SYSTEMATIC REVIEW AND META-ANALYSIS

Diagnostic and therapeutic yields of early capsule endoscopy and device-assisted enteroscopy in the setting of overt GI bleeding: a systematic review with meta-analysis

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Background and Aims: Small-bowel capsule endoscopy (SBCE) and device-assisted enteroscopy (DAE) are essential in obscure GI bleeding (OGIB) management. However, the best timing for such procedures remains unknown. This meta-analysis aimed to compare, for the first time, diagnostic and therapeutic yields, detection of active bleeding and vascular lesions, recurrent bleeding, and mortality of "early" versus "nonearly" SBCE and DAE.

Methods: MEDLINE, ScienceDirect, and Cochrane Central Register of Controlled Trials were searched to identify studies comparing early versus nonearly SBCE and DAE. Random-effects meta-analysis was performed; reporting quality was assessed.

Results: From 1974 records, 39 were included (4825 patients). Time intervals for the early approach varied, within 14 days in SBCE and 72 hours in DAE. The pooled diagnostic and therapeutic yields of early DAE were superior to those of SBCE (7.97% and 20.89%, respectively; $P < .05$). The odds for active bleeding (odds ratio [OR], 5.09; $I^2 = 53\%$), positive diagnosis (OR, 3.99; $I^2 = 45\%$), and therapeutic intervention (OR, 3.86; $I^2 = 67\%$) were higher in the early group for SBCE and DAE ($P < .01$). Subgroup effects in diagnostic yield were only identified for the early group sample size. Our study failed to identify differences when studies were classified according to time intervals for early DAE ($I^2 < 5\%$), but the analysis was limited because of a lack of data availability. Lower recurrent bleeding in early SBCE and DAE was observed (OR, .40; $P < .01$; $I^2 = 0\%$).

Conclusions: The role of small-bowel studies in the early evaluation of OGIB is unquestionable, impacting diagnosis, therapeutic intervention, and prognosis. Comparative studies are still needed to identify optimal timing. (Gastrointest Endosc 2021;■:1-16.)

Small-bowel capsule endoscopy (SBCE), in clinical use for 2 decades, remains the recommended first-line diagnostic tool for small-bowel evaluation because of its noninvasiveness, high diagnostic yield, and ability to select the best route for device-assisted enteroscopy (DAE).[1] Possible indications for SBCE are obscure GI bleeding (OGIB; defined as bleeding of unknown origin that persists or recurs after a negative colonoscopy and upper endoscopy), suspicion or monitoring of Crohn's disease, small-intestinal polyps, tumors, and celiac disease.[2] DAE —encompassing single-balloon, double-balloon, or spiral techniques—may be performed to allow therapeutic procedures or to clarify the diagnosis when lesions are detected in SBCE or directly in the emergent setting.[3,4]

Abbreviations: CI, confidence interval; DAE, device-assisted enteroscopy; OGIB, obscure GI bleeding; OR, odds ratio; SBCE, small-bowel capsule endoscopy.

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Ongoing overt OGIB is commonly self-limited; however, it carries a significant risk of recurrence, with an increased risk of mortality and morbidity.[5] Therefore, the bleeding source must be identified as soon as possible to allow therapeutic management in a timely manner.[6] Notwithstanding, to date no definite evidence exists regarding the most appropriate timing for both SBCE and DAE in the setting of acute GI bleeding. The European Society of Gastrointestinal Endoscopy recommends that SBCE should be performed as soon as possible after the overt bleeding episode, ideally within 14 days,[7] an arbitrarily defined cutoff. However, no agreement exists regarding the best timing within the 14 days or the definition of emergent or urgent SBCE. Concerning DAE, a recent Iberian guideline raised the recommendation that enteroscopy should be performed within the first 72 hours of overt OGIB presentation, although with limited supporting evidence.[4]

In this context, to fill in the knowledge gap, we performed a systematic review and meta-analysis of studies evaluating the diagnostic and/or therapeutic yield of SBCE and/or DAE performed emergently, urgently, or during the bleeding episode. Therefore, our intention was to provide good quality evidence to support future recommendations on the best timing for early small-bowel studies.

METHODS

Search strategy

This study followed the Cochrane Collaboration guidelines for systematic reviews[8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[9] MEDLINE (via PubMed, https://pubmed.ncbi.nlm.nih.gov), Web of Science (https://www.webofknowledge.com), and SCOPUS (https://www.scopus.com) databases were searched from inception to June 15, 2021 using the following keywords or medical subject heading terms: (emergent OR early OR urgent OR ongoing) and (enteroscopy OR capsule endoscopy OR double-balloon enteroscopy OR single-balloon enteroscopy). No language or publication date restrictions were imposed. The reference lists of the included studies and of reviews on the topic were hand-searched to identify further relevant publications.

Eligibility criteria

Inclusion criteria were studies analyzing the diagnostic and/or therapeutic yield of SBCE and/or enteroscopy performed in an early setting (emergently, urgently, for ongoing bleeding, within 14 days of clinical presentation in SBCE and within 72 hours in DAE). Both single-arm (enrolling only patients with "early" small-bowel studies) and double-arm (comparing "early" vs "nonearly" approach) studies were included. Exclusion criteria were systematic or narrative reviews, animal studies, guidelines, editorial or correspondence, meeting abstracts, and case reports and studies where small-bowel investigations were not performed within 14 days of the bleeding episode.

Study selection and data collection

First, 2 authors independently reviewed titles and abstracts of the studies identified in the search and excluded those that did not meet the eligibility criteria. The full text of the remaining studies was evaluated to determine their inclusion or exclusion. The list of studies selected for inclusion by each author was compared; disagreements were solved by discussion until consensus. The following information was abstracted from each study into a data extraction form: first author's last name, year of publication, study design, groups under comparison, time to procedure, procedure (SBCE and/or DAE), type of capsule or enteroscope, insertion route for DAE, completion rate for SBCE, preparation before the procedure, number of patients, population characteristics (age, sex, mean hemoglobin levels at admission and transfusion requirements, clinical presentation, exclusion criteria), diagnostic yield (for positive findings and vascular lesions), proportion of patients with active bleeding, therapeutic yield, recurrent bleeding rate, and mortality. Differences in data extraction were settled by consensus.

Quality assessment

Methodology and reporting quality of the studies were assessed independently by 2 authors using the validated Critical Appraisal Skills Programme checklist for cohort studies.[10] The risk of bias across studies was analyzed by evaluating funnel plots for asymmetry.

Statistical analysis

The primary endpoints of this meta-analysis were diagnostic yield, corresponding to the proportion of patients with findings that were very likely to explain GI bleeding (vascular lesions but also others, like tumors or ulcers), and therapeutic yield, defined as the ability to perform therapeutic procedures after capsule endoscopy or during enteroscopy. Secondary endpoints were proportion of active bleeding detected; detection rate of vascular lesions; recurrent bleeding, defined as a reduction in hemoglobin above 2 g/dL, need for blood transfusions, or presence of overt bleeding; and mortality. The definitions of these outcomes in each study are presented in Supplementary Table 1 (available online at www.giejournal.org).

Data were extracted or calculated from available information. The odds ratio (OR) for positive findings, vascular lesions, active bleeding, and ulterior therapeutic procedures and their 95% confidence intervals (CIs) were calculated for double-arm studies (comparing cohorts of early vs nonearly approaches). Also, the difference of proportions achieved in the 2 cohorts and the pooled diagnostic

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and therapeutic yields per cutoff were calculated. The pooled percentages of patients achieving each of the endpoints were calculated for both single- and double-arm studies.

Review Manager version 5.3 was used to perform data analysis, applying a random-effects method (Mantel-Haenszel model with the DerSimonian and Laird extension), and to generate the funnel and forest plots. Statistical heterogeneity was assessed using the Cochran χ^2 method and the I^2 statistic, with $I^2 > 50\%$ corresponding to substantial heterogeneity. The stability of the estimations and the weight of each study in heterogeneity was assessed with sensitivity analysis.

Subgroup analyses were performed, whenever adequate, to understand whether an earlier approach (less/more than 48 or 72 hours for SBCE; less/more than 24 hours for DAE), bowel preparation requirements for SBCE, DAE procedure (single or double balloon), SBCE before DAE, or sample size influenced the pooled OR for positive findings and subsequent therapeutics. Two-sided P values with a 5% significance level were used.

RESULTS

Literature search and study selection

The database search yielded 1974 records: 825 were found in PubMed, 585 in SCOPUS, and 564 in Web of Science (Fig. 1). After the removal of duplicates, 1334 records remained, of which 1241 were excluded. Then, 93 full texts were assessed for eligibility, and 39 were included.

Characteristics of included studies

Study characteristics are summarized in Table 1. Thirty-nine studies were included; 30 were double arm, comparing early versus nonearly small-bowel evaluation procedures. From these, 16 involved capsule endoscopy, 12 DAE, and 2 analyzed both procedures. Nine single-arm studies were selected, 7[11-17] of which concerned capsule endoscopy.

Globally, the studies enrolled 4825 patients, most with overt bleeding; only 2 studies included patients with iron deficiency anemia without visible blood losses (in 4%[18] and 10%[19] of the included patients). Early small-bowel studies, within 14 days after the bleeding episode for SBCE and within 72 hours for DAE, were performed in 2154 patients (1535 SBCE and 619 DAE). SBCE was performed in the first 72 hours in 3 studies,[20-22] in the first 48 hours in 7,[6,17,23-27] in the first 24 hours in 3,[11,13,14] and during ongoing bleeding in 6.[19,28-32].

DAE was performed in the first 72 hours in 5 studies,[33-37] in the first 24 hours in 9,[35,36,38-44] and during ongoing bleeding in 3.[29,45,46] Small-bowel studies were performed for OGIB (after negative bidirectional endoscopies) in all but 2 single-arm studies. In the study by Marya et al,[11] SBCE was the first endoscopic study to be performed. Schlag et al[13] analyzed the performance of SBCE placed endoscopically in the duodenum, after upper endoscopy but without prior colonoscopy. Most studies on capsule endoscopy (11/18) used more than 1 equipment model; the more common were Given M2A, SB, or SB2. No bowel preparation was done before SBCE in 10[6,11,19,21,23,26,28-31] of 18 studies.

Detection of active bleeding

Table 2 presents, for each study, the proportion of patients who achieved the primary and secondary endpoints. The identification of active bleeding was evaluated in 8 double-arm studies (5[6,21,23,32,47] on SBCE and 3[33,36,37] on DAE) and in 7 single-arm studies (5[12,13,15-17] on SBCE and 2[43,44] on DAE). The proportions varied widely: between 13.0%[32] and 91.9%[17] in the early SBCE group and among 19.2%[36] and 100.0%[33] in the early DAE group. Despite that, the presence of active bleeding was consistently higher in patients submitted to early small-bowel studies ($P < .05$). The odds of detecting active bleeding were 3.22 ($P < .01$) and 19.78 ($P = .02$) times higher in early versus nonearly SBCE and DAE, respectively (Supplementary Table 2, available online at www.giejournal.org).

Diagnostic yield

The diagnostic yield was evaluated in all included studies. Early small-bowel investigations ranged between 44.4% (for SBCE in the first 72 hours[21]) and 100.0% (for SBCE[31] and DAE[45] performed during ongoing bleeding or DAE performed in the first 24 hours[44] or 48 hours[24]) (Table 2). The pooled diagnostic yield for early studies (considering time cutoffs defined by each individual study) was 80.35 (95% CI, 73.85-86.85; $P < .01$; $I^2 = 93\%$) for SBCE and 88.32 (95% CI, 84.73-91.91; $P < .01$; $I^2 = 89\%$) for DAE (Supplementary Table 2); these values were significantly different ($I^2 = 77\%$, $P = .04$). The pooled diagnostic yields for early SBCE were 63.6%, 81.3%, and 83.4% when the procedure was performed in the first 24, 48, and 72 hours, respectively. For DAE, the pooled yield varied between 82.7% (first 72 hours) and 92.9% (first 24 hours) (Supplementary Table 3, available online at www.giejournal.org).

Early diagnostic yield was significantly superior compared with the nonearly approach (variable cutoff definitions) in all studies except 2[23,40] (Table 2). This is corroborated by the pooled difference of proportions: diagnostic yields in early SBCE and DAE groups were 33.33 (95% CI, 25.09-41.57) and 27.80 (95% CI, 21.74-33.85) points superior, respectively (Supplementary Fig. 3, available online at www.giejournal.org). The odds of detecting positive findings (those very likely to explain bleeding) in patients submitted to early small-bowel studies were 3.99 times the odds of the nonearly approach ($P < .01$, $I^2 = 45\%$) (Fig. 2). For SBCE, no subgroup differences were obtained when the studies were separated according to the factors "less/more than 48 hours" and "less/more than 72 hours" or "bowel preparation yes/no" ($I^2 > 50\%$, $P > .100$) (Supplementary

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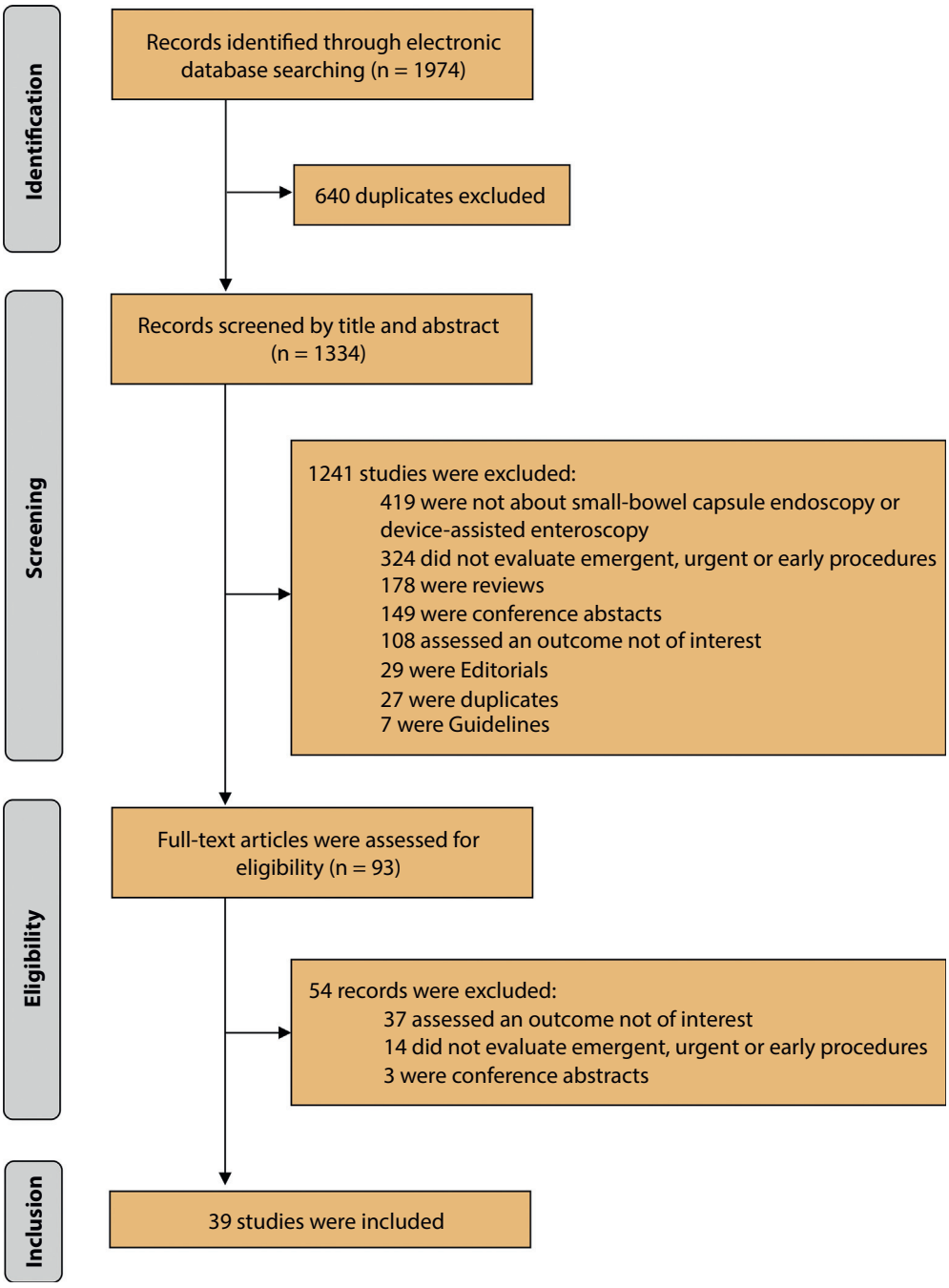

Figure 1. Flow diagram of study selection and data collection process.

Table 2). Inversely, the studies enrolling fewer than 49 patients in the early approach had a significantly superior OR for positive findings (6.12 vs 2.87, $P = .01$). For DAE, no subgroup effects were detected for the tested variables.

Detection of vascular lesions

The proportion of patients with vascular lesions was evaluated in 25 studies (9 of which were single arm) and varied widely (Table 2). In the double-arm studies, the detection of vascular lesions was significantly superior ($P < .05$) in the early group in half of the studies (4/8) for both SBCE and DAE studies. Overall, the odds of detecting vascular lesions in early SBCE and DAE were not significantly different from the nonearly approach (both 95% CIs included the unit) (Supplementary Table 2).

Therapeutic yield

The therapeutic yield for SBCE ranged between 26.2%[11] and 78.2%[15] when only the early approach was

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TABLE 1. Characteristics of the studies included in the meta-analysis (n = 39)

Author, year, country	Study design	Groups under comparison	Time to procedure: early approach	Procedure (SBCE or DAE)	Type of capsule or enteroscope	Preparation	No. of patients	Patient characteristics	Presenting signs	Exclusions
Chao et al, 2021, Taiwan[20]	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	First 72 h	SBCE	Not specified	Bowel preparation on the evening before, 12 h fasting	Total n = 60, early n = 49	42% male	Overt OGIB-melena (90%) or hematochezia (10%)	Less than 16 y old, inability to swallow, suspected small-bowel obstruction, cardiac pacemaker
Zhao et al, 2021, Japan and China[18]	Retrospective cohort study, 2 centers	1) Early SBCE; 2) late SBCE	First 14 days	SBCE (81% reached cecum)	PillCam SB and SB2 capsules (Given)	Bowel preparation only in the Chinese center	Total n = 997, early n = 678	Mean age 63.0 ± 13.4 y, 54% male, mean Hg 8.7 ± 2.3 g/dL	OGIB: overt (96%) or occult (4%)	No data regarding bleeding onset, <1 y of follow-up; indications other than OGIB; "not excellent" bowel preparation
Silva et al, 2020, Portugal[33]	Retrospective cohort study, single center	1) Urgent BAE; 2) nonurgent BAE	First 72 h	SBE (87% previous SBCE; antegrade in 76%)	Single-balloon enteroscope (SIF-Q180, Olympus)	Overnight fasting for antegrade procedures, retrograde BAE required PEG solution (4 L)	Total n = 54, early n = 17	Mean age 68.9 ± 11.1 y, 59% male, mean Hg 8.4 ± 2.3 g/dL	Overt OGIB-melena (76%), hematochezia (18%)	Less than 18 years old, incomplete study (incomplete SBCE or no reachable lesions)
Yin et al, 2020, China[34]	Retrospective cohort study, single center	1) Urgent BAE; 2) nonurgent BAE	First 72 h	DBE (none previously submitted to SBCE; antegrade in 29%)	Double-balloon endoscope (EN-530T, Fujifilm, Saitama, Japan)	12 h fasting for antegrade DBE; retrograde DBE required preparation with PEG solution (4 L)	Total n = 178; early n = 32	Mean age 44.7 ± 17.3 y, 67% male, mean Hg 7.6 ± 2.1 g/dL	Overt OGIB-melena (22%) or hematochezia (63%)	Prior positive findings on SBCE and/or radiographic imaging
Hashimoto et al, 2019, Japan[38]	Retrospective cohort study, single center	1) DAE with findings; 2) DAE without findings	First 24 h	DBE (57% previous SBCE)	Not reported	Not reported	Total n = 165, early n = 60	Mean age 64.2 ± 15.4 y, 70% male	Overt OGIB-melena (62%) or hematochezia (38%)	Suspicion of bleeding from source other than small bowel
Iio et al, 2019, Japan[6]	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	First 48 h	SBCE	PillCam SB2 or SB3 capsules (Given)	Fasting for 12 h; simethicone	Total n = 127, early n = 15	Mean age 66.2 y (range 17-88), 59% male	Not reported	GI tract stenosis or small-bowel disease
Liu et al, 2019, China[39]	Retrospective cohort study, single center	1) Emergent BAE; 2) nonemergent BAE	First 24 h	SBE (none previously submitted to SBCE; antegrade in 36%)	Single-balloon enteroscope (SIF-Q260, Olympus)	Fasting for 12 h, PEG for patients undergoing retrograde SBE	Total n = 102, early n = 50	Age range 14-83 y, 45% male	Overt OGIB-melena or hematochezia	Motility disorders, suspected obstruction or fistula, abdominal surgeries, electromedical equipment; severe hepatic conditions, abnormal coagulation, psychosis, or dementia; pregnancy
Tu et al, 2019, Taiwan[35]	Retrospective cohort study, single center	1) Emergent BAE; 2) nonemergent BAE	First 24 h or ongoing bleeding	SBE (none previously submitted to SBCE; antegrade in 65%)	Single-balloon enteroscope (SIF-Q260, Olympus)	Fasting >6 h before antegrade SBE; early morning ingestion of a PEG solution before retrograde SBE	Total n = 220, early n = 64	Mean age 65.6 ± 18.1 y, 48% male	Overt OGIB-melena (61%) or hematochezia (24%)	Not overt OGIB, patients who underwent SBCE or a nuclear bleeding scan before BAE
		1) Urgent BAE; 2) nonurgent BAE	First 72 h				Total n = 220, early n = 92			
Gomes et al, 2018, Portugal[3]	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	First 48 h	SBCE (90% reached cecum)	PillCam SB (Given) and Mirocam capsules (IntroMedic)	Liquid diet the night before and overnight fasting	Total n = 115, early n = 39	Mean age 63.0 ± 14.2 y, 54% male, mean Hg 8.5 ± 2.6 g/dL	Overt OGIB-melena (55%) or hematochezia (45%)	Indications other than overt OGIB

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TABLE 1. Continued

Author, year, country	Study design	Groups under comparison	Time to procedure: early approach	Procedure (SBCE or DAE)	Type of capsule or enteroscope	Preparation	No. of patients	Patient characteristics	Presenting signs	Exclusions
Marya et al, 2018; USA[11]	Randomized controlled trial, single center	1) Emergent SBCE (further workup based on findings)	First 24 h	SBCE; no previous upper endoscopy or colonoscopy	EC-S10 small-bowel capsule (Olympus)	Fasting for 10 h, no bowel preparation	n = 42	Mean age 67.0 ± 12.6 y, 55% male, mean Hg 9.4 ± 3.0 g/dL	Melena (62%), hematochezia (26%), anemia (12%)	Less than 18 years old, hemodynamic instability, dysphagia, hematemesis, suspicion of supectious colitis, suspicion of bowel obstruction
Rodrigues et al, 2018, Portugal[36]	Retrospective cohort study, single center	1) Emergent BAE; 2) nonemergent BAE	First 24 h	SBE (79% previous SBCE; antegrade in 77%)	Single-balloon enteroscope (SIF-Q180, Olympus)	Fasting for 8 h for antegrade procedures; retrograde BAE required preparation with PEG solution (4 L)	Total n = 70, early n = 6	Mean age 70.2 ± 10.3 y, 46% male, mean Hg 8.2 ± 2.1 g/dL	Overt OGIB-melena (69%), hematochezia (31%)	Nonbleeding indications or for occult bleeding
		1) Urgent BAE; 2) nonurgent BAE	First 72 h				Total n = 70, early n = 26			
Üçüncü et al, 2017, Turkey[12]	Retrospective cohort study, single center	1) Emergent SBCE	Immediately after negative bidirectional endoscopies	SBCE	Pillcam SB2 capsule (Given)	PEG solution (4L)	n = 38	Mean age 55.6 y, 68% male	Overt OGIB-melena or hematochezia	Not reported
Nelson et al, 2016, USA[40]	Retrospective cohort study, single center	1) Emergent BAE; 2) nonemergent BAE	First 24 h	SBE (no SBCE before emergent procedures); antegrade in 97%)	Single-balloon enteroscope (SIF-Q180, Olympus)	Overnight fasting, PEG solution (4 L) for retrograde procedures	Total n = 110, early n = 30	Mean age 63.1 ± 13.4 y, 53% male, mean Hg 8.7 ± 2.3 g/dL	Overt OGIB	Outpatient or nonbleeding indications
Ooka et al, 2016, Japan[24]	Retrospective cohort study, single center	1) Ongoing bleeding; 2) previous bleeding	First 48 h	SBCE (79% reached cecum)	PillCam SB capsule (Given) or EndoCapsule (Olympus)	12 h fasting; 800 mL of magnesium citrate solution after capsule ingestion	Total n = 103; early n = 11	Mean age 63.0 ± 16.0 y, 47% male, mean Hg 7.8 ± 2.1 g/dL	Overt OGIB	Not reported
				SBE	Single-balloon enteroscope (SIF-Q260Y, Olympus)	PEG solution (1-2 L)	Total n = 91; early n = 27	Mean age 68.0 ± 17.0 y, 51% male, mean Hg 7.6 ± 1.9 g/dL	Overt OGIB	Not reported
Kim et al, 2015, Korea[25]	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	First 48 h	SBCE	PillCam SB and SB2 capsules (Given)	Bowel preparation (PEG solution, 2-4 L)	Total n = 94, early n = 30	Mean age 54.5 ± 18.7 y, 62% male, mean Hg 9.5 ± 2.3 g/dL	Overt OGIB-melena (47%) or hematochezia (53%)	Indications other than overt OGIB, unstable patients
Ribeiro et al, 2015, Portugal[28]	Retrospective cohort study, single center	1) Ongoing bleeding; 2) Previous bleeding	Ongoing bleeding	SBCE (87% reached cecum)	PillCam SB (Given) and Mirocam capsules (IntroMedic)	Overnight fasting for 12 h and liquid diet for lunch in the previous day	Total n = 76, early n = 28	Mean age 62.2 ± 18.1 y, 40% male, mean RBC transfusion 1.5 ± 6.9	Overt OGIB-melena or hematochezia	Small-bowel transit time <1 h, poor small-bowel visualization
Schlag et al, 2015, Germany[13]	Prospective cohort study, single center	1) Emergent SBCE	First 24 h	SBCE (85% reached cecum); no prior colonoscopy	Pillcam SB 2-4 capsules (Given)	PEG solution (.5 L) was endoscopically instilled into the duodenum	n = 20	Mean age 74.2 ± 10.6 y, 60% male, mean Hg 7.0 ± 1.8 g/dL, mean RBC transfusion 2 (range, 2-4)	Melena	Hematemesis or rectal fresh red blood, <18 y, pregnant women, contraindications for SBCE
Aniwan et al, 2014, Thailand[37]	Retrospective cohort study, single center	1) Urgent BAE; 2) nonurgent BAE	First 72 h	DBE (none previously submitted to SBCE; antegrade in 54%)	Double-balloon enteroscope (EN-450P5/28, Fujifilm)	PEG solution (2-4 L) only when the effect of a recent bowel preparation for colonoscopy	Total n = 120, early n = 74	Mean age 60.0 ± 2.4 y, 43% male, mean Hg 7.1 ± 0.2 g/dL	Overt OGIB-melena or hematochezia	Indications other than overt OGIB

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TABLE 1. Continued

Author, year, country	Study design	Groups under comparison	Time to procedure: early approach	Procedure (SBCE or DAE)	Type of capsule or enteroscope	Preparation	No. of patients	Patient characteristics	Presenting signs	Exclusions
						was considered inadequate				
Pérez-Cuadrado Robles et al, 2014, Spain[4]	Retrospective cohort study, single center	1) Emergent DAE	First 24 h	DBE (59% submitted to emergent SBCE antegrade in 76%)	Double-balloon enteroscope (Fujinon EN-450P5, EN-450T5 or EN-580T, Toshiba)	Bowel preparation for retrograde DBE	n = 27	Mean age 64.6 ± 17.9 y, 59.3% male; mean Hg 7.2 g/dL ± 1.6; mean RBC transfusion 4 (range, 0-8)	Overt OGIB-hematemesis, melena or hematochezia	Severe ongoing bleeding >24 h
Pinto-Pais et al, 2014, Portugal[41]	Retrospective cohort study, single center	1) Emergent BAE; 2) nonemergent BAE	First 24 h	SBE (98% previous SBCE; antegrade in 60%)	Single-balloon enteroscope (SIF-Q180, Olympus)	Overnight fast for antegrade procedures; PEG solution (4 L) for retrograde BAE	Total n = 43; early n = 15	Mean age 65.4 ± 10.9 y, 58% male	Overt OGIB-melena (27%) or hematochezia (73%)	Indications other than overt OGIB
Singh et al, 2013, USA[21]	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	First 72 h	SBCE	PillCam SB and SB2 capsules (Given)	Overnight fast (>8 h)	Total n = 144, early n = 90	Mean age 66.9 ± 15.5 y, 56% male, mean RBC transfusion 4.5 (range, 0-50)	Overt OGIB-melena or hematochezia	Occult OGIB, iron deficiency anemia, abdominal pain, and evaluation of Crohn's disease
Lecleire et al, 2012, France[15]	Retrospective cohort study, single center	1) Emergent SBCE	24-48 h after negative bidirectional endoscopies	SBCE (93% reached cecum)	Pillcam SB capsule (Given)	PEG solution (2 L) in the evening before the procedure	n = 55	Mean age 61.0 ± 20.8 y, 67% male	Severe OGIB (hemodynamic instability and/or need ≥2 RBC transfusions)	Not reported
Leung et al, 2012, China[14]	Randomized controlled trial, single center	1) Emergent SBCE	First 24 h	SBCE	Pillcam SB capsule (Given)	PEG solution before colonoscopy; no further preparation was needed for SBCE	n = 30	Mean age 58.6 ± 19.9 y, 57% male, mean Hg 9.5 ± 1.7 g/dL; mean RBC transfusion 1.8 ± 2.0	Overt OGIB-melena or hematochezia	Less than 18 years old, pregnancy, moribund conditions, swallowing difficulties, suspected intestinal obstruction, implantable electromedical devices
Yamada et al, 2012, Japan[26]	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	First 48 h	SBCE	Pillcam SB and SB2 capsules (Given)	Fasting for 12 h; simethicone	Total n = 90, early n = 22	Mean age 66.0 ± 14.8 y, 64% male, mean Hg 9.5 ± 1.8 g/dL	Overt OGIB-melena or hematochezia	Not reported
Goenka et al, 2011, India[27]	Retrospective cohort study, single center	1) Ongoing bleeding; 2) previous bleeding	First 48 h	SBCE	Given M2A/SB capsules (Given)	Light diet for 24 h, overnight fasting, bowel preparation (PEG solution, 2 L) in the evening	Total n = 289, early n = 157	Age range 12-80 y, 71.0% male	Not reported	Not reported
Esaki et al, 2010, Japan[22]	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	First 72 h	SBCE (75% reached cecum)	Pillcam SB capsule (Given)	Fasting for 12 h; 53% bowel preparation (magnesium citrate)	Total n = 68, early n = 29	Mean age 58.6 ± 19.9 y, 57% male	Overt OGIB-melena or hematochezia	Sources of bleeding outside the small bowel or follow-up data not available
Katsinelos et al, 2010, Greece	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	First 5 days	SBCE (98% reached cecum)	EndoCapsule (Olympus)	Bowel preparation (PEG solution, 4 L) 12 h before the examination	Total n = 20, early n = 9	Mean age 51.48 ± 16 y, 44% male	Overt OGIB-visible red or altered blood in feces	Pregnancy, children, severe motility or swallowing disorders, known or suspected obstruction, strictures or fistulas, use of narcotics, pacemaker

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TABLE 1. Continued

Author, year, country	Study design	Groups under comparison	Time to procedure: early approach	Procedure (SBCE or DAE)	Type of capsule or enteroscope	Preparation	No. of patients	Patient characteristics	Presenting signs	Exclusions
Shinozaki et al, 2010, Japan[42]	Retrospective cohort study, single center	1) Ongoing bleeding; 2) previous bleeding	First 24 h	DBE	Double-balloon enteroscope (Fujinon EN-450P5 or EN-450T5, Toshiba)	PEG solution	Total n = 170, early n = 30	Median age 60 y (range, 11-88), 61% male; mean RBC transfusion 4.5 (range, 0-40)	Overt OGIB-melena or hematochezia	Indications other than overt OGIB
Almeida et al, 2009, Portugal[16]	Retrospective cohort study, single center	1) Urgent SBCE	Immediately after negative bidirectional endoscopies	SBCE (73% reached cecum)	Pillcam SB capsule (Given)	PEG solution before colonoscopy; no further preparation was needed	n = 15	Mean age 62.0 ± 19.0 y, 53% male	Severe OGIB (hemodynamic instability and/or need ≥2 RBC transfusions)	Not reported
Arakawa et al, 2009, Japan[29]	Retrospective cohort study, single center	1) Ongoing bleeding; 2) previous bleeding	Ongoing bleeding	SBCE	Given M2A and SB capsules (Given)	No bowel preparation	Total n = 110, early n = 16	Not reported	Overt OGIB	Not reported
Mönkemüller et al, 2009, Germany[43]	Retrospective cohort study, single center	1) Emergent DAE	First 24 h	DBE (antegrade in 53%)	Double-balloon enteroscope (Fujinon EN-450P5 or EN-450T5, Toshiba)	Bowel preparation for anal DBE	n = 10	Mean age 68 y (range, 35-83), 40% male	Overt OGIB-melena or hematochezia	Not reported
Tanaka et al, 2008, Japan[45]	Retrospective cohort study, single center	1) Ongoing bleeding; 2) previous bleeding	Ongoing bleeding	DBE	Double-balloon enteroscope (Fujinon EN-450P5 or EN-450T5, Toshiba)	Fasting for 12 h, bowel cleansing for retrograde procedures; dimethicone 2 h before	Total n = 143, early n = 15	Median age 63.0 y (range, 2-97), 62% male; mean Hg 8.2 ± 2.5 g/dL	Overt OGIB	Not reported
Apostolopoulos et al, 2007, Greece[17]	Prospective study, single center	1) Early SBCE	First 48 h	SBCE (78% reached the cecum)	PillCam SB capsule (Given)	Bowel preparation (PEG solution) before colonoscopy; no further preparation was needed	n = 37	Median age 67 y (range, 40-72), 62% male; mean Hg 9.5 g/dL (range, 7.2-11.3)	Overt OGIB-melena (60%) or hematochezia (40%)	Severe GI hemorrhage; suspected ileus, small-bowel obstruction, history of major intra-abdominal surgery; implantable electromedical device
Carey et al, 2007, USA[30]	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	Ongoing bleeding	SBCE (74% reached cecum)	Given M2A capsule (Given)	Clear liquid diet for 24 h, overnight fast	Total n = 126, early n = 15	Mean age 65.4 ± 14.4 y, 54% male	Overt OGIB-melena or hematochezia	Not reported
Ge et al, 2007, China[19]	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	Ongoing bleeding	SBCE	Given M2A capsule (Given)	Fasting for 8 h	Total n = 91, early n = 41	Median age 51 y (range, 4-86), 59% male, median Hg 6.2 g/dL (range, 2.1-15.4)	Overt OGIB (melena 90%) or occult bleeding (10%)	Recent history of GI obstruction, pregnancy
Ohmiya et al, 2007, Japan[46]	Retrospective cohort study, multicenter	1) Ongoing bleeding; 2) previous bleeding	Ongoing bleeding	DBE (18% submitted to SBCE)	Double-balloon enteroscope (Fujinon EN-450P5 or EN-450T5, Toshiba)	Fasting for 12 h, bowel cleansing for retrograde procedures; dimethicone 2 h before the examination	Total n = 413, early n = 31	Not reported	Overt OGIB	Not reported
Bresci et al, 2005, Italy	Retrospective cohort study, single center	1) Early SBCE; 2) late SBCE	First 14 days	SBCE	Given M2A capsule (Given)	Bowel preparation (PEG solution on the day before), 12-h fasting, simethicone	Total n = 64, early n = 32	Mean age 54.0 y (range, 30-73), 44% male	Overt OGIB-melena (87%) or hematochezia (13%)	Bowel obstruction, pacemaker implantation, small intestine diverticula, and pregnancy

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TABLE 1. Continued

Author, year, country	Study design	Groups under comparison	Time to procedure: early approach	Procedure (SBCE or DAE)	Type of capsule or enteroscope	Preparation	No. of patients	Patient characteristics	Presenting signs	Exclusions
Hartmann et al, 2005, Germany[31]	Retrospective cohort study, multicenter	1) Ongoing bleeding; 2) previous bleeding	Ongoing bleeding	SBCE (66% reached cecum)	Given M2A capsule (Given)	Fasting for 12 h	Total n = 35, early n = 11	Mean age 61.0 ± 17.0 y, 64% male, mean RBC transfusion 12.8 ± 14.2	Overt OGIB-melena or hematochezia	Pregnant women, patients with low-grade iron deficiency anemia (Hb >10 g/dL), bleeding sources outside the small bowel
Pennazio et al, 2004, Italy[32]	Retrospective cohort study, multicenter	1) Ongoing-bleeding; 2) previous bleeding	Ongoing bleeding	SBCE (80% reached cecum)	Given M2A capsule (Given)	Fluid diet for 24 h, bowel preparation (PEG solution 2 L, in the afternoon), overnight fasting	Total n = 57, early n = 26	Median age 65.0 y (range, 22-88), 65% male	Overt OGIB-melena or hematochezia	Recent history of bowel obstruction, pacemaker implantation, pregnancy, and swallowing disorders

DAE, Device-assisted enteroscopy; *DBE*, double-balloon enteroscopy; *Hg*, hemoglobin; *OGIB*, obscure GI bleeding; *RBC*, red blood cell; *SBE*, single-balloon enteroscopy; *SBCE*, small-bowel capsule endoscopy; *BAE*, balloon-assisted enteroscopy; *PEG*, polyethylene glycol.

evaluated, whereas it ranged between 18.9% (SBCE in the first 72 hours[21]) and 87.0% (for ongoing bleeding[32]) in studies comparing early with nonearly approach. Concerning DAE performed in the first 24 hours, Rodrigues et al[36] reported a therapeutic yield of 100.0%, whereas Nelson et al[40] obtained a yield of 30.0%. In this latter study, opposite to all others, both diagnostic and therapeutic yields were inferior on the early group but without statistical significance. The pooled therapeutic yield for early SBCE was 52.25% (95% CI, 37.65-66.85; $P < .01$; $I^2 = 92\%$) and for early DAE was 73.14% (95% CI, 55.34-90.94; $P < .01$; $I^2 = 97\%$) (Supplementary Table 2).

As observed for the pooled diagnostic yield, significant differences were found between the 2 techniques ($I^2 = 68\%$). When divided by cutoffs, the therapeutic yield varied between 59.1% (first 48 hours) and 18.9% (first 72 hours) for SBCE and between 73.5% (first 24 hours) and 68.5% (first 72 hours) for DAE (Supplementary Table 3, available online at www.giejournal.org). The therapeutic yield was significantly superior in early groups ($P < .05$) in 5[33,34,36,37,45] of 6 double-arm studies (Table 2). Again, this was corroborated by significant differences of proportions (early vs nonearly): 27.99 (95% CI, 11.04-44.95; $P < .01$; $I^2 = 82\%$) for SBCE and 29.92 (95% CI, 15.96-43.88; $P < .01$; $I^2 = 72\%$) for DAE (Supplementary Fig. 1). The OR for receiving therapeutics were significantly superior for early SBCE and DAE: 4.01 (95% CI, 2.18-7.35; $P < .01$; $I^2 = 44\%$) and 3.93 (95% CI, 1.40-10.99; $P < .01$; $I^2 = 77\%$), respectively (Fig. 3).

Recurrent bleeding rate

Recurrent bleeding rate was provided in 14 studies, 10[6,11,13-18,23,25] evaluating SBCE (Table 2). In the double-arm reports, a tendency toward lower recurrent bleeding rates in the early groups was visible, despite differences in the definition of the early approach and follow-up duration. The OR for recurrent bleeding in early SBCE and DAE was .39 (95% CI, .30-.52; $P < .01$; $I^2 = 0\%$) and .41 (95% CI, .17-1.00; $P = .05$; $I^2 = 40\%$), respectively (Supplementary Table 2).

Mortality

Information regarding mortality was only provided in 6 studies, of which 5[11-14,23] concerned SBCE and 1[23] compared early versus nonearly small-bowel evaluation. The follow-up time allowed until the event varied widely (Table 2); the mortality rate ranged between .0% (at 30 days)[33] and 25.0% (at 50 months).[23] Considering the limited information available and its variability, pooled mortality was not calculated.

Quality of studies and publication bias

The funnel plots suggested a low risk of publication bias (even scattering to both sides; Supplementary Fig. 1, available online at www.giejournal.org). Overall, the reporting quality was adequate. Nevertheless, some doubts exist regarding identification and control of confounding factors. Also, the ability to extrapolate findings to the general population is limited (Supplementary Fig. 2, available online at www.giejournal.org).

DISCUSSION

The diagnostic yield of SBCE and DAE in OGIB has been reported to vary between 35% and 80% in clinical trials and among 40% to 75% in real-life settings.[48,49] Therefore, a significant percentage of patients with OGIB may remain undiagnosed. This may be related to suboptimal visualization because of unsatisfactory bowel preparations before SBCE, features of the current capsule equipment, and time from symptom onset to small-bowel examination.

TABLE 2. Proportion of patients, in each study, with active bleeding, with findings with a high likelihood of justifying GI bleeding (diagnostic yield), who were submitted to therapy (therapeutic yield), who presented recurrent bleeding, and who died

Procedure	Study	Timing early approach	Identification of active bleeding	Diagnostic yield	Detection of vascular lesions	Therapeutic yield	Recurrent bleeding rate	Mortality
				Double-arm studies				
CE	Chao et al, 2021[20]	First 72 h	NR	73.5% (36/49) vs 36.4% (4/11), $P < .05$	8.2% (4/49) vs .0% (0/11), $P > .05$	NR	NR	NR
	Zhao et al, 2021[18]	First 14 days	NR	72.1% (489/678) vs 47.3% (151/319), $P < .05$	22.3% (151/678) vs 14.7% (47/319), $P < .05$	NR	20.4% (138/678) vs 39.5% (126/319), $P < .05$	NR
	Iio et al, 2019[6]	First 48 h	80.0% (12/15) vs 47.3% (53/112), $P < .05$	80.0% (12/15) vs 47.3% (53/112), $P < .05$	33.3% (5/15) vs 21.4% (21/112), $P < .05$	53.3% (8/15) vs 36.6% (41/112), $P < .05$	.0% (0/12) vs 1.9% (1/53), $P > .05$	NR
	Gomes et al, 2018[3]	First 48 h	43.6% (17/39) vs 23.7% (18/76), $P < .05$	82.1% (32/39) vs 78.9% (60/76), $P > .05$	17.9% (7/39) vs 35.5% (27/76), $P > .05$	66.7% (26/39) vs 35.5% (27/76), $P < .05$	15.4% (6/39) vs 30.8% (31/76), $P < .05$	23.1% (9/39) vs 25.0% (19/76), $P > .05$
	Ooka et al, 2016[24]	First 48 h	NR	90.9% (10/11) vs 51.8% (28/54), $P < .05$	NR	NR	NR	NR
	Kim et al, 2015[25]	First 48 h	20.0% (6/30) vs 1.6% (1/64), $P < .05$	66.7% (20/30) vs 40.6% (26/64), $P < .05$	13.3% (4/30) vs 12.5% (8/64), $P > .05$	26.7% (8/30) vs 9.4% (6/64), $P < .05$	10.0% (3/30) vs 10.9% (7/64), $P > .05$	NR
	Ribeiro et al, 2015[28]	Ongoing bleeding	NR	92.8% (26/28) vs 45.8 (22/48), $P < .05$	NR	NR	NR	NR
	Singh et al, 2013[21]	First 72 h	28.9% (26/90) vs 13.0% (7/54), $P < .05$	44.4% (40/90) vs 27.8% (15/54), $P < .05$	NR	18.9% (17/90) vs 7.4% (4/54), $P < .05$	NR	NR
	Yamada et al, 2012[26]	First 48 h	NR	72.7% (16/22) vs 44.1% (30/68), $P < .05$	54.5% (n = 12/22) vs 13.2% (9/68), $P < .05$	36.4% (8/22) vs 13.2% (9/68), $P < .05$	NR	NR
	Goenka et al, 2011[27]	First 48 h	NR	87.2% (137/157) vs 68.2% (90/132), $P < .05$	NR	NR	NR	NR
	Esaki et al, 2010[22]	First 72 h	NR	72.4% (21/29) vs 38.5% (15/39), $P < .05$	NR	NR	NR	NR
	Katsinelos et al, 2010	First 5 d	NR	88.9% (8/9) vs 36.4% (4/11), $P < .05$	NR	NR	NR	NR
	Arakawa et al, 2009[29]	Ongoing bleeding	NR	87.5% (14/16) vs 47.9% (45/94), $P < .05$	NR	NR	NR	NR
	Carey et al, 2007[30]	Ongoing bleeding	NR	86.7% (13/15) vs 55.6% (70/126), $P < .05$	NR	NR	NR	NR
	Ge et al, 2007[19]	Ongoing bleeding	NR	95.1% (39/41) vs 78.0% (39/50), $P < .05$	36.6% (15/41) vs 28.0% (14/50), $P > .05$	NR	NR	NR
	Bresci et al, 2005	First 14 days	NR	90.6% (29/32) vs 34.4% (11/32), $P < .05$	37.5% (12/32) vs 18.8% (6/32), $P < .05$	NR	NR	NR

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TABLE 2. Continued

Procedure	Study	Timing early approach	Identification of active bleeding	Diagnostic yield	Detection of vascular lesions	Therapeutic yield	Recurrent bleeding rate	Mortality
	Hartmann et al, 2005[31]	Ongoing bleeding	NR	100.0% (11/11) vs 66.7% (16/24), $P < .05$	NR	NR	NR	NR
	Pennazio et al, 2004[32]	Ongoing bleeding	13.0% (3/23) vs 3.4% (1/29), $P < .05$	92.3% (24/26) vs 12.9% (4/31), $P < .05$	NR	87.0% (20/23) vs 17.2% (5/29), $P < .05$	NR	NR
DAE	Silva et al, 2020	First 72 h	100.0% (17/17) vs .0% (0/37), $P < .05$	88.2% (15/17) vs 59.5% (22/37), $P < .05$	NR	94.1% (16/17) vs 45.9% (17/37), $P < .05$	17.6% (3/17) vs 45.9% (17/37), $P < .05$	0% (0/17) vs 5.4% (2/37), $P < .05$
	Yin et al, 2020[34]	First 72 h	NR	84.4% (27/32) vs 65.1% (95/146), $P < .05$	37.5% (12/32) vs 18.5% (27/146), $P < .05$	78.1% (25/32) vs 58.2% (85/146), $P < .05$	NR	NR
	Hashimoto et al, 2019	First 24 h	NR	83.3% (50/60) vs 49.5% (52/102), $P < .05$	NR	NR	NR	NR
	Liu et al, 2019[39]	First 24 h	NR	76.0% (38/50) vs 53.8% (28/52), $P < .05$	20.0% (10/50) vs 11.5% (6/52), $P > .05$	NR	NR	NR
	Tu et al, 2019[35]	First 24 h or ongoing bleeding	NR	90.6% (58/64) vs 55.8% (87/156), $P < .05$	31.3% (20/64) vs 23.1% (36/156), $P > .05$	NR	NR	NR
		First 72 h	NR	83.7% (77/92) vs 52.3% (67/128), $P < .05$	30.4% (28/92) vs 21.9% (28/128), $P < .05$	NR	NR	NR
	Rodrigues et al, 2018[36]	First 24 h	NR	83.3% (5/6) vs 60.9% (39/64), $P < .05$	NR	100.0% (6/6) vs 35.9% (23/64), $P < .05$	NR	NR
		First 72 h	19.2% (5/26) vs 4.5% (2/44), $P < .05$	84.5% (22/26) vs 50.0% (22/44), $P < .05$	34.7% (9/26) vs 31.8% (14/44), $P > .05$	57.7% (15/26) vs 31.8% (14/44), $P < .05$	NR	NR
	Nelson et al, 2016[40]	First 24 h	NR	53.3% (16/30) vs 62.5% (50/80), $P > .05$	23.3% (7/30) vs 32.5% (26/80), $P > .05$	30.0% (9/30) vs 42.5% (34/80), $P > .05$	NR	NR
	Ooka et al, 2016[24]	First 48 h	NR	100.0% (27/27) vs 68.2% (28/41), $P < .05$	NR	NR	NR	NR
	Aniwan et al, 2014[37]	First 72 h	27.0% (20/74) vs 6.5% (3/46), $P < .05$	70.3% (52/74) vs 30.4% (14/46), $P < .05$	13.1% (18/74) vs 8.7% (4/46), $P < .05$	43.2% (32/74) vs 13.0% (6/46), $P < .05$	9.6% (5/52) vs 28.6% (4/14), $P > .05$	NR
	Pinto-Pais et al, 2014[41]	First 24 h	NR	93.3% (14/15) vs 64.3% (18/28), $P < .05$	33.3% (5/15) vs 46.4% (13/28), $P < .05$	60.0% (9/15) vs 53.6% (15/28), $P > .05$	NR	NR
	Shinozaki et al, 2010[42]	First 24 h	NR	83.3% (25/30) vs 57.9% (81/140), $P < .05$	30.0% (9/30) vs 27.7% (23/83), $P > .05$	NR	NR	NR
	Arakawa et al, 2009[29]	Ongoing bleeding	NR	86.7% (13/15) vs 59.4% (76/128), $P < .05$	NR	NR	NR	NR
	Tanaka et al, 2008[45]	Ongoing bleeding	NR	100.0% (13/13) vs 56.6% (43/76), $P < .05$	NR	84.6% (11/13) vs 19.7% (15/76), $P < .05$	15.4% (2/13) vs 9.8% (6/61), $P > .05$)	NR

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TABLE 2. Continued

Procedure	Study	Timing early approach	Identification of active bleeding	Diagnostic yield	Detection of vascular lesions	Therapeutic yield	Recurrent bleeding rate	Mortality
	Ohmiya et al, 2007[46]	Ongoing bleeding	NR	77.4% (24/31) vs 55.8% (213/382), $P < .05$	NR	NR	NR	NR
Single-arm studies								
CE	Marya et al, 2018[11]	First 24 h	NR	69.0% (29/42)	21.4% (9/42)	26.2% (11/42)	.0% (0/42)	2.4% (1/42)
	Üçüncü et al, 2017[12]	Immediately after negative BE	31.6% (12/38)	78.9% (30/38)	50.0% (19/38)	50.0% (19/38)	NR	10.5% (4/38)
	Schlag et al, 2015[13]	First 24 h	20.0% (4/20)	75.0% (15/20)	45.0% (9/20)	75.0% (15/20)	5.0% (1/20)	5.0% (1/20)
	Leung et al, 2012[14]	First 24 h	NR	53.3% (16/30)	6.7% (2/30)	33.3% (10/30)	33.3% (10/30)	13.3% (4/30)
	Lecleire et al, 2012[15]	24-48 h after urgent BE	74.54% (41/55)	74.5% (41/55)	45.5% (25/55)	78.2% (43/55)	10.9% (6/55)	NR
	Almeida et al, 2009[16]	Immediately after negative BE	46.7% (7/15)	80.0% (12/15)	13.3% (2/15)	73.3% (11/15)	13.3% (2/15)	NR
	Apostolopoulos et al, 2007[17]	First 48 h	91.9% (34/37)	91.9% (34/37)	48.6% (18/37)	56.8% (21/37)	15.6% (5/32)	NR
DAE	Pérez-Cuadrado Robles et al, 2014[4]	First 24 h	81.5% (22/27)	100.0% (27/27)	66.7% (18/27)	85.2% (23/27)	18.5% (5/27)	NR
	Mönkemüller et al, 2009[43]	First 24 h	80.0% (8/10)	90.0% (9/10)	40.0% (4/10)	80.0% (8/10)	NR	NR

For double-arm studies (comparing early and nonearly approaches), both proportions are presented (early vs non-early). For single-arm studies, only early approach proportions are presented.

BE, Bidirectional endoscopy; *DAE*, device-assisted enteroscopy; *NR*, not reported; *CE*, small-bowel capsule endoscopy.

In this study, we aimed to summarize the evidence regarding early small-bowel endoscopy. For such analysis, we used the cutoffs defined in each study; these differed among authors but were always within 14 days after bleeding presentation for SBCE and 72 hours for DAE. It was also our intention to explore differences in diagnostic and therapeutic yields when the small-bowel studies were performed in the first 24, 48, and 72 hours. As far as we know, this is the first systematic review and meta-analysis assessing both early capsule endoscopy and DAE, including both single- and double-arm studies and evaluating not only diagnostic and therapeutic yields but also the presence of active bleeding and vascular lesions, recurrent bleeding, and mortality.

This meta-analysis included 39 studies with adequate reporting quality but with low external validity. Studies were heterogeneous, mostly regarding enteroscopy timing, number of patients, bowel preparation requirements, and follow-up duration. To estimate the importance of timing on the diagnostic and therapeutic yields, we determined the pooled percentages for each cutoff of the early groups; a tendency toward lower yields for later procedures was detected.

The pooled diagnostic yield for early DAE was significantly superior from that of early SBCE (pooled difference of 7.97%, $P = .04$), a tendency also observed in a previous meta-analysis in which 22 studies had been included.[5] This may correspond to a detection bias, because in 42.86% of the DAE studies at least two-thirds of the patients were first submitted to SBCE. In agreement with previous reports, no differences existed between single- and double-balloon techniques[50]; no data were available to compare anterograde and retrograde insertion routes. The global therapeutic yield of early DAE was superior to that of early SBCE in 20.89 percentage points ($P = .05$), a pattern opposite that reported by Uchida et al,[5] highlighting the importance of increasing the number of studies. One may question whether this superior value may be because of a tendency to perform urgent DAE earlier in higher-risk patients, yet no data are available in this regard.

In the pooled analysis of double-arm studies, the odds for a positive diagnosis (OR, 3.99; $P < .01$; $I^2 = 45\%$) and subsequent therapeutic intervention (OR, 3.86; $P < .01$; $I^2 = 67\%$) were significantly superior in the early group, either for SBCE and DAE, reinforcing the

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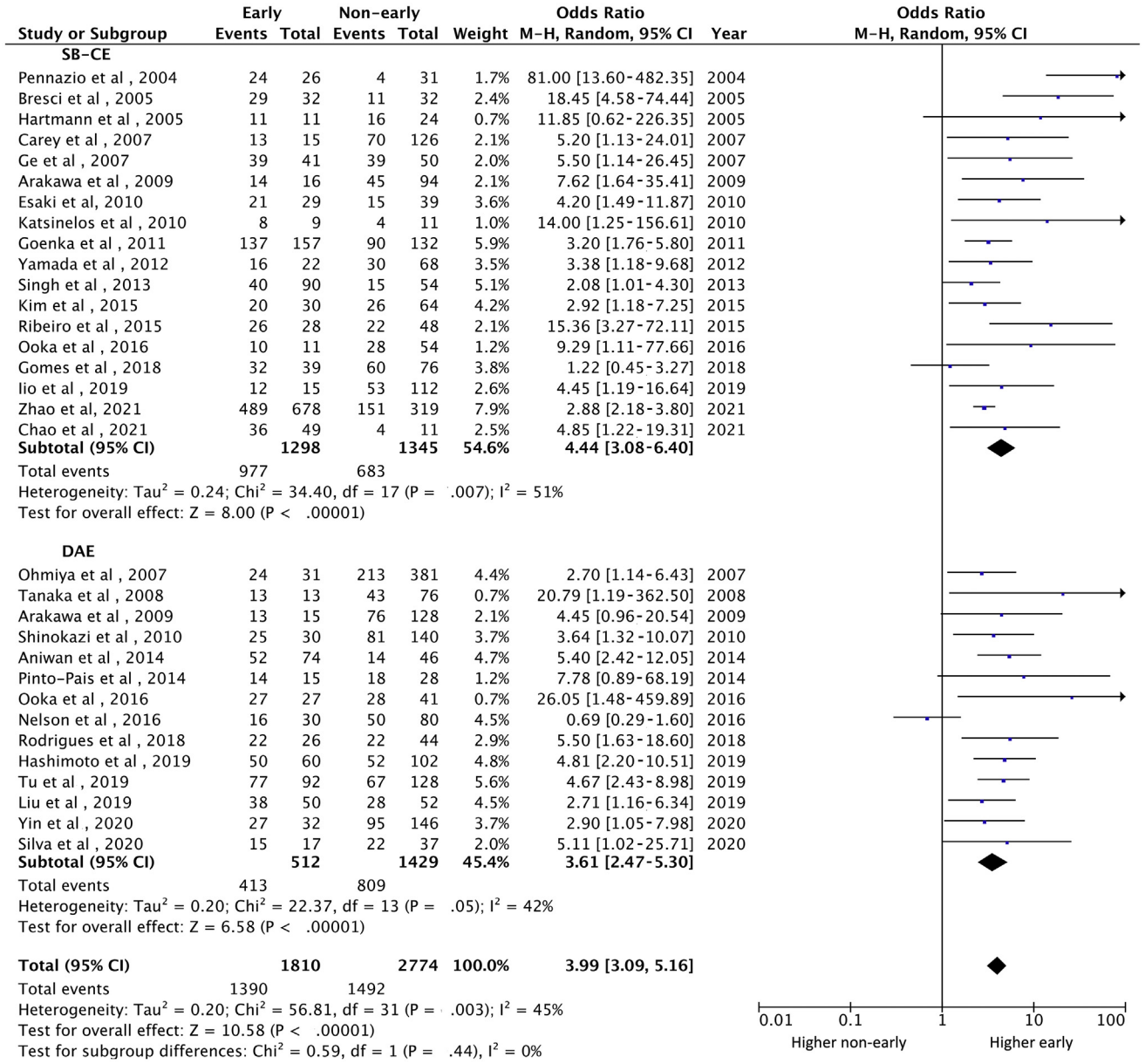

Figure 2. Odds ratio for diagnostic yield of the patients submitted to early versus nonearly small-bowel capsule endoscopy (SBCE) and device-assisted enteroscopy (DAE), regardless of the specific timing. The results of the subgroup analysis are presented as supplementary Table 2. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

importance of applying these techniques in the urgent setting. Overall, heterogeneity among studies was moderate. For therapeutic yield, the removal of the study by Nelson et al[40] (whose results had a unique and different pattern, as explained above) reduced heterogeneity from 67% to 48%. The detection of active bleeding (global OR, 5.09; $P < .01$; $I^2 = 53\%$) was superior in the early DAE versus early SBCE. The great difference obtained between those techniques may be biased by the low number of studies (that increases the ponderation of each individual study, which may be itself biased) but also may be related to the propensity to use DAE in more severe bleeding contexts. The odds for the diagnosis of vascular lesions, the most common cause of OGIB,[51] were not significantly different between early and nonearly groups. The great heterogeneity that exists in the definition, relevance, and clinical management of vascular lesions may also play a role. Recurrent bleeding was evaluated in 7 studies at very different time points. Early small-bowel endoscopy was associated with lower recurrent bleeding (OR, .40; $P < .01$; $I^2 = 0\%$). This is the first meta-analysis to report such findings; a recent study[3] comprising 15 DAE studies had failed to find differences.

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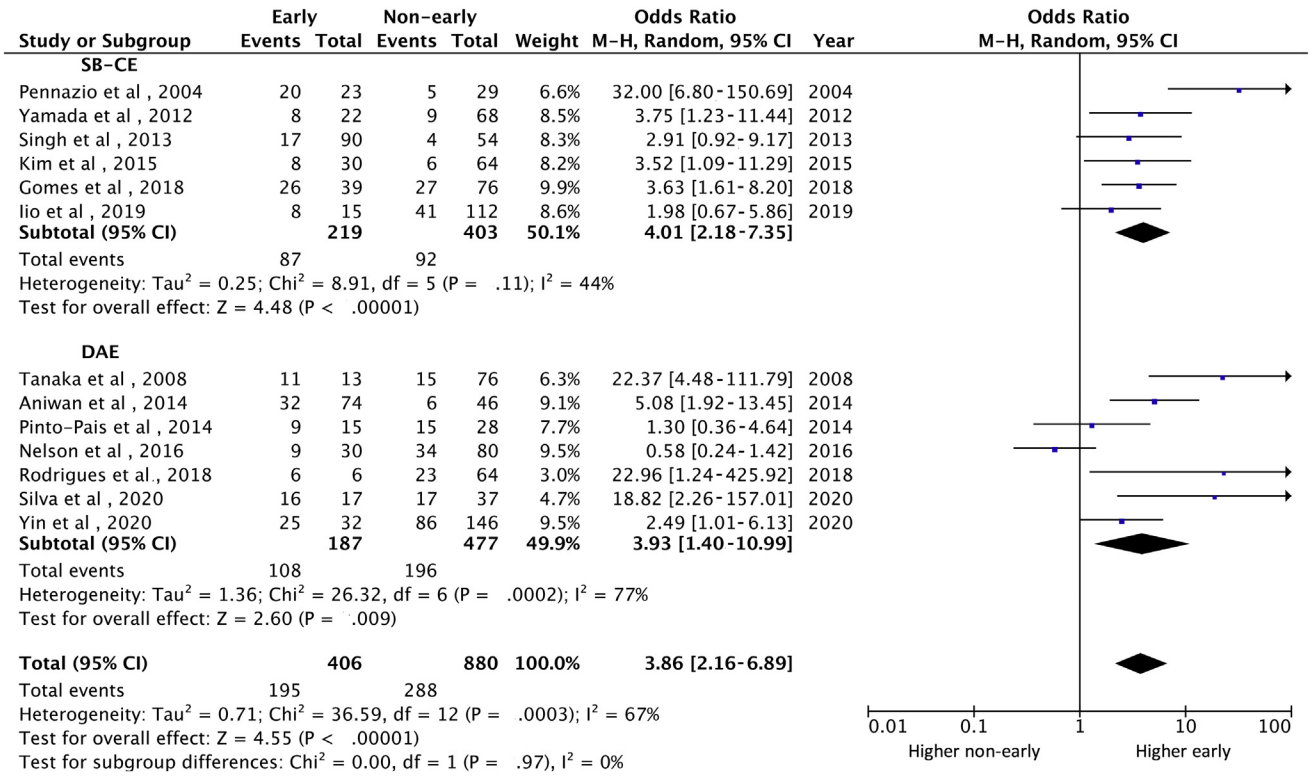

Figure 3. Odds ratio for therapeutic yield of the patients submitted to early versus nonearly small-bowel capsule endoscopy (SBCE) and device-assisted enteroscopy (DAE), regardless of the specific timing. *CI*, Confidence interval; *M-H*, Mantel-Haenszel.

Even though our study reached some important conclusions, some limitations must be acknowledged. First, different intervals in the early approach were found, because patients from the early group in 1 study could have been classified into nonearly in another. The analysis of specific timings was only approached using pooled yields for the early groups and subgroup analysis, because we did not possess patient-level data that would have allowed computing each endpoint at different timings. In that analysis, the separation of the timing of early SBCE and DAE did not change the OR. However, it must be considered that the number of studies in some subgroups was limited, and significant heterogeneity existed and was not reduced by the exclusion of any individual study, which may have camouflaged differences.

Second, the fact that we pooled data obtained using different SBCE systems and enteroscope models may have influenced both diagnostic and therapeutic yields. However, we were not able to separate data because most studies used different platforms and presented mixed results.

Third, subgroup analyses within each technique were only performed for diagnostic yield. Indeed, the Cochrane Handbook and several other authors advise that it is unlikely that subgroup analysis or other heterogeneity investigations will produce useful findings unless there are at least 10 studies in the meta-analysis, and even this number may be insufficient if observations are unevenly distributed.[52]

Fourth, data to compare, in a more objective way, the severity of bleeding were lacking, which may be an extraneous determinant. Indeed, the hemoglobin at admission, the need for transfusion, and bleeding scores were available in a few studies. Fifth, the paucity and diversity of some data, especially regarding recurrent bleeding and mortality, require caution in interpreting the results.

Sixth, most available evidence came from observational, retrospective, and single-center studies. Such studies possess limited internal and external validity and may have introduced bias in the summary effect. Further high-quality research, including randomized studies, is needed to clarify the open questions and enlighten clinical management of mid-GI bleeding. Comparative studies may identify the best timing for small-bowel endoscopy, particularly for SBCE in which the time frame currently considered as early is extended up to 14 days. Future recommendations may also evaluate the significance of reducing such a cutoff, currently somehow arbitrary, with the aim of unifying clinical practice procedures and converging with what is already known in DAE. In fact, performing DAE in the first 72 hours is dependent, most times, on SBCE performed in the first 48 hours. The 48 hours' timeframe has proven to be feasible in previous studies.[3] With the current widespread availability of SBCE and lack of reasons to

defer it up to 14 days, this recommendation could be reassessed. Finally, to confirm the tendency observed for recurrent bleeding and to evaluate the impact on mortality, it is essential to broaden follow-up periods.[53]

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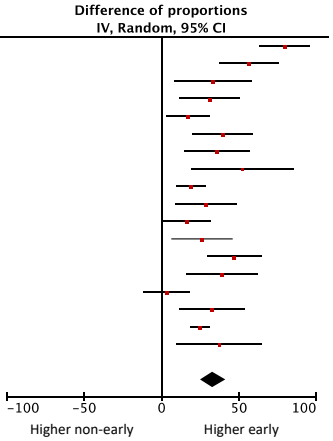
1.1 Diagnostic yield SBCE

Study or Subgroup	Difference of proportions	SE	Weight	Difference of proportions IV, Random, 95% CI	Year
Pennazio et al., 2004	79.4	8.28	6.0%	79.40 [63.17, 95.63]	2004
Bresci et al., 2005	56.2	9.71	5.5%	56.20 [37.17, 75.23]	2005
Hartmann et al., 2005	33.3	12.76	4.6%	33.30 [8.29, 58.31]	2005
Carey et al., 2007	31.1	9.92	5.5%	31.10 [11.66, 50.54]	2007
Ge et al., 2007	17.1	7.21	6.4%	17.10 [2.97, 31.23]	2007
Arakawa et al., 2009	39.6	9.92	5.5%	39.60 [20.16, 59.04]	2009
Esaki et al, 2010	35.7	10.78	5.2%	35.70 [14.57, 56.83]	2010
Katsinelos et al., 2010	52.5	16.85	3.5%	52.50 [19.47, 85.53]	2010
Goenka et al., 2011	19	4.84	7.1%	19.00 [9.51, 28.49]	2011
Yamada et al., 2012	28.6	10.2	5.4%	28.60 [8.61, 48.59]	2012
Singh et al., 2013	16.6	7.87	6.2%	16.60 [1.18, 32.02]	2013
Kim et al., 2015	26.1	10.11	5.4%	26.10 [6.28, 45.92]	2015
Ribeiro et al., 2015	47	8.94	5.8%	47.00 [29.48, 64.52]	2015
Ooka et al., 2016	39.1	11.82	4.9%	39.10 [15.93, 62.27]	2016
Gomes et al., 2018	3.2	7.71	6.2%	3.20 [−11.91, 18.31]	2018
Iio et al., 2019	32.7	10.86	5.2%	32.70 [11.41, 53.99]	2019
Zhao et al, 2021	24.8	3.27	7.5%	24.80 [18.39, 31.21]	2021
Chao et al., 2021	37.1	14.03	4.2%	37.10 [9.60, 64.60]	2021
Total (95% CI)			**100.0%**	**33.33 [25.09, 41.57]**	

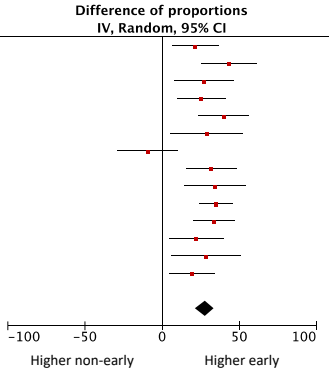
Heterogeneity: $Tau^2 = 224.64$; $Chi^2 = 76.17$, df = 17 ($P < 0.00001$); $I^2 = 78\%$
Test for overall effect: $Z = 7.93$ ($P < 0.00001$)



1.2 Diagnostic yield DAE

Study or Subgroup	Difference of proportions	SE	Weight	Difference of proportions IV, Random, 95% CI	Year
Ohmiya et al., 2007	21.6	7.68	8.1%	21.60 [6.55, 36.65]	2007
Tanaka et al., 2008	43.4	9.27	6.6%	43.40 [25.23, 61.57]	2008
Arakawa et al., 2009	27.3	9.88	6.1%	27.30 [7.94, 46.66]	2009
Shinokazi et al., 2010	25.4	7.94	7.8%	25.40 [9.84, 40.96]	2010
Aniwan et al., 2014	39.9	8.38	7.4%	39.90 [23.48, 56.32]	2014
Pinto-Pais et al., 2014	29	11.95	4.7%	29.00 [5.58, 52.42]	2014
Nelson et al., 2016	−9.2	10.07	6.0%	−9.20 [−28.94, 10.54]	2016
Ooka et al., 2016	31.8	8.33	7.4%	31.80 [15.47, 48.13]	2016
Rodrigues et al., 2018	34.5	10.2	5.9%	34.50 [14.51, 54.49]	2018
Tu et al., 2019	34.8	5.5	10.7%	34.80 [24.02, 45.58]	2019
Hashimoto et al., 2019	33.8	6.85	9.0%	33.80 [20.37, 47.23]	2019
Liu et al., 2019	22.2	8.94	6.9%	22.20 [4.68, 39.72]	2019
Silva et al., 2020	28.7	11.42	5.0%	28.70 [6.32, 51.08]	2020
Yin et al., 2020	19.3	7.54	8.3%	19.30 [4.52, 34.08]	2020
Total (95% CI)			**100.0%**	**27.80 [21.74, 33.85]**	

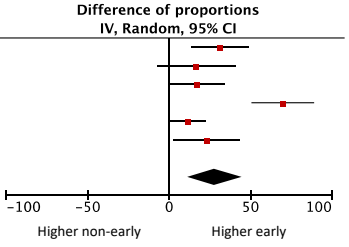
Heterogeneity: $Tau^2 = 58.62$; $Chi^2 = 23.82$, df = 13 ($P = 0.03$); $I^2 = 45\%$
Test for overall effect: $Z = 9.00$ ($P < 0.00001$)



1.3 Therapeutic yield SBCE

Study or Subgroup	Difference of proportions	SE	Weight	Difference of proportions IV, Random, 95% CI
Gomes et al., 2018	31.2	9.02	16.9%	31.20 [13.52, 48.88]
Iio et al., 2019	16.7	12.3	14.6%	16.70 [−7.41, 40.81]
Kim et al., 2015	17.3	8.74	17.1%	17.30 [0.17, 34.43]
Pennazio et al., 2004	69.8	9.84	16.4%	69.80 [50.51, 89.09]
Singh et al., 2013	11.5	5.73	19.0%	11.50 [0.27, 22.73]
Yamada et al., 2012	23.2	10.47	15.9%	23.20 [2.68, 43.72]
Total (95% CI)			**100.0%**	**27.99 [11.04, 44.95]**

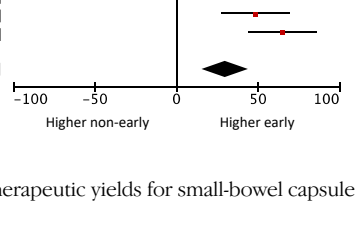
Heterogeneity: $Tau^2 = 360.42$; $Chi^2 = 27.99$, df = 5 ($P < 0.0001$); $I^2 = 82\%$
Test for overall effect: $Z = 3.24$ ($P = 0.001$)



1.4 Therapeutic yield DAE

Study or Subgroup	Difference of porportions	SE	Weight	Difference of porportions IV, Random, 95% CI
Pinto-Pais et al., 2014	6.4	13.6	11.6%	6.40 [−20.26, 33.06]
Nelson et al., 2016	12.5	9.65	14.8%	12.50 [−6.41, 31.41]
Yin et al., 2020	19.9	8.19	16.0%	19.90 [3.85, 35.95]
Rodrigues et al., 2018	25.9	11.3	13.4%	25.90 [3.75, 48.05]
Aniwan et al., 2014	30.2	7.6	16.4%	30.20 [15.30, 45.10]
Silva et al., 2020	48.2	10.7	13.9%	48.20 [27.23, 69.17]
Tanaka et al., 2008	64.9	10.7	13.9%	64.90 [43.93, 85.87]
Total (95% CI)			**100.0%**	**29.92 [15.96, 43.88]**

Heterogeneity: $Tau^2 = 250.70$; $Chi^2 = 21.47$, df = 6 ($P = 0.002$); $I^2 = 72\%$
Test for overall effect: $Z = 4.20$ ($P < 0.0001$)



Supplementary Figure 1. Difference of proportions (early vs nonearly) for diagnostic and therapeutic yields for small-bowel capsule endoscopy (SBCE) and device-assisted enteroscopy (DAE). *CI*, Confidence interval.

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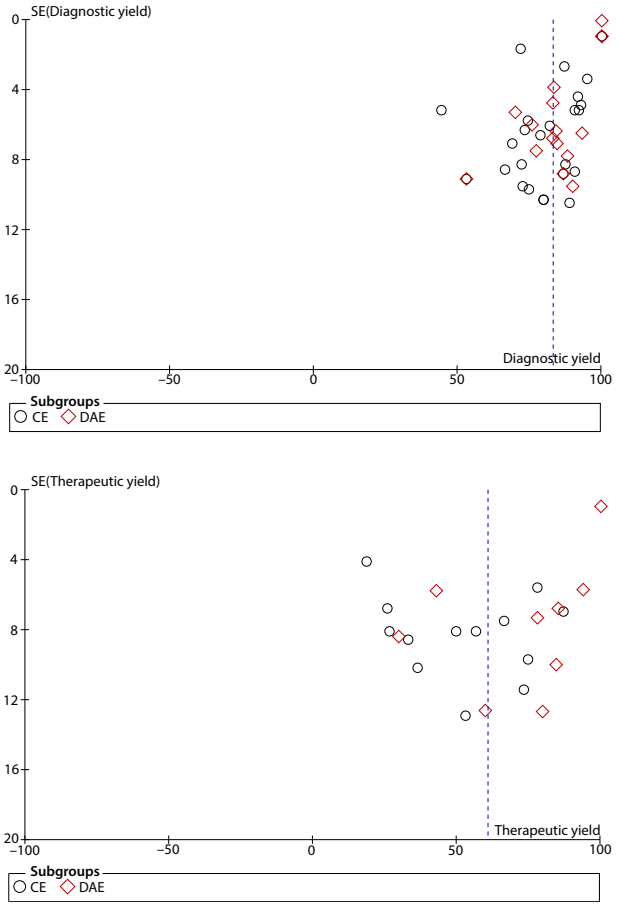

Supplementary Figure 2. Funnel plots for the primary endpoints. *CE*, Capsule endoscopy data; *DAE*, device-assisted enteroscopy data.

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	CASP criteria												
Study	1	2	3	4	5a	5b	6a	6b	7	8	9	10	11
Chao et al., 2021	●	●	●	●	●	●	●	●	●	●	●	●	●
Zhao et al., 2021	●	●	●	●	●	●	●	●	●	●	●	●	●
Silva et al., 2020	●	●	●	●	●	●	●	●	●	●	●	●	●
Yin et al., 2020	●	●	●	●	●	●	●	●	●	●	●	●	●
Iio et al., 2019	●	●	●	●	●	●	●	●	●	●	●	●	●
Gomes et al., 2018	●	●	●	●	●	●	●	●	●	●	●	●	●
Hashimoto et al., 2019	●	●	●	●	●	●	●	●	●	●	●	●	●
Liu et al., 2019	●	●	●	●	●	●	●	●	●	●	●	●	●
Tu et al., 2019	●	●	●	●	●	●	●	●	●	●	●	●	●
Marya et al., 201 9	●	●	●	●	●	●	●	●	●	●	●	●	●
Rodrigues et al., 2018	●	●	●	●	●	●	●	●	●	●	●	●	●
Üçüncü et al., 2017	●	●	●	●	●	●	●	●	●	●	●	●	●
Nelson et al., 2016	●	●	●	●	●	●	●	●	●	●	●	●	●
Ooka et al., 2016	●	●	●	●	●	●	●	●	●	●	●	●	●
Kim et al., 2015	●	●	●	●	●	●	●	●	●	●	●	●	●
Ribeiro et al., 2015	●	●	●	●	●	●	●	●	●	●	●	●	●
Schlag et al., 2015	●	●	●	●	●	●	●	●	●	●	●	●	●
Aniwan et al., 2014	●	●	●	●	●	●	●	●	●	●	●	●	●
Pérez-Cuadrado Robles et al., 2014	●	●	●	●	●	●	●	●	●	●	●	●	●
Pinto-Pais et al., 2014	●	●	●	●	●	●	●	●	●	●	●	●	●
Singh et al., 2013	●	●	●	●	●	●	●	●	●	●	●	●	●
Lecleire et al., 2012	●	●	●	●	●	●	●	●	●	●	●	●	●
Leung et al., 2012	●	●	●	●	●	●	●	●	●	●	●	●	●
Yamada et al., 2012	●	●	●	●	●	●	●	●	●	●	●	●	●
Goenka et al., 2011	●	●	●	●	●	●	●	●	●	●	●	●	●
Esaki et al., 2010	●	●	●	●	●	●	●	●	●	●	●	●	●
Katsinelos et al., 2010	●	●	●	●	●	●	●	●	●	●	●	●	●
Shinokazi et al., 2010	●	●	●	●	●	●	●	●	●	●	●	●	●
Almeida et al., 2009	●	●	●	●	●	●	●	●	●	●	●	●	●
Arakawa et al., 2009	●	●	●	●	●	●	●	●	●	●	●	●	●
Mönkemüller et al., 2009	●	●	●	●	●	●	●	●	●	●	●	●	●
Tanaka et al., 2008	●	●	●	●	●	●	●	●	●	●	●	●	●
Apostolopoulos et al., 2007	●	●	●	●	●	●	●	●	●	●	●	●	●
Carey et al., 2007	●	●	●	●	●	●	●	●	●	●	●	●	●
Ge et al., 2007	●	●	●	●	●	●	●	●	●	●	●	●	●
Ohmiya et al., 2007	●	●	●	●	●	●	●	●	●	●	●	●	●
Bresci et al., 2005	●	●	●	●	●	●	●	●	●	●	●	●	●
Hartmann et al., 2005	●	●	●	●	●	●	●	●	●	●	●	●	●
Pennazio et al., 2004	●	●	●	●	●	●	●	●	●	●	●	●	●

Supplementary Figure 3. Results of the reporting quality analysis, using the Critical Appraisal Skills Programme (CASP) checklist.

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SUPPLEMENTARY TABLE 1. Definitions of positive findings (used to calculate diagnostic yield), vascular lesions, and therapeutic modalities used in each included study; timing until rebleeding and until mortality analysis

Study	Positive findings	Vascular lesions	Therapy used	Rebleeding	Mortality
Chao et al, 2021	Active bleeding (without underlying etiology), tumor, angioectasia, ulcers, others	Angioectasia	NR	NR	NR
Zhao et al, 2021	Active bleeding with no identifiable lesions, angioectasia, small-bowel ulcer or tumor, diverticulum, Crohn's disease, others	Angioectasia	NR	At 12 mo	NR
Silva et al, 2020	Active bleeding or recent bleeding stigmata, small-bowel tumors >20 mm	NR	Endoscopic or surgical	At 36 mo	At 30 days
Yin et al, 2020	Ulcers >10 mm, angiodysplasia >10 mm, tumors >20 mm, tumors/polyp with ulcer/erosion, diverticulum with ulcer/vessel	Angiodysplasia	Endoscopic	NR	NR
Hashimoto et al, 2019	Ulcer >10 mm, angiodysplasia >10 mm (or smaller if oozing), bleeding polyp, diverticulum with signs of bleeding	NR	NR	NR	NR
Iio et al, 2019	Vascular, ulcerative, or neoplastic lesions, Meckel's diverticulum	Not specified	Endoscopic or surgical	At 2 mo	NR
Liu et al, 2019	Ulcer, tumor, vascular malformation	Polyp, stale hemorrhage	NR	NR	NR
Tu et al, 2019	Visible bleeding, or an inactive lesion likely to be relevant, angiodysplasia >10 mm (or smaller with bleeding stigmata), diverticulum with signs of bleeding	Not specified	NR	NR	NR
Gomes et al, 2018	Bleeding without visible lesions, angiodysplasia, varices, hemangioma, ulcer, erosion, eroded polyps, diverticulum with bleeding stigmata, tumor, or extra–small-bowel causes	Angiodysplasia, varices, hemangioma, ulcers/erosions	Endoscopic, angiographic, or surgical	At 50 mo	At 50 mo
Marya et al, 2018	Identification of blood or a lesion with recent bleeding stigmata	Angioectasia	Endoscopic	At 30 days	At 30 days
Rodrigues et al, 2018	Lesions with bleeding stigmata, including ulcers/erosions and tumors, polyps, diverticula. small-bowel tumors >2 mm without bleeding stigmata, angiodysplasia >10 mm (or smaller with bleeding stigmata)	Angiodysplasia, Dieulafoy's lesion	Endoscopic	NR	NR
Üçüncü et al, 2017	Active bleeding, vascular lesions, mass	Angiodysplasia, erosion, ulcers, vascular ectasia	Endoscopic, angiographic, or surgical	NR	Time not specified
Nelson et al, 2016	Erosion, ulcer, stricture, angiodysplasia/arteriovenous malformation, polyp, mass, Dieulafoy's lesion, varices, pigmented lesion, or active bleeding	Angiodysplasia/arteriovenous malformation, Dieulafoy's lesion, varices	Endoscopic	NR	NR

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SUPPLEMENTARY TABLE 1. Continued

Study	Positive findings	Vascular lesions	Therapy used	Rebleeding	Mortality
Ooka et al, 2016	Vascular lesion, ulcer, tumor, diverticulum	NR	NR	NR	NR
Kim et al, 2015	Active bleeding or clots, angiodysplasia, ulcer, diverticulum with stigmata of recent bleeding, small-bowel tumor, or bleeding outside the small bowel	Angiodysplasia	Endoscopic, angiographic, or surgical	Time not specified	NR
Ribeiro et al, 2015	Typical angiomata, multiple erosions, ulcers, visible blood, tumors, and varices	NR	NR	NR	NR
Schlag et al, 2015	Lesions with stigmata of a recent hemorrhage or blood	Angiodysplasia	Endoscopic, or surgical	At 4 wk	At 4 wk
Aniwan et al, 2014	Ulcers (>10 mm in diameter), angiodysplasia >10 mm (or smaller with bleeding stigmata), tumors/polyps with ulcer/erosion, and diverticula with ulcers/vessels	Angiodysplasia, varices	Endoscopic, angiographic, or surgical	Mean follow-up 16.3 ± 1.8 mo	NR
Pérez-Cuadrado Robles et al, 2014,	Angiodysplasia, Dieulafoy's lesion, ulcers/erosions, tumors, diverticulum with signs of bleeding	Angiodysplasia, Dieulafoy's lesion	Endoscopic or surgical	At 15 mo	NR
Pinto-Pais et al, 2014	Ulcers/erosions, tumors, or polyps with bleeding stigmata, angiodysplasia	Angiodysplasia	Endoscopic	NR	NR
Singh et al, 2013	Any abnormal finding that could explain the patient's source of bleeding	NR	Endoscopic or surgical	NR	NR
Lecleire et al, 2012	Specific lesions causing bleeding (angiodysplasia, ulcers, tumors, or varices) or fresh blood without lesion	Angiodysplasia, varices	Endoscopic, angiographic, or surgical	At 36 mo	NR
Leung et al, 2012	Lesions with high probability of bleeding (area with fresh bleeding, ulcers, and erosions of at least 2 mm in size, tumors, and varices)	Angiodysplasia, varices, vascular ectasia	Endoscopic or surgical	At 48.5 mo	At 48.5 mo
Yamada et al, 2012	Angioectasia, erosion, diverticula, tumor, and bleeding	Angioectasia	Endoscopic or surgical	NR	NR
Goenka et al, 2011	Lesions with bleeding potential (ulcers/erosions, tumors, vascular)	NR	NR	NR	NR
Esaki et al, 2010	Findings that explained clinical symptoms and were proven by other examinations (double-balloon enteroscopy, small-bowel radiography, or CT) or surgery	NR	NR	NR	NR
Katsinelos et al, 2010	Angiodysplasias, ulcerations, tumors, varices, multiple erosions	NR	NR	NR	NR

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SUPPLEMENTARY TABLE 1. Continued

Study	Positive findings	Vascular lesions	Therapy used	Rebleeding	Mortality
Shinokazi et al, 2010	Ulcers >10 mm, vascular lesions >10 mm (or smaller with bleeding stigmata), and tumors/polyps >20 mm, bleeding lesions	Angioectasia, Dieulafoy's lesion, and arteriovenous malformation	Endoscopic, angiographic, or surgical	NR	NR
Almeida et al, 2009	Typical angiomas or angiodysplasias, varices, tumors, large ulcerations and multiple erosions, active bleeding	Angiodysplasia, varices	Endoscopic, angiographic, or surgical	Time not specified	NR
Arakawa et al, 2009	Blood or a bleeding source (angiodysplasia, Dieulafoy's lesion, varices, arteriovenous malformation, erosion, ulcer, tumor, polyp, or diverticulum)	NR	NR	NR	NR
Mönkemüller et al, 2009	Identification of blood or a lesion with bleeding stigmata	Angiodysplasias, large arteriovenous malformation	Endoscopic, angiographic, or surgical	NR	NR
Tanaka et al, 2008	Angioectasia, varices, ulcerations, or erosions with bleeding stigmata, tumors with ulcers or vascularization	NR	Endoscopic or surgical	Time not specified	NR
Apostolopoulos et al, 2007	Identification of blood or a lesion with bleeding stigmata	Angiodysplasias, arteriovenous malformation	Endoscopic or surgical	At 12 mo	NR
Carey et al, 2007	Angioectasia, tumors, active bleeding, blood clots, or mucosal breaks	NR	NR	NR	NR
Ge et al, 2007	Clear explanation of the bleeding	Angiodysplasias, angioma	NR	NR	NR
Ohmiya et al, 2007	Identification of blood or a lesion with bleeding potential	NR	Endoscopic	NR	NR
Bresci et al, 2005	Findings with bleeding potential; classified as diagnostic if observed by all 3 investigators who independently reviewed the images	Angioectasia	NR	NR	NR
Hartmann et al, 2005	Findings that allowed a clear explanation of the clinical situation (multiple angioectasia, actively bleeding lesions, ulcers, tumors)	NR	NR	NR	NR
Pennazio et al, 2004	Findings that allowed a clear explanation of the clinical situation (multiple angioectasia, actively bleeding lesions, ulcers, tumors)	NR	Endoscopic or surgical	NR	NR

NR, Not reported.

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SUPPLEMENTARY TABLE 2. Results of the meta-analysis, including the odds ratio for positive findings (diagnostic yield), active bleeding, detection of vascular lesions, and therapeutic approach (therapeutic yield)

Outcome	Analysis	No. of studies	Pooled value (%)	95% Confidence interval	Heterogeneity I^2 = %	Overall effect	Subgroup differences
Single-arm + double-arm studies							
Diagnostic yield	SBCE + DAE	39	83.12	79.80-86.43	94	$P < .001$	—
	SBCE	25	80.35	73.85-86.85	93	$P < .001$	$I^2 = 77\%$, $P = .040$
	DAE	16	88.32	84.73-91.91	89	$P < .001$	
Therapeutic yield	SBCE + DAE	22	60.79	45.83-75.75	97	$P < .001$	—
	SBCE	13	52.25	37.65-66.85	92	$P < .001$	$I^2 = 68\%$, $P = .050$
	DAE	9	73.14	55.34-90.94	96	$P < .001$	
Single-arm studies							
Diagnostic yield	SBCE + DAE	9	80.00	68.72-91.27	91	$P < .001$	—
	SBCE	7	75.65	66.23-85.08	69	$P < .001$	$I^2 = 95\%$, $P < .001$
	DAE	2	99.51	95.29-103.73	10	$P < .001$	
Detection of vascular lesions	SBCE + DAE	9	36.83	22.07-51.58	87	$P < .001$	—
	SBCE	7	32.32	17.17-47.48	88	$P < .001$	$I^2 = 60\%$, $P = .110$
	DAE	2	56.30	30.78-81.82	55	$P < .001$	
Detection of active bleeding	SBCE + DAE	7	61.26	39.89-82.62	93	$P < .001$	—
	SBCE	5	53.58	25.04-82.11	95	$P = .002$	$I^2 = 67\%$, $P = .008$
	DAE	2	81.12	68.61-93.62	0	$P < .001$	
Therapeutic yield	SBCE + DAE	9	61.60	46.34-76.86	88	$P < .001$	—
	SBCE	7	55.80	39.00-72.61	88	$P < .001$	$I^2 = 86\%$, $P = .007$
	DAE	2	84.04	72.29-95.79	0	$P < .001$	
Outcome	Subgroup analysis	No. of studies	Odds ratio	95% Confidence interval	Heterogeneity I^2 = %	Overall effect	Subgroup differences
Double-arm studies							
Overall diagnostic yield	SBCE + DAE	30	3.99	3.09-5.16	45	$P < .001$	—
Diagnostic yield SBCE	All studies SBCE	18	4.44	3.08-6.40	51	$P < .001$	—
	Cutoff defined as early approach						
	<48 h	12	5.01	2.93-8.59	52	$P < .001$	$I^2 = 0\%$, $P = .530$
	>48 h	6	3.92	2.30-6.70	50	$P < .001$	
	<72 h	15	4.34	2.84-6.62	46	$P < .001$	$I^2 = 0\%$, $P = .500$
	>72 h	3	7.39	1.69-32.23	75	$P < .001$	
	Bowel preparation						
	Yes	8	5.85	3.14-10.90	35	$P < .001$	$I^2 = 16\%$, $P = .270$
	No	10	3.71	2.18-6.31	68	$P < .001$	

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SUPPLEMENTARY TABLE 2. Continued

Outcome	Analysis	No. of studies	Pooled value (%)	95% Confidence interval	Heterogeneity I^2 = %	Overall effect	Subgroup differences
	No. of patients early approach						
	<49	14	6.12	3.55-10.53	41	$P < .001$	$I^2 = 84\%$, $P = .010$
	≥49	4	2.87	2.27-3.63	0	$P < .001$	
Diagnostic yield DAE	All studies DAE	14	3.61	2.47-5.30	42	$P < .001$	—
	Cutoff defined as early approach						
	<24 h	6	2.97	1.53-5.80	68	$P = .001$	$I^2 = 5\%$, $P = .310$
	>24 h	9	4.41	3.09-6.29	0	$P < .001$	
	Procedure						
	SBE	7	3.48	1.61-7.51	66	$P = .001$	$I^2 = 0\%$, $P = .730$
	DBE	7	4.05	2.78-5.91	0	$P < .001$	
	Previous SBCE in more than two-thirds of patients						
	Yes	6	4.92	3.21-7.56	0	$P < .001$	$I^2 = 39\%$, $P = .200$
	No	8	3.01	1.61-5.60	61	$P < .001$	
Detection of active bleeding	SBCE + DAE	8	5.09	2.39-10.85	53	$P < .001$	—
	SBCE	5	3.22	1.90-5.44	0	$P < .001$	$I^2 = 47\%$, $P = .170$
	DAE	3	19.78	1.57-249.68	79	$P = .020$	
Detection of vascular lesions	SBCE + DAE	16	1.53	1.11-2.11	46	$P = .010$	—
	SBCE	8	1.70	.97-2.97	61	$P = .060$	$I^2 = 0\%$, $P = .600$
	DAE	8	1.41	.95-2.10	27	$P = .090$	
Therapeutic yield	SBCE + DAE	13	3.86	2.16-6.89	67	$P < .001$	—
	SBCE	6	4.01	2.18-7.35	44	$P < .001$	$I^2 = 6\%$, $P = .410$
	DAE	7	3.93	1.40-10.99	77	$P = .009$	
Rebleeding	SBCE + DAE	7	.40	.30-.51	0	$P < .001$	—
	SBCE	4	.39	.30-.52	0	$P < .001$	$I^2 = 0\%$, $P = .920$
	DAE	3	.41	.17-1.00	40	$P = .050$	

For the diagnostic yield, subgroup analyses were performed considering the time interval defined as an early approach (48 or 72 h for SBCE; 24 h for DAE), bowel preparation requirements for SBCE, DAE procedure (single or double balloon), and SBCE before DAE or sample size.
DAE, Device-assisted enteroscopy; *SBCE*, small-bowel capsule endoscopy; SBE, single balloon enteroscopy; DBE, double balloon enteroscopy.

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SUPPLEMENTARY TABLE 3. Pooled diagnostic and therapeutic yields for early SBCE and DAE, divided per cutoff

Procedure	Cutoff	Pooled diagnostic yield	Pooled therapeutic yield
SBCE	<24 h	83.38% (95% CI, 76.30-90.46) I^2 = 95%, n = 11	57.56% (95% CI, 36.95-78.16) I^2 = 97%, n = 6
	<48 h	81.31% (95% CI, 75.20-87.43) I^2 = 93%, n = 8	59.09% (95% CI, 43.66-74.52) I^2 = 95%, n = 6
	<72 h	63.55% (95% CI, 45.59-81.51) I^2 = 91%, n = 3	18.90% (95% CI, 11.26-26.54) n = 1
	<14 days	84.43% (95% CI, 74.59-94.26), I^2 = 84%, n = 3	No studies
DAE	<24 h	92.94% (95% CI, 91.35-94.54) I^2 = 96%, n = 12	73.54% (95% CI, 54.18-92.90) I^2 = 99%, n = 6
	<48 h	100.0% (95% CI, 99.80-100.20) n = 1	No studies
	<72 h	82.69% (95% CI, 77.42-87.96) I^2 = 60%, n = 12	68.52% (95% CI, 45.15-91.89) I^2 = 97%, n = 4

DAE, Device-assisted enteroscopy; *SBCE*, small-bowel capsule endoscopy.

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