2020 [36]	0	1	1	1	1	1	0	0	5	Medium
Gill *et al*, 2014 [22]	0	0.5	1	1	1	1	1	1	6.5	High
Halloran *et al*, 2013 [23]	0	0.5	1	1	1	1	1	1	6.5	High
Hirai *et al*, 2010 [24]	0	0.5	1	1	1	1	1	1	6.5	High
Hirai *et al*, 2014 [26]	0	1	1	1	1	1	0	0	5	Medium
Hirai *et al*, 2018 [40]	0.5	1	1	1	1	1	0	0	5.5	Medium
Irani *et al*, 2012 [41]	0	0	1	1	1	1	1	1	6	High
Kim *et al*, 2016 [25]	0	0	1	1	1	1	1	1	6	High
Kita *et al*, 2007 [42]	0	1	1	1	1	1	0	0	5	Medium
Kroner *et al*, 2016 [32]	0	1	1	1	1	1	0	0	5	Medium
Milewski *et al*, 2013 [27]	0	1	1	1	1	1	0	0	5	Medium
Morishima *et al*, 2009 [28]	0	0.5	1	1	1	1	1	1	6.5	High
Navaneethan *et al*, 2014 [29]	0	1	1	1	1	1	0	0	5	Medium
Ning *et al*, 2023 [37]	0.5	0.5	1	1	1	1	1	1	7	High
Nishida *et al*, 2017 [30]	0	0.5	1	1	1	1	1	1	6.5	High
Nishimura *et al*, 2011 [43]	0	0	1	1	1	1	1	1	6	High
Ohmiya *et al*, 2009 [31]	0	1	1	1	1	1	1	1	6	High
Parakkal *et al*, 2013 [19]	0	1	1	1	1	1	1	1	6	High
Pohl *et al*, 2007 [33]	0	0	1	1	1	1	1	1	6	High
Sunada *et al*, 2016 [34]	0	1	1	1	1	1	1	1	7	High
Yamada *et al*, 2012 [35]	0	1	1	1	1	1	1	1	7	High
Yoshida *et al*, 2020 [38]	0	0	1	1	1	1	1	1	6	High



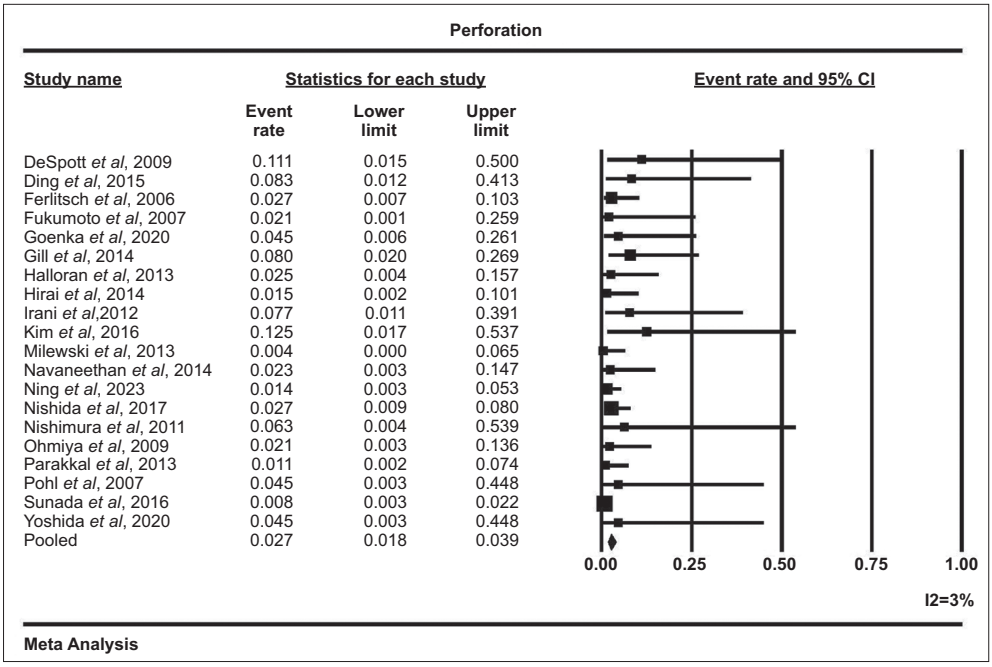
Supplementary Figure 1 PRISMA study selection flow chart



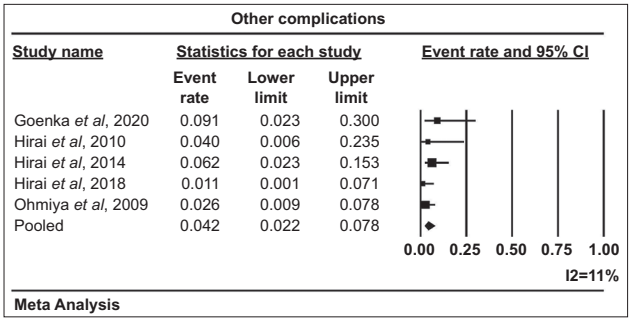
Supplementary Figure 2 Forest plot, major complications with balloon-assisted endoscopy
CI, confidence interval



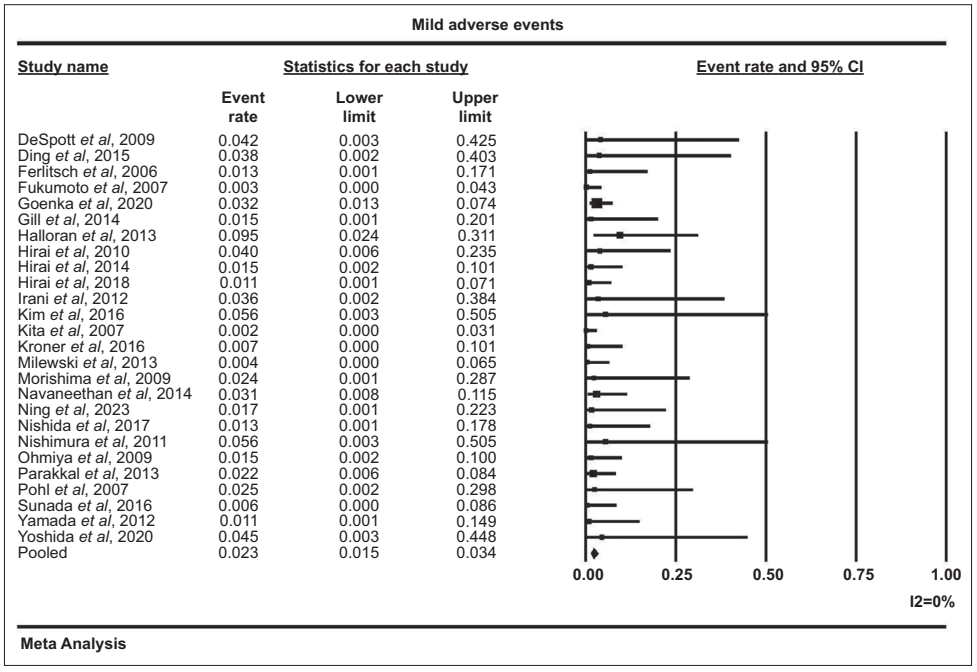
Supplementary Figure 3 Forest plot, risk of bleeding associated with balloon-assisted endoscopy
CI, confidence interval



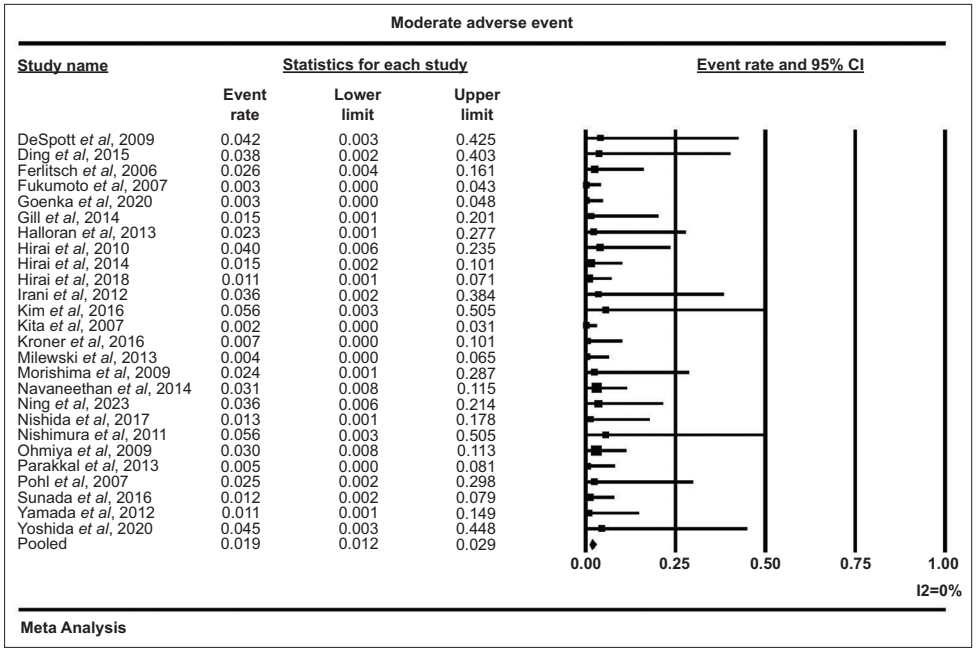
Supplementary Figure 4 Forest plot, risk of perforation associated with balloon-assisted endoscopy
CI, confidence interval



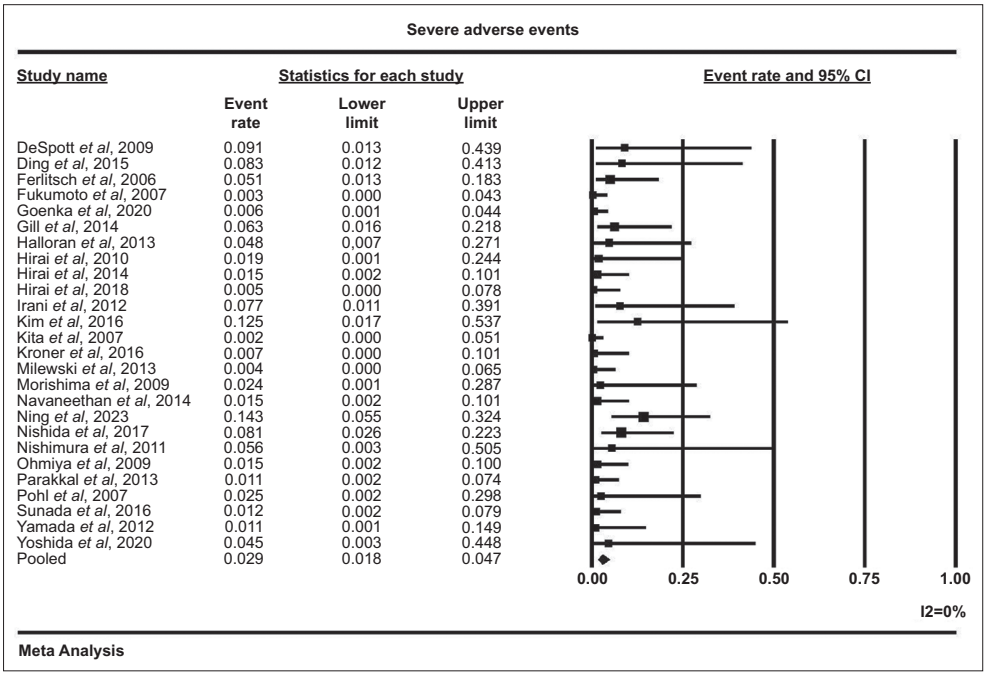
Supplementary Figure 5 Forest plot, other complications with balloon-assisted endoscopy
CI, confidence interval



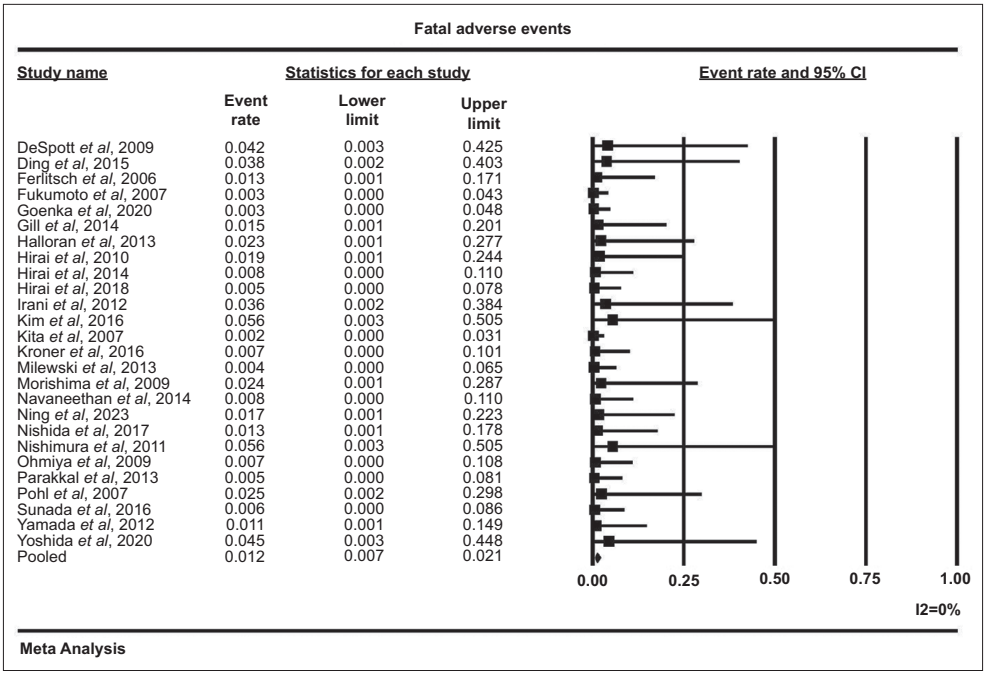
Supplementary Figure 6 Forest plot, mild adverse events with balloon-assisted endoscopy
CI, confidence interval



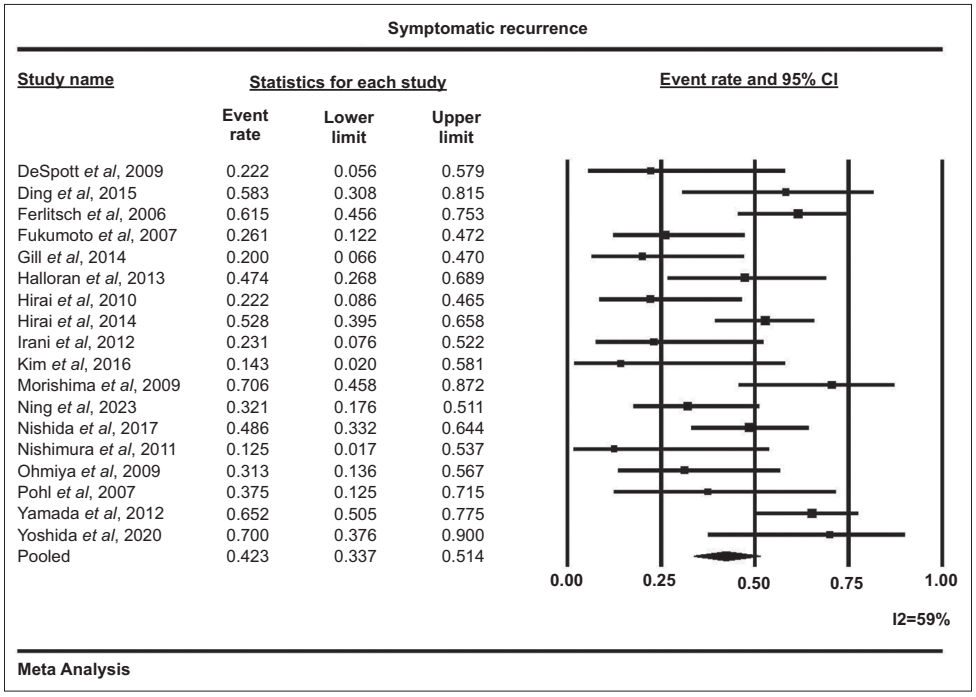
Supplementary Figure 7 Forest plot, moderate adverse events with balloon-assisted endoscopy
CI, confidence interval



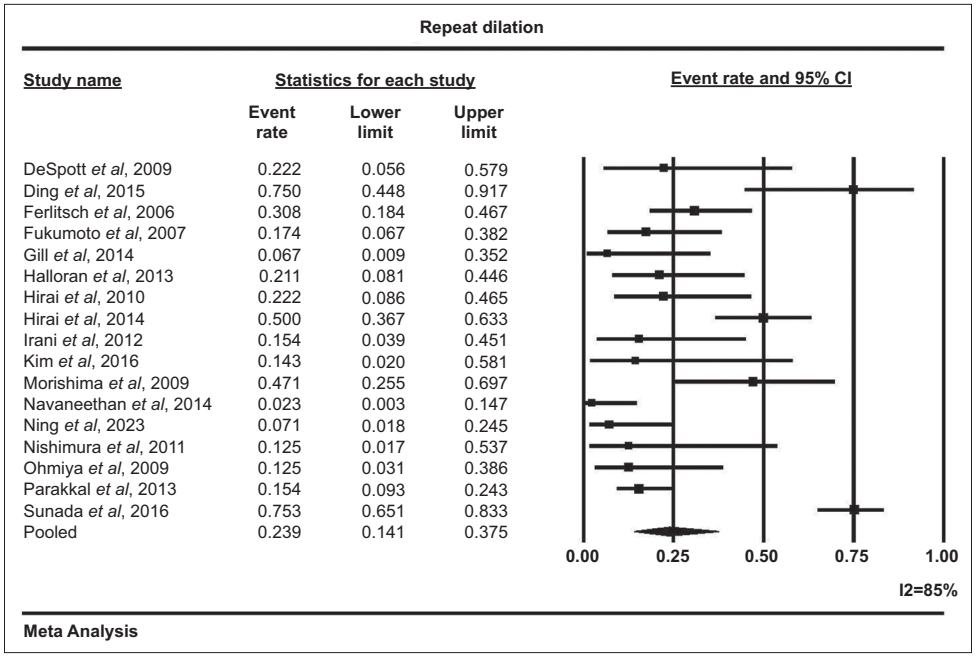
Supplementary Figure 8 Forest plot, severe adverse events with balloon-assisted endoscopy
CI, confidence interval



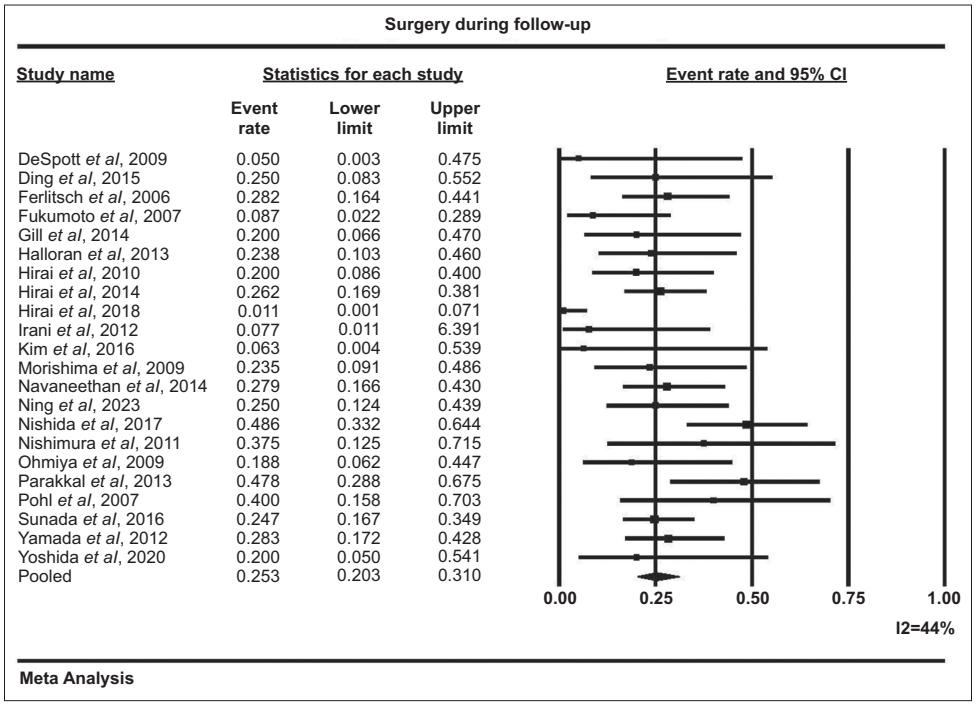
Supplementary Figure 9 Forest plot, fatal adverse events with balloon-assisted endoscopy
CI, confidence interval



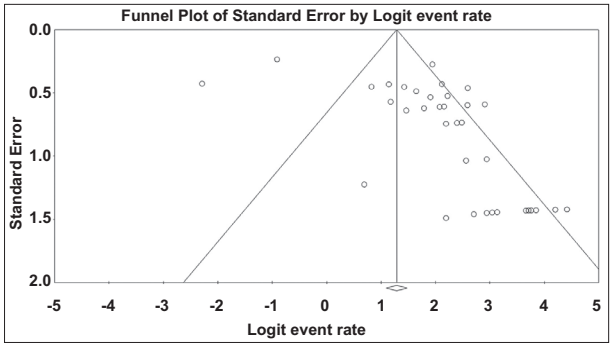
Supplementary Figure 10 Forest plot, rates of symptomatic recurrence with balloon-assisted endoscopy
CI, confidence interval



Supplementary Figure 11 Forest plot, rates of repeat dilation with balloon-assisted endoscopy
CI, confidence interval



Supplementary Figure 12 Forest plot, rates of surgery required during follow up after balloon-assisted endoscopy
CI, confidence interval



Supplementary Figure 13 Funnel plot, publication bias