REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
Timing of enteroscopy in overt-obscure gastrointestinal bleeding - a systematic review and meta-analysis

Authors:
Ana Catarina Gomes, Rolando Taveira Pinho, Ana Ponte, Manuela Estevinho, João Carvalho

DOI: 10.17235/reed.2021.7976/2021
Link: PubMed (Epub ahead of print)

Please cite this article as:
Gomes Ana Catarina, Pinho Rolando Taveira, Ponte Ana, Estevinho Manuela, Carvalho João. Timing of enteroscopy in overt-obscure gastrointestinal bleeding - a systematic review and meta-analysis. Rev Esp Enferm Dig 2021. doi: 10.17235/reed.2021.7976/2021.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

REV 7976

Timing of enteroscopy in overt-obscure gastrointestinal bleeding: a systematic review and meta-analysis

Ana Catarina Gomes, Rolando Taveira Pinho, Ana Ponte, Manuela Estevinho and João Carvalho

Gastroenterology Department. Centro Hospitalar Vila Nova de Gaia/Espinho. Vila Nova de Gaia, Portugal

Received: 18/03/2021

Accepted: 23/05/2021

Correspondence: Ana Catarina Gomes. Gastroenterology Department. Centro Hospitalar Vila Nova de Gaia/Espinho. Vila Nova de Gaia, Portugal

e-mail: Catarina.rib.gomes@gmail.com

Conflict of interest: the authors declare no conflict of interest.

ABSTRACT

Background: the impact of early enteroscopy on the outcome of overt-obscure gastrointestinal bleeding (OGIB) is still unclear. Our aim was to evaluate the impact of early enteroscopy on overt-OGIB.

Methods: the PubMed-MEDLINE, Web of Science, and Scopus databases were systematically reviewed. Observational retrospective studies comparing early *versus* non-early enteroscopy in overt-OGIB were identified. Data on diagnosis, treatment, and rebleeding were extracted from each study, and a meta-analysis was performed.

Results: fifteen studies (comprising 1,907 patients) were included. Early enteroscopy was performed in 470 patients and non-early enteroscopy in 1,437 patients. Early enteroscopy was associated with a significantly higher diagnostic yield (odds ratio [OR] = 3.2, 95 % CI: 1.9-5.3; p = 0.002) and therapeutic yield (OR = 4.9, 95 % CI: 1.2-20.5; p = 0.03). However, moderate and high heterogeneity was observed in both analyses (DY I^2

= 60.4 %; p = 0.002; TY I^2 = 83.1 %; p < 0.001). When considering only studies where enteroscopy was performed during ongoing bleeding or within ≤ 24 h, ≤ 48 h, and ≤ 72 h of bleeding, heterogeneity was removed while the positive effect on diagnostic yield was maintained (OR = 4.7, 95 % CI: 3.4-6.6, p < 0.001, I^2 = 0 %). Early enteroscopy did not significantly influence rebleeding rate (OR = 0.87, 95 % CI: 0.40-1.89, p = 0.72) in our analysis.

Conclusions: in conclusion, early enteroscopy, especially when performed during ongoing bleeding or within 24 h, 48 h or 72 h of the bleeding episode, may increase diagnostic yield. Although an effect on therapeutic yield was observed, the value of early intervention has to be cautiously evaluated due to the high heterogeneity found among results. In our meta-analysis, early enteroscopy did not significantly influence rebleeding rate.

Keywords: Obscure gastrointestinal bleeding. Small bowel. Enteroscopy. Emergency.

INTRODUCTION

Rationale

Small-bowel bleeding accounts for approximately 1.2-5 % of all gastrointestinal bleeding cases (1,2) and this concept typically overlaps with obscure-gastrointestinal bleeding (OGIB). OGIB is defined as any acute or chronic bleeding that persists or recurs despite negative findings from bidirectional endoscopy (3) and is frequently due to a small-bowel lesion presenting with bleeding (4). OGIB is further subdivided into occult or overt-OGIB. Occult-OGIB is defined by recurrent iron-deficiency anemia and/or recurrent positive fecal blood tests. On the other hand, overt-OGIB refers to recurrent or persistent visible bleeding (hematochezia, melena or hematemesis) (3).

Capsule endoscopy (CE) is recommended as the first-line examination for small-bowel evaluation due to its non-invasiveness and high diagnostic yield (4). In overt-OGIB the European Society of Gastrointestinal Endoscopy (ESGE) recommends CE as soon as possible after a bleeding episode, optimally within 14 days (4). Device-assisted enteroscopy, which encompasses spiral, single (SBE), and double-balloon enteroscopy (DBE), may be the first-line therapeutic procedure following a positive CE in an OGIB

setting (4,5).

There is no consensus regarding the most appropriate timing of enteroscopy in overt-OGIB (4,6). Although with a low-quality level of evidence, a recent Portuguese and Spanish guideline (5) already recommended that in overt-OGIB, enteroscopy should be performed whenever possible in the first 72 h after the bleeding episode (5).

Evidence about the timing of enteroscopy in the setting of overt-OGIB is limited to retrospective studies with a small number of patients, and the concept of urgent or emergent enteroscopy is not consistent. Moreover, most data regarding OGIB do not divide results according to type of presentation (overt or occult). This is the first systematic review and meta-analysis evaluating the impact of early enteroscopy on the setting of overt-OGIB.

Objectives

The authors reviewed observational studies that assessed the diagnostic and/or therapeutic yield in both an urgent and non-urgent setting. The question being addressed will follow the five "PICOS" components:

- Participants: adult patients with overt-OGIB.
- Interventions: enteroscopy in an early setting.
- Comparison: enteroscopy in a non-early setting.
- Outcomes: diagnostic, therapeutic yield and rebleeding rates.
- Study design: observational studies.

METHODS

Protocol

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

Eligibility criteria

Types of studies

Studies analyzing the diagnostic or therapeutic yield of early enteroscopy in overt-OGIB were considered. The article was excluded if the language was not amenable for

translation. No publication date or publication status restrictions were imposed.

Types of participants

Participants older than 18 years with overt-OGIB were considered. Patients with occult-OGIB were excluded.

Types of interventions

Studies evaluating different timelines of enteroscopy application in overt-OGIB. An early enteroscopy was considered when performed in the following situations: a) ongoing overt-OGIB; b) within a time interval from bleeding onset; c) within a time interval from the last bleeding episode; and d) within a time interval from hospital admission.

Types of outcomes

Primary outcome measures: diagnostic yield, defined as the likelihood that the findings detected by enteroscopy will explain gastrointestinal bleeding. Secondary outcomes measures: therapeutic yield, defined as the ability to successfully perform therapeutic endoscopic procedures; rebleeding, defined as the need for blood transfusion, the presence of overt bleeding (melena, hematemesis, or hematochezia), or a reduction in hemoglobin higher than 2 g/dl after exclusion of all other causes of anemia.

Information sources

Studies were identified by searching electronic databases and scanning reference lists of articles. No limits were applied for language or publication date. The search query was applied to the PubMed platform-MEDLINE, Web of Science, and Scopus Databases. The last search was run on April 15th, 2021.

Search

The authors used the following search terms to search in the different databases:

– MEDLINE (PubMed): (Enteroscopy[Title/Abstract] OR double-balloon[Title/Abstract] OR DBE[Title/Abstract] OR single-balloon[Title/Abstract]

OR SBE[Title/Abstract]) AND (obscure gastrointestinal bleeding[Title/Abstract] OR OGIB[Title/Abstract] OR small-bowel bleeding[Title/Abstract]).

- Web of Science: TI=((enteroscopy OR double-balloon OR DBE OR single-ballon OR SBE) AND (obscure gastrointestinal bleeding OR OGIB OR small-bowel bledding)) OR AB=((enteroscopy OR double-balloon OR DBE OR single-ballon OR SBE) AND (obscure gastrointestinal bleeding OR OGIB OR small-bowel bledding))
- Scopus: TITLE-ABS((enteroscopy OR double-balloon OR DBE OR single-ballon OR SBE) AND ("obscure gastrointestinal bleeding" OR OGIB OR "small-bowel bleeding"))

Study selection

A screening was performed on the title and abstract, and original studies that evaluated the diagnostic or therapeutic yield of enteroscopy in OGIB were considered. Case reports, review articles, editorials, letters to the editor, comments, systematic reviews, meta-analyses, and congress or abstract reports were excluded.

The eligibility assessment was performed independently in an unblind, standardized manner by two authors by means of reviewing the full text publication. Disagreements between reviewers were resolved by consensus. The reasons for exclusion were: wrong patient population, wrong outcomes, wrong intervention, and wrong comparator. The authors checked for duplication based on overlapping authorship, study description, number of participants, and participant characteristics. When duplication occurred, the study with the most recent data and most comprehensive description of the outcomes was used.

Data collection process

Prior to the detailed analysis, an extraction sheet was developed by two authors. One author extracted the data from the included studies and a second author confirmed their accuracy. Disagreements were resolved by discussion between these two authors. If no agreement could be reached, a third author was planned to decide.

Data items

Information was extracted from each included study on: a) study characteristics (year, country, design, total number of patients); b) type of intervention (including types of bleeding presentations and timings of enteroscopy); and c) type of outcome measure (including diagnostic yield, therapeutic yield, and rebleeding rate).

Methodological and reporting quality

The reporting quality of the studies was evaluated using the Critical Appraisal Skills Programme (CASP) cohort studies checklist (7); this tool was independently applied by two reviewers, and discrepancies were solved by consensus. The risk of bias across studies was analyzed by evaluating funnel plots (9) for asymmetry. A regression asymmetry test (Egger's test) (10) was also performed to aid visual assessment.

Statistical analysis

A random-effects model was used to create an overall combined estimate of early enteroscopy across all studies, and to evaluate the effect of intervention on diagnostic yield, therapeutic yield, and rebleeding rate. The summary measures used were odds ratios (OR) with confidence intervals (CI) to evaluate differences between groups. The I-squared was used to assess heterogeneity, and the method proposed by Higgins et al. (8) was used to measure effects inconsistency (the percentage of total variation across studies due to heterogeneity) across early use of enteroscopy results. This approach allows for studies with zero cells (i.e., 0 % rate). Analyses were conducted using the Software for Statistics and Data Science (STATA) 13.1. A p-value < 0.05 was considered to indicate statistical significance.

RESULTS

Study selection

The search in the PubMed (MEDLINE), Web of Science, and Scopus databases provided a total of 1,769 citations (808 PubMed; 508 Web of Science; 453 Scopus) with 704 duplicates. Four studies were additionally identified by checking the references of the relevant papers. At the screening process by a single reviewer, 987 studies were

dismissed for not meeting inclusion criteria when reviewing their abstracts. Six additional studies were excluded because the full text of the study was not available or the paper could not be feasibly translated into English. The full text of the 76 potentially relevant studies (predominantly related to the main outcomes of enteroscopy in OGIB) were examined in more detail. From these, 58 studies did not meet the inclusion criteria as described previously (e.g., no differentiation of outcomes between occult/overt-OGIB and between different timings for enteroscopy use in overt-OGIB). Three studies (11-13) were excluded due to authorship/department overlap with similar inclusion periods, since data could be related to the same patients. Fifteen studies (14-28) met the inclusion criteria and were included in the systematic review, two (20,21) of which were excluded from the meta-analysis since there was no arm comparator. No unpublished relevant studies were obtained. Figure 1 shows the flow diagram for study selection.

Study characteristics

All 15 studies were observational studies published in English, with a retrospective design, and a majority (n = 14) of single-center research (Supplementary Table 1). The quality assessment of the studies is displayed in table 1. Globally, the selected studies had good reporting quality. The studies conveyed information on the majority of the topics defined in the CASP tool. However, none explicitly referred to whether confounding factors had been taken into account for the study's design or data analysis, or had evaluated the external validity of the findings. The first study was published in 2007 and the latest in 2020.

Participants

The included studies involved 1,907 participants who underwent enteroscopy (DBE or SBE) in the setting of overt-OGIB. Some studies included patients with occult and overt-OGIB (14-17,19,22,23,25) although the outcomes according to type of OGIB were clearly differentiated.

Intervention

The intervention (enteroscopy) was performed at different times for overt-OGIB.

First reports from Ohmiya et al. (14), Tanaka et al. (15) and Arakawa et al. (16) subdivided overt-OGIB into two categories: overt-ongoing and overt-previous, the latter defined by no bleeding symptoms but previous episodes of overt bleeding. Afterwards, different time intervals were used to classify the intervention with enteroscopy, such as 24 h (17,20-22,24,25,28), 48 h (23), 72 h (18,26,27) and one week (17) intervals. Some studies still considered other time intervals to further investigate the most favorable timing (14,18,27,28). Most of these studies evaluated the interval of enteroscopy in relation to the bleeding episode. However, in two studies, Nelson et al. (22) and Liu et al. (25), the timing considered was relative to hospital admission.

Primary outcome

All studies assessed the diagnostic yield of enteroscopy in overt-OGIB, although the definition of positive findings in the setting of bleeding slightly varied between studies. Most studies considered as bleeding source vascular lesions (angiectasia, Dieulafoy's lesion, varices, arteriovenous malformation), inflammatory lesions (mainly ulcerations), eroded or ulcerated tumors/polyps (eroded, ulcerated, or larger than 2 cm), and diverticula with bleeding stigmata. Angiectasia with less than 1 mm without oozing (Yano classification type 1a [29]), red spots, erosions, diverticulum without bleeding stigmata, non-bleeding polyp, lipoma, and lymphangiectasia were usually not considered as a positive finding.

Secondary and additional outcomes

Only five and four studies, respectively, evaluated the impact of early enteroscopy in overt-OGIB in regard to therapeutic yield (15,18,22,26,27) and rebleeding rate (15,18,24,26). In some of the remaining studies, although treatment (14,16,17,23) and rebleeding (16,17) were addressed, there was no differentiation of results according to enteroscopy timing. The therapeutic intervention could be endoscopic, surgical, or angiographic. The median follow-up period for evaluating rebleeding was 23.3 months (IQR, 15.3-31.4).

Synthesis of results

Primary outcome: diagnostic yield

Types of findings/lesions were not usually differentiated according to bleeding presentation or timing of enteroscopy.

Diagnostic data were available for all studies, although only 13 studies had an intervention and comparator group, corresponding to a total of 1,870 patients (early: 433; non-early: 1,437), of whom 1,171 had a positive diagnosis (early: 384; non-early: 823) (Table 2). Early enteroscopy was associated with a significantly higher diagnostic yield (OR = 3.2, 95 % CI: 1.9-5.3, p = 0.002). Moderate heterogeneity within this comparison (I^2 = 60.4 %; p = 0.002) was detected (Fig. 2A). The funnel plot showed evidence of symmetry (Supplementary Fig. 1) and Eger's test confirmed there was no small-study effects, in other words, no publication bias (p = 0.85).

A retrospective exploration identified two studies (Nelson et al. [22] and Liu et al. [25]) that differ from the others in that they analyzed the use of enteroscopy in overt-OGIB according to timing from hospital admission rather than bleeding onset. Excluding these, studies maintained the effect of early enteroscopy on diagnostic yield, although with lower heterogeneity (I2 = 48.2 %; p = 0.04). Considering only the ten studies (14-18,23,24,26-28) that evaluated the performance of enteroscopy for ongoing-bleeding or at ≤ 24 h, ≤ 48 h and ≤ 72 h in the setting of overt-OGIB, statistical heterogeneity was removed, with early enteroscopy improving significantly diagnostic yield (OR = 4.7, 95 % CI: 3.4-6.6, p < 0.001, I2 = 0 %) (Fig. 2B).

Secondary outcomes: therapeutic yield

Therapeutic data according to type of overt-OGIB were available for analysis in five studies (15,18,22,26,27), our estimate being based on 591 patients (early: 157; non-early: 434), 277 of whom had a therapeutic intervention (early: 98; non-early: 179) (Table 2). Early enteroscopy was associated with a higher therapeutic yield (OR = 4.9, 95 % CI: 1.2-20.5, p = 0.03), although with strong evidence of heterogeneity among studies (I^2 = 83.1 %; p < 0.001) (Fig. 3). The funnel plot revealed no asymmetry (Supplementary Fig. 2).

By evaluating only studies comparing timing of enteroscopy in relation to bleeding (15,18,26,27) rather than hospital admission, our analysis preserves the effect of early enteroscopy on therapeutic yield, although with moderate heterogeneity among studies (OR = 7.9, 95 % CI: 2.9-21.8, $p < 0.001$; $I^2 = 52.9$ %, $p = 0.095$).

Secondary outcomes: rebleeding rate

For the analysis of rebleeding rate four studies reported data concerning 390 patients (early: 150; non-early: 240) (Table 2). From the total, 96 patients experienced rebleeding (early: 34; non-early: 62), and early enteroscopy did not influence rebleeding rate (OR = 0.9, 95 % CI: 0.4-1.9, $p = 0.7$; $I^2 = 39.6$ %; $p = 0.17$). As with the other outcomes, the funnel plot was symmetric (Supplementary Fig. 3).

DISCUSSION

In overt-OGIB, enteroscopy should be performed after the detection of a bleeding lesion on a previous, non-invasive small-bowel investigation (e.g., capsule endoscopy), or in the acute setting in patients with active bleeding (4,30). Nonetheless, there are still uncertainties regarding appropriate timing in emergency small-bowel enteroscopy for overt-OGIB (5,6), since data focusing on the use of this procedure in this clinical scenario are mainly limited to retrospective studies.

This is the first systematic review with meta-analysis to analyze the influence of early enteroscopy on the management of patients with overt-OGIB. Even though the studies encompassed different definitions of early enteroscopy, all studies exhibited a homogeneous intervention, namely an early approach concerning an overt bleeding event.

In overt-OGIB results showed a diagnostic yield between 50 % and 100 % for early intervention, compared to 30.4-69.6 % for non-early intervention. Apparently, active bleeding (18,26) and vascular lesions (15,18,27) were more frequently detected in the early enteroscopy group. Vascular lesions are usually the most common cause of small-bowel bleeding, and since bleeding tends to be intermittent (31) an early evaluation could contribute to better detection. Comparing early and non-early enteroscopy for overt-OGIB the authors found that the former could influence diagnostic yield, despite

some moderate heterogeneity among studies. In line with recent consensus (5), performing an enteroscopy within 24-72 h from bleeding onset or in an ongoing bleeding presentation has an effect on diagnostic yield without any heterogeneity among studies. The impact of enteroscopy was lost when timing from hospital admission rather than from bleeding onset was assessed. This is important because patients with certain overt bleeding presentations (e.g., melena) may not present immediately to the Emergency Department. From all the studies evaluating diagnostic yield, only the study by Hussan et al. (19) showed that enteroscopy performed worse in the earlier group in terms of diagnostic and therapeutic yield when a one-week interval was considered.

The therapeutic yield of enteroscopy performed in the overt-OGIB setting ranges from 40 % to 90 % (5), and our results found rates of 28.6-94.1 % in the early group, *versus* rates of 15.2-51.1 % for non-early intervention. The evidence in our study is not sufficiently robust to determine if early enteroscopy in the setting of overt-OGIB may improve therapeutic yield. Although there are few studies evaluating the therapeutic yield of enteroscopy in overt-OGIB (5), a majority of these did not explicitly address therapeutic efficacy according to bleeding type (ongoing or previous) or time from bleeding/admission to enteroscopy. Only aggregated data of five included studies showed that early enteroscopy in overt bleeding improved therapeutic yield, conditioned by high heterogeneity amongst studies (I^2 > 75 %). When excluding studies analyzing timing according to hospital admission results improved even though heterogeneity was still present (I^2 = 52.9 %).

There are less available data evaluating rebleeding rates, since studies have to report a follow-up period and the significance of the lesions identified and their impact on clinical outcome have not been consistently evaluated. Similar to therapeutic yield, there is less evidence to determine the impact of early enteroscopy on rebleeding rate, and only four of the selected studies had data to be analyzed with this intent. These studies did not compare enough patients to allow definitive conclusions. Nonetheless, it was not possible to observe any effect of early enteroscopy on rebleeding rates in overt-OGIB patients.

This meta-analysis combines data across studies in order to estimate the effects of early enteroscopy on overt-OGIB with more precision than is possible with a single study. However, the applicability of the review may be affected due to limited data assessing the outcomes of interest.

The main limitation is the interval between bleeding presentation and the enteroscopy procedure, which was not the same across studies and may be subjected to recall bias, and a patient could be classified into the early group in one study and the non-early group in another study. Also, therapeutic yield was heterogeneous, as some authors considered only an endoscopic endpoint whereas others encompassed an endoscopic, surgical or even radiological treatment. All the studies were retrospective, which make selection bias inevitable. Patients undergoing an earlier enteroscopy procedure in the setting of bleeding could have other baseline characteristics, such as severe bleeding, that motivated a more timely approach. Patients from the earlier group could have a lower hemoglobin level (15) or a higher number of units of blood transfused (15,18), which could motivate a quicker approach. Adjusting for some confounders, namely units of blood transfused/transfusion requirement, Aniwan et al. (18) and Tu et al. (27) showed that enteroscopy (within 72 h and within 24 h, respectively) was the only independent factor for diagnostic yield. Ten of our studies (19-25,28,29,32) reported a type of small-bowel evaluation before enteroscopy, which could influence results. Tanaka et al. (20) claimed that enteroscopy was performed regardless of CE results, and Tu et al. (27) and Yin et al. (33) excluded patients with known small-bowel findings prior to enteroscopy in order to minimize selection bias. Silva et al. (32) excluded patients with an incomplete study of the small bowel (incomplete CE or enteroscopy unable to reach lesions previously identified by CE), which could also led to selection bias. Another limitation the authors would like to point out is the fact that only one study was performed in Europe, which could fail to reflect the real scenario in European countries.

A random-effects analysis gives relatively greater weight to smaller studies, leading to greater uncertainty with our results, which means that our odds ratios should be interpreted with caution, especially regarding therapeutic yield. Also, we did not perform any subgroup analyses according to time intervals, but rather excluded some

groups according to time definition. Once again, this could lead to misinterpretation of the results, and metaregression, for instance, would have been better to examine and test between-group differences. We acknowledge that smaller studies are analyzed with less methodological rigor, although the symmetric funnel plots suggested that there was an adequate estimate of the effect of early intervention on outcomes.

In conclusion, early enteroscopy, especially when performed for ongoing bleeding or within 24 h, 48 h and 72 h timeframes as related to the bleeding episode, is able to detect more lesions and increases diagnostic yield. Although an effect on therapeutic yield was also observed, the true value of early enteroscopy for treatment has to be cautiously evaluated. Early enteroscopy failed to influence rebleeding rate in our analysis.

REFERENCES

1. Gralnek IM. Obscure-overt gastrointestinal bleeding. Gastroenterology 2005;128(5):1424-30. DOI: 10.1053/j.gastro.2005.03.067

2. Longstreth GF. Epidemiology and outcome of patients hospitalized with acute lower gastrointestinal hemorrhage: a population-based study. Am J Gastroenterol 1997;92:419-24.

3. ASGE Standards of Practice Committee, Fisher L, Lee Krinsky M, et al. The role of endoscopy in the management of obscure GI bleeding. Gastrointest Endosc 2010;72(3):471-9. DOI: 10.1016/j.gie.2010.04.032

4. Pennazio M, Spada C, Eliakim R, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2015;47:352-76. DOI: 10.1055/s-0034-1391855

5. Perez-Cuadrado-Robles E, Pinho R, González B, et al. Small bowel enteroscopy - A joint clinical guideline from the Spanish and Portuguese Small Bowel Study Groups. GE Port J Gastroenterol 2020;27(5):324-35. DOI: 10.1159/000507375

6. ASGE Standards of Practice Committee, Gurudu SR, Bruining DH, et al. The role of endoscopy in the management of suspected small-bowel bleeding. Gastrointest Endosc 2017;85(1):22-31. DOI: 10.1016/j.gie.2016.06.013

7. Critical Appraisal Skills Programme. CASP Cohort Checklist; 2019. Accessed: April 20th, 2021. Available from: https://casp-uk.net/wp-content/uploads/2018/01/CASP-Cohort-Study-Checklist_2018.pdf

8. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60. DOI: 10.1136/bmj.327.7414.557

9. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. J Clin Epidemiol 2001;54(10):1046-55. DOI: 10.1016/S0895-4356(01)00377-8

10. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-34. DOI: 10.1136/bmj.315.7109.629

11. Aniwan S, Viriyautsahakul V, Angsuwatcharakon P, et al. Comparison of urgent video capsule endoscopy and urgent double-balloon endoscopy in massive obscure gastrointestinal bleeding. Hepato-gastroenterology 2014;61(135):1990-4.

12. Pinto-Pais T, Pinho R, Rodrigues A, et al. Emergency single-balloon enteroscopy in overt obscure gastrointestinal bleeding: efficacy and safety. United European Gastroenterol J 2014;2(6):490-6. DOI: 10.1177/2050640614554850

13. Rodrigues JP, Pinho R, Rodrigues A, et al. Diagnostic and therapeutic yields of urgent balloon-assisted enteroscopy in overt obscure gastrointestinal bleeding. Eur J Gastroenterol Hepatol 2018;30(11):1304-8. DOI: 10.1097/MEG.0000000000001244

14. Ohmiya N, Yano T, Yamamoto H, et al. Diagnosis and treatment of obscure GI bleeding at double balloon endoscopy. Gastrointest Endosc 2007;66:S72-7. DOI: 10.1016/j.gie.2007.05.041

15. Tanaka S, Mitsui K, Yamada Y, et al. Diagnostic yield of double-balloon endoscopy in patients with obscure GI bleeding. Gastrointest Endosc 2008;68(4):683-91. DOI: 10.1016/j.gie.2008.03.1062

16. Arakawa D, Ohmiya N, Nakamura M, et al. Outcome after enteroscopy for patients with obscure GI bleeding: diagnostic comparison between double-balloon endoscopy and videocapsule endoscopy. Gastrointest Endosc 2009;69(4):866-74. DOI: 10.1016/j.gie.2008.06.008

17. Shinozaki S, Yamamoto H, Yano T, et al. Long-term outcome of patients with obscure gastrointestinal bleeding investigated by double-balloon endoscopy. Clin

Gastroenterol Hepatol 2010;8(2):151-8. DOI: 10.1016/j.cgh.2009.10.023

18. Aniwan S, Viriyautsahakul V, Rerknimitr R, et al. Urgent double balloon endoscopy provides higher yields than non-urgent double balloon endoscopy in overt obscure gastrointestinal bleeding. Endosc Int Open 2014;2(2):E90-5. DOI: 10.1055/s-0034-1365543

19. Hussan H, Crews NR, Geremakis CM, et al. Predictors of double balloon endoscopy outcomes in the evaluation of gastrointestinal bleeding. World J Gastrointest Endosc 2014;6:248-53. DOI: 10.4253/wjge.v6.i6.248

20. Mönkemüller K, Neumann H, Meyer F, et al. A retrospective analysis of emergency double-balloon enteroscopy for small-bowel bleeding. Endoscopy 2009;41(8):715-7. DOI: 10.1055/s-0029-1214974

21. Pérez-Cuadrado Robles E, Bebia Conesa P, Esteban Delgado P, et al. Emergency double-balloon enteroscopy combined with real-time viewing of capsule endoscopy: a feasible combined approach in acute overt-obscure gastrointestinal bleeding? Dig Endosc 2015;27(3):338-44.

22. Nelson KK, Lipka S, Davis-Yadley AH, et al. Timing of single balloon enteroscopy: significant or not? Endosc Int Open 2016;4(7):E761-6. DOI: 10.1055/s-0042-108189

23. Ooka S, Kobayashi K, Kawagishi K, et al. Roles of capsule endoscopy and single-balloon enteroscopy in diagnosing unexplained gastrointestinal bleeding. Clin Endosc 2016;49(1):56-60. DOI: 10.5946/ce.2016.49.1.56

24. Hashimoto R, Matsuda T, Nakahori M. False-negative double-balloon enteroscopy in overt small bowel bleeding: long-term follow-up after negative results. Surg Endosc 2019;33(8):2635-41. DOI: 10.1007/s00464-018-6561-x

25. Liu Y, Jiang W, Chen G. Diagnostic Value and safety of emergency single-balloon enteroscopy for obscure gastrointestinal bleeding. Gastroenterol Res Pract 2019;2019:9026278.

26. Silva JC, Pinho R, Ponte A, et al. Does urgent balloon-assisted enteroscopy impact rebleeding and short-term mortality in overt obscure gastrointestinal bleeding? Scand J Gastroenterol 2020;55(10):1243-7.

27. Yin A, Zhao L, Ding Y, et al. Emergent double balloon enteroscopy in overt suspected small bowel bleeding: diagnosis and therapy. Rev Esp Enferm Dig

2020;26:e920555. DOI: 10.12659/MSM.920555

28. Tu CH, Kao JY, Tseng PH, et al. Early timing of single balloon enteroscopy is associated with increased diagnostic yield in patients with overt small bowel bleeding. J Formos Med Assoc 2019;118(12):1644-51. DOI: 10.1016/j.jfma.2019.01.003

29. Yano T, Yamamoto H, Sunada K, et al. Endoscopic classification of vascular lesions of the small intestine (with videos). Gastrointest Endosc 2008;67(1):169-72. DOI: 10.1016/j.gie.2007.08.005

30. Pérez-Cuadrado-Robles E, Pérez-Cuadrado-Martínez E. The role of emergency endoscopy in small bowel bleeding: a review. GE Port J Gastroenterol 2016;23(2):84-90. DOI: 10.1016/j.jpge.2015.11.002

31. Nojkov B, Cappell MS. Gastrointestinal bleeding from Dieulafoy's lesion: clinical presentation, endoscopic findings, and endoscopic therapy. World J Gastrointest Endosc 2015;7(4):295-307. DOI: 10.4253/wjge.v7.i4.295

32. Robles EP, Delgado PE, Conesa PB, et al. Role of double-balloon enteroscopy in malignant small bowel tumors. World J Gastrointest Endosc 2015;7(6):652-8. DOI: 10.4253/wjge.v7.i6.652

Table 1. Summary of included studies evaluating the impact of early enteroscopy on overt-OGIB

Source	*Study design*	*Country*	*n*	*Inclusion criteria*	*Groups according to bleeding type/timing of enteroscopy*	*Inclusion groups*	
						Early	*Non-early*
Ohmiya et al. (14), 2007	Retrospective multicentric	Japan	479 (413 overt-OGIB)	OGIB patients with DBE	– Overt-ongoing – Overt-previous - sporadic – Overt-previous - first attack – Occult-continuous with FOBT – Occult-iron deficiency anemia	Overt-ongoing	Overt-previous
Tanaka et al. (15), 2008	Retrospective unicentric	Japan	108 (89 overt-OGIB) 93 follow-up	OGIB patients with DBE	– Overt-ongoing – Overt-previous – Occult	Overt-ongoing	Overt-previous
Arakawa et al. (16), 2009	Retrospective unicentric	Japan	162 (143 overt-OGIB)	OGIB patients with DBE	– Overt-ongoing – Overt-previous – Occult	Overt-ongoing	Overt-previous

Mönkemüller et al. (20), 2009	Retrospective unicentric	Germany	10	Overt-OGIB patients with DBE within 24 h	– Emergent: DBE within 24 h of clinical presentation	*Only* emergent (< 24 h)	-
Shinozaki et al. (17), 2010	Retrospective unicentric	Japan	200 (170 overt-OGIB)	OGIB patients with DBE	– Overt-ongoing: DBE within 24 h from last bleeding – Overt-previous: DBE beyond 24 h from last bleeding episode – Occult	Overt-ongoing (< 24 h)	Overt-previous (> 24)
Hussan et al. (19), 2014	Retrospective unicentric	USA	55 (43 overt-OGIB)	OGIB patients with DBE	– Active overt: DBE within 1 week from last bleeding – Non-active overt: DBE beyond 1 week from last bleeding – Occult	Active overt (< 1 w)	Non-active overt (> 1 w)
Aniwan et al. (18), 2014	Retrospective unicentric	Thailand	120 97 Follow-up	Overt-OGIB patients with DBE	– Urgent: DBE within 72 h from last bleeding – Subdivided:	Urgent (< 72 h)	Non-urgent (> 72 h)

					• Ongoing: bleeding on the day of DBE (within 24 h) • Recent: no bleeding on the day of DBE, but within 72 h (24-72 h) – Non-urgent/previous: DBE beyond 72 h from last bleeding		
Robles et al. (21), 2015	Retrospective unicentric	Spain	27	Overt-OGIB patients with DBE within 24 h	– Emergent: DBE within 24 h of onset of symptoms	Only emergent (< 24 h)	-
Ooka et al. (23), 2016	Retrospective unicentric	Japan	91 (68 overt-OGIB)	OGIB patients with SBE	– Overt-ongoing: DBE within 48 h from last bleeding – Overt-previous: DBE beyond 48 h from last bleeding – Occult	Overt-ongoing (< 48 h)	Overt-previous (> 48 h)

Nelson et al. (22), 2016	Retrospective unicentric	USA	110 (63 overt-OGIB)	Hospitalized OGIB patients with SBE	– Overt-OGIB, subdivided: • Emergent: SBE within 24 h from hospitalization • Non-emergent: SBE beyond 24 h from hospitalization – Occult-OGIB, subdivided: • Emergent: SBE within 24 h from hospitalization • Non-emergent: SBE beyond 24 h from hospitalization	Emergent (< 24 h*)	Non-emergent (> 24 h*)
Tu et al. (28), 2019	Retrospective unicentric	Taiwan	220	Overt-OGIB patients with SBE without a prior diagnosis or information on	– Emergency: SBE within 24 h of onset of bleeding or ongoing bleeding on the day of SBE	Emergent (< 24 h)	Non-emergent(> 24 h)

				the small bowel	– Non-emergency: SBE beyond 24 h of onset of bleeding, subdivided: • 24-72 h after onset of bleeding • 3-7 days after onset of bleeding • More than 7 days after onset of bleeding		

				Overt-OGIB patients with SBE without a prior diagnosis or information on the small bowel			
Hashimoto et al. (24), 2019	Retrospective unicentric	Japan	165	Overt-OGIB patients with DBE and with interview follow-up	– Urgent: DBE within 24 h of last bleeding – Non-urgent: DBE beyond 24 h from last bleeding	Urgent (< 24 h)	Non-urgent (> 24 h)
Liu et al. (25), 2019	Retrospective unicentric	China	102 (57 overt-OGIB)	OGIB patients with SBE	– Overt-OGIB, subdivided: • Emergent: SBE within 24 h from hospitalization • Non-emergent: SBE beyond 24 h from hospitalization – Occult-OGIB, subdivided:	Emergent (< 24 h*)	Non-emergent (> 24 h*)

					• Emergent: SBE within 24 h from hospitalization • Non-emergent: SBE beyond 24 h from hospitalization		
Silva et al. (26), 2020	Retrospective unicentric	Portugal	54	Overt-OGIB patients with SBE	– Urgent: DBE within 72 h of clinical presentation – Non-urgent: DBE beyond 72 h of clinical presentation	Urgent (< 72 h)	Non-urgent (> 72 h)
Yin et al. (27), 2020	Retrospective unicentric	China	265	Overt-OGIB patients with DBE without a prior diagnosis or information on the small bowel	– Emergent: DBE within 3 days of onset of bleeding – Non-emergent: DBE beyond 3 days of onset of bleeding, subdivided: • 3-7 days after onset of bleeding	Emergent DBE (< 3 d)	Non-emergent (> 3 d)

					• More than 7 days after onset of bleeding		

OGIB: overt-obscure gastrointestinal bleeding; DBE: double-balloon enteroscopy; FOBT: fecal occult blood test; SBE: single-balloon enteroscopy.

Table 2. Study results: diagnostic yield, therapeutic yield and rebleeding rate according to early and non-early enteroscopy in overt-OGIB patients

Source	*Inclusion groups (n, each arm)*		*Experience outcome DY (n, %)*				*Experience outcome TY (n, %)*				*Experience outcome RR (n, %)*				*Other remarks*
	Early	*Non-early*	*Early*	*Non-early*	*p-value*	*OR 95 % CI*	*Early*	*Non-early*	*p-value*	*OR 95 % CI*	*Early*	*Non-early*	*p-value*	*OR 95 % CI*	
Ohmiya et al. (14), 2007	31	382	24	213	*0.02*	2.7 (1.1 to 6.5)	-	-	-	-					Major lesions: ulcers
Tanaka et al. (15), 2008	13	76	13	43	*0.04*	20.8 (1.2 to 362.5)	11	15	< *0.001*	22.3 (4.5 to 111.8)	2	6	0.56[†]	1.7 (0.3 to 9.4)	Major lesions: ulcers Vascular and tumors more frequently in the early group Therapy: endoscopic or surgical

Arakawa et al. (16), 2009	15	128	13	76	0.06	4.4 (0.96 to 20.5)	-	-	-	-					Vascular
Mönkemüller et al. (20), 2009	10	-	9	-	-	-	9	-	-	-					Vascular Therapy: endoscopic
Shinozaki et al. (17), 2010	30	140	25	81	*0.01*	3.6 (1.3 to 10.1)	-	-	-	-					Ulcers
Hussan et al. (19), 2014‡	20	23	10	16	0.19	0.4 (0.1 to 1.5)	-	-	-	-					Vascular
Aniwan et al. (18), 2014	74	46	52	14	< *0.001*	5.4 (2.4 to 12.0)	40	7	< *0.001*	6.5 (2.6 to 16.5)	5	4	0.68†	0.8 (0.2 to 3.0)	Ulcers Active bleeding (p = 0.007) and vascular lesions (p = 0.04) were diagnosed more

															frequently in the urgent group Therapy: endoscopic, angiographic or surgical
Robles et al. (32), 2015	27	-	27	-	-	-	26	-	-	-					Vascular Therapy: endoscopic or surgical
Ooka et al. (23), 2016	27	41	27	28	*0.03*	26.1 (1.5 to 459.9)	-	-	-	-					Vascular
Nelson et al. (22), 2016	21	42	11	26	0.47	0.68 (0.2 to 1.9)	6	21	0.11	0.4 (0.1 to 1.2)					Vascular Therapy: endoscopic

Tu et al. (28), 2019	64	156	58	86	< *0.001*	7.9 (3.2 to 19.3)	-	-	-	-					Vascular
Hashimoto et al. (24), 2019	60	105	50	52	< *0.001*	5.1 (2.3 to 11.1)	-	-	-	-	24	35	0.39[†]	1.3 (0.7 to 2.6)	NA
Liu et al. (25), 2019	29	28	23	19	0.33	1.8 (0.5 to 6.0)	-	-	-	-					Ulcers
Silva et al. (26), 2020	17	37	15	22	0.05	5.1 (1.0 to 25.7)	16	17	*0.007*	18.8 (2.3 to 157.0)	3	17	0.05*	0.25 (0.1 to 1.0)	Vascular Active bleeding was more frequent in the urgent group (p < 0.001) Therapy: endoscopic or surgical
Yin et al. (27), 2020	32	233	27	147	*0.02*	3.2 (1.2 to 8.5)	25	119	*0.006*	3.4 (1.4 to 8.2)					Vascular

															Angiectasias were more frequent in the emergent group (p = 0.007) Therapy: endoscopic

DY: diagnostic yield; TY: therapeutic yield; RR: rebleeding rate; NA: not available; CI: confidence interval; OR: odds ratio. Difference in proportions is not statistically significant (p > 0.05). *Kaplan-Meier curve analysis: in the non-urgent enteroscopy group, rebleeding tended to occur earlier (log-rank test, p = 0.05). †A survival analysis was not conducted. ‡Hussan et al., apart from the analysis comparing outcomes regarding the last bleeding episode, compared outcomes in all OGIB patients (overt and occult) according to bleeding onset, and found that enteroscopy within one week of bleeding onset led less often to a final diagnosis or therapeutics (DY ≤ 1 w: 2/8 *vs* > 1 w: 29/44, 0.41, 95 % CI: 0.04-0.62, p = 0.03; TY (≤ 1 w: 1/8 *vs* > 1 w: 24/44, 0.42, 95 % CI: 0.05-0.59, p = 0.03).

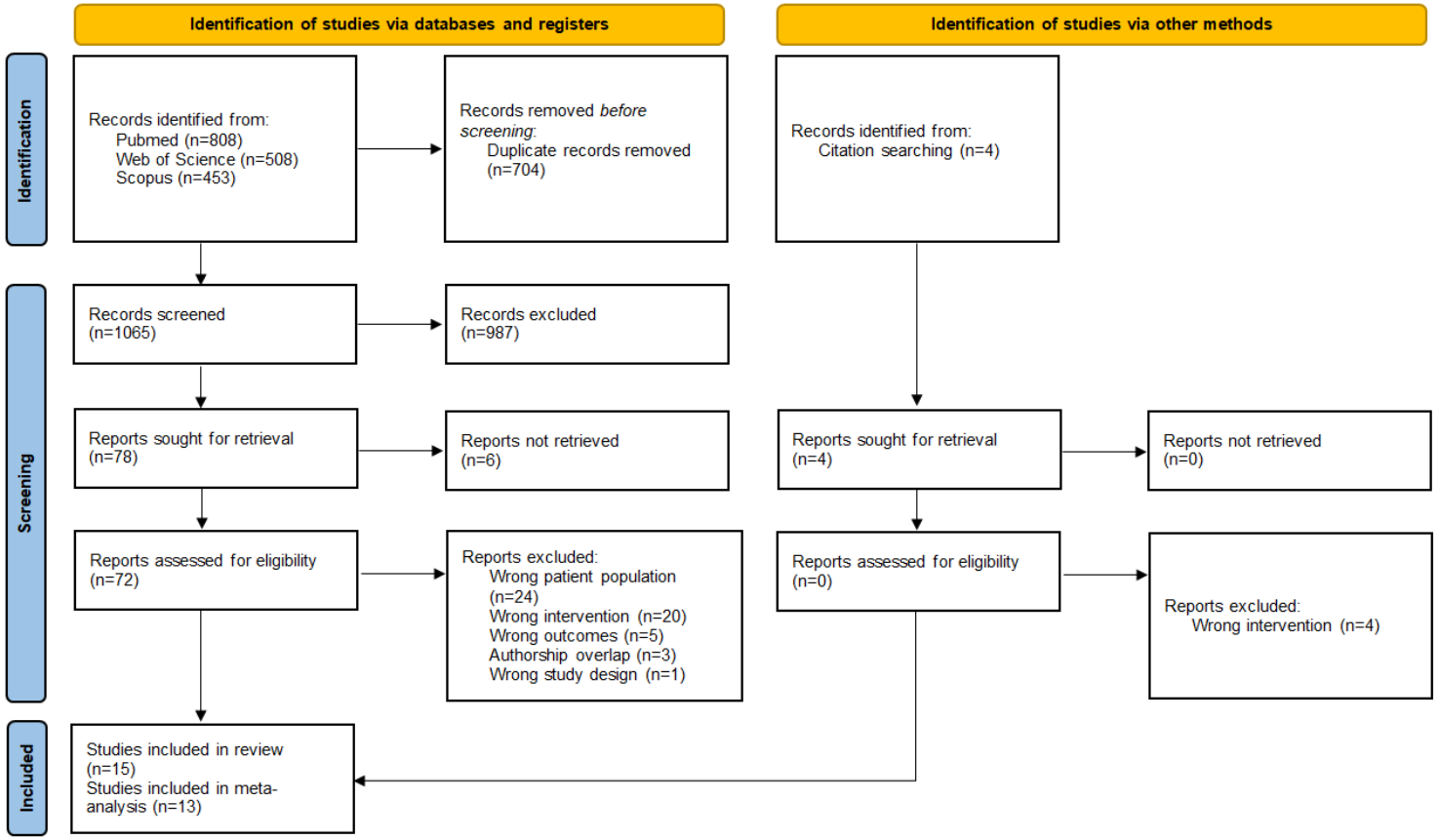


Fig. 1. Flow diagram of study selection. From: Page MJ, McKenzie JE, Bossuyt PM, et al. *The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.* BMJ 2021;372:n71. DOI: 10.1136/bmj.n71.

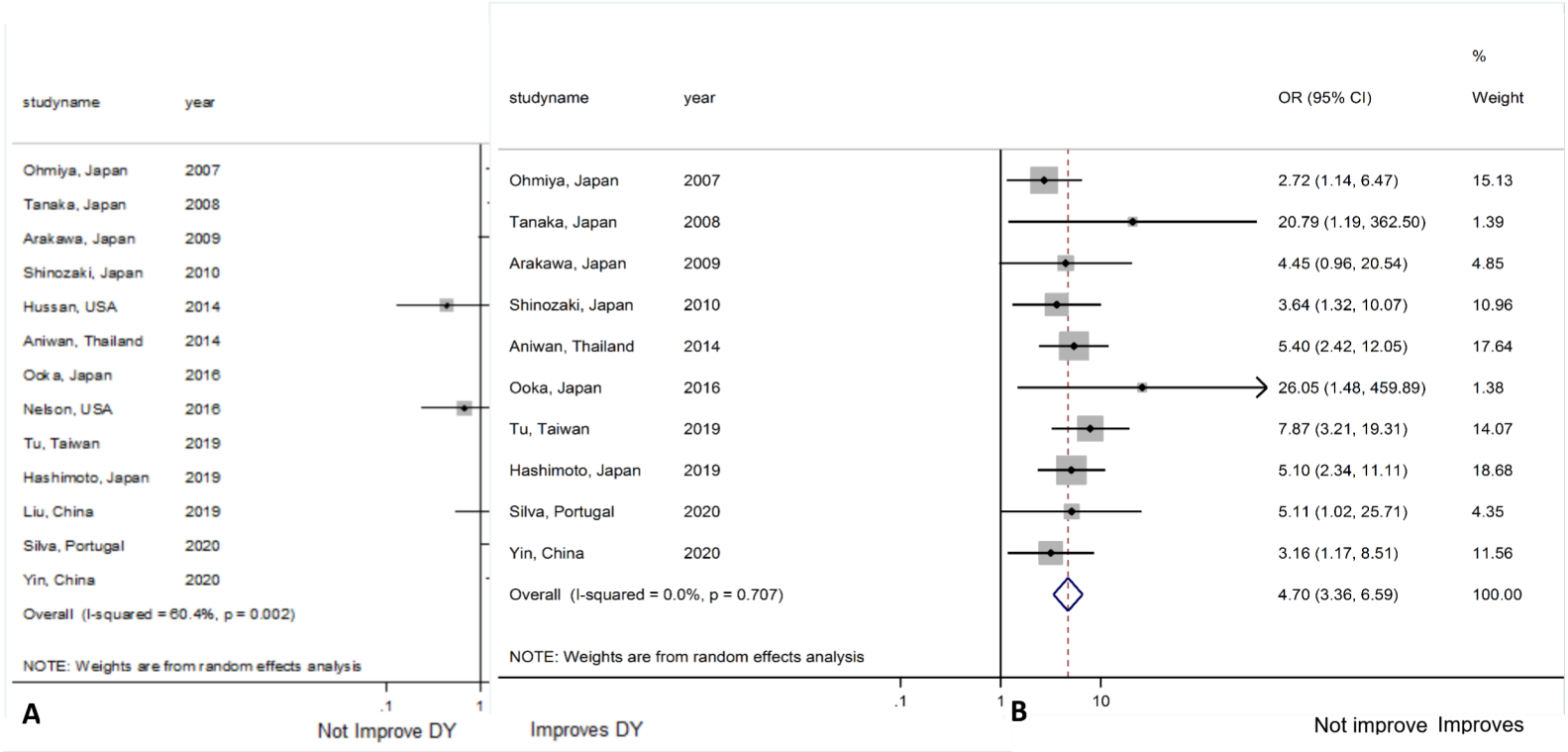


Fig. 2. A. Overall diagnostic yield with early enteroscopy in overt-OGIB. B. Diagnostic yield with early enteroscopy in overt-OGIB with ongoing bleeding and at ≤ 24 h, ≤ 48 h and ≤ 72 h from the bleeding event. DT: diagnostic yield; CI: confidence interval for odds ratio.

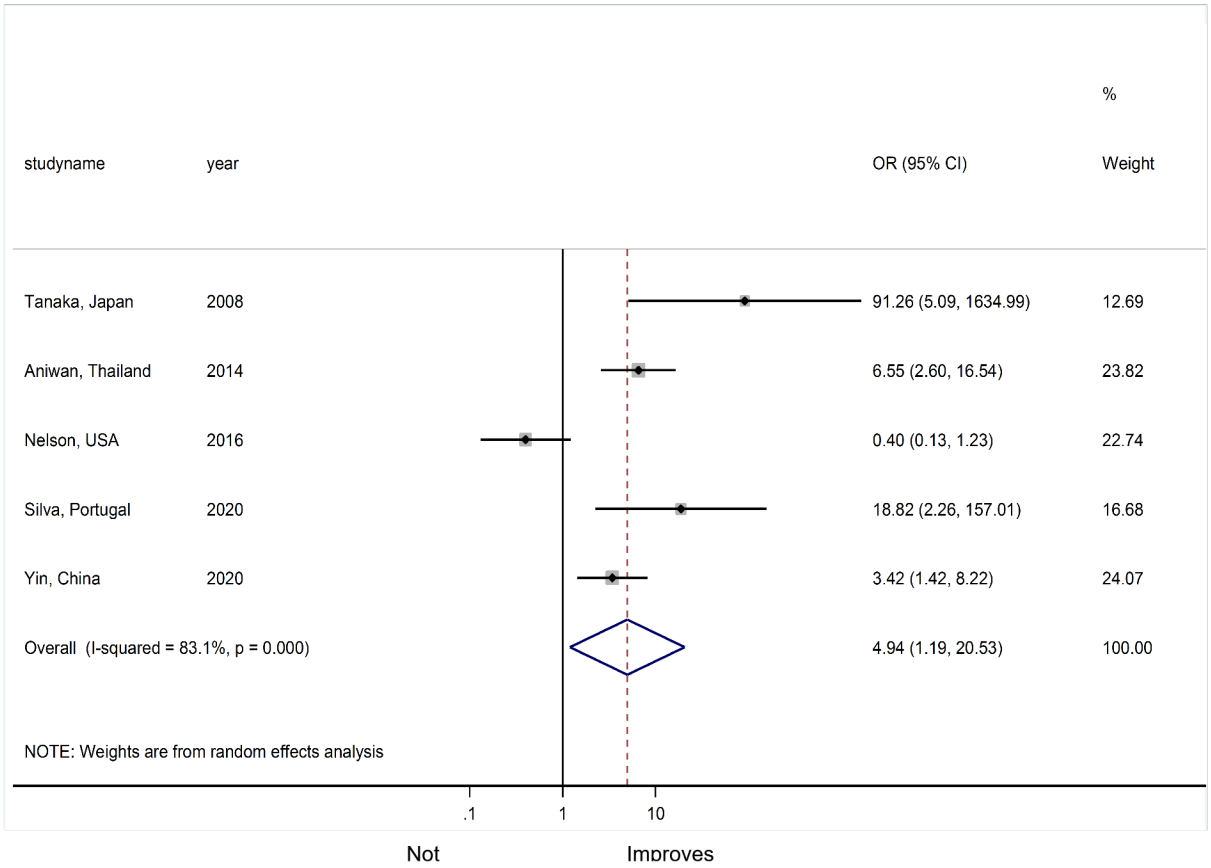


Fig. 3. Overall therapeutic yield with early enteroscopy in overt-OGIB. CI: confidence interval for odds ratio.

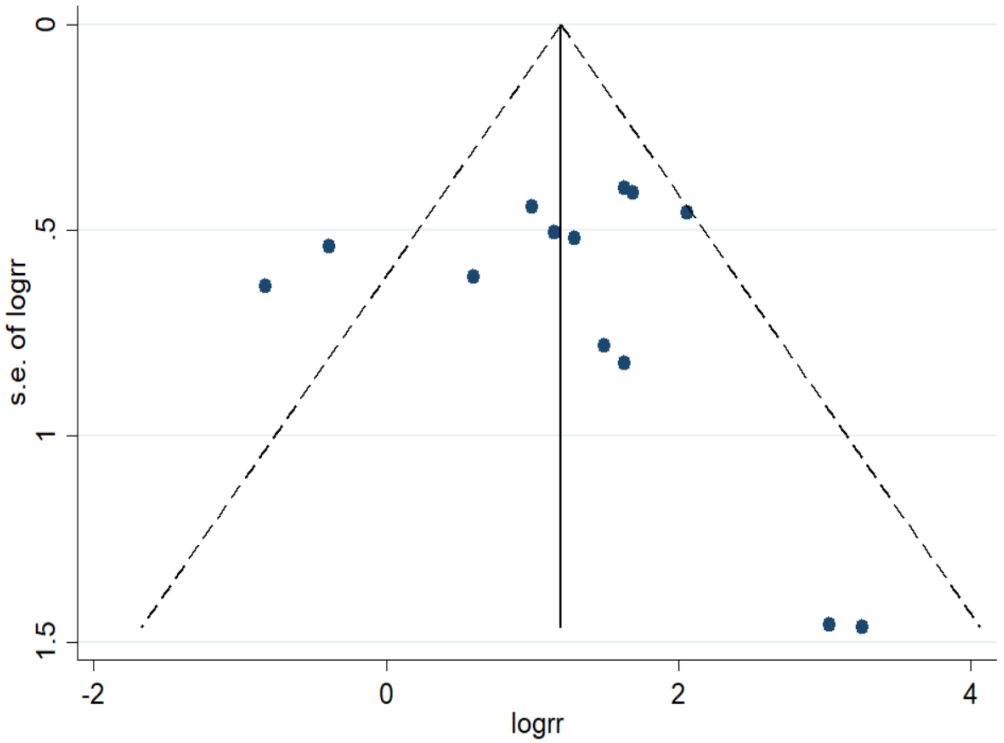
Supplementary Table 1. Reporting quality assessment

CASP Checklist - Cohort Study	Ohmiya et al., 2007	Tanaka et al., 2008	Arakawa et al., 2009	Mönkemüller et al., 2009	Shinokazi et al., 2010	Aniwan et al., 2014	Hussan et al., 2014	Pérez-Cuadrado Robles et al., 2014	Ooka et al., 2016	Nelson et al., 2016	Tu et al., 2019	Hashimoto et al., 2019	Liu et al., 2019	Silva et al., 2020	Yin et al., 2020
1. Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the cohort recruited in an acceptable way?	Can't tell	Yes	Can't tell	Can't tell	Yes	Yes	Can't tell	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	Yes
3. Was exposure accurately measured to minimize bias?	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Can't tell	Yes	Yes	Yes
4.Was the outcome accurately	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Can't tell	Can't tell	Yes	Can't tell	Yes	Yes	Yes

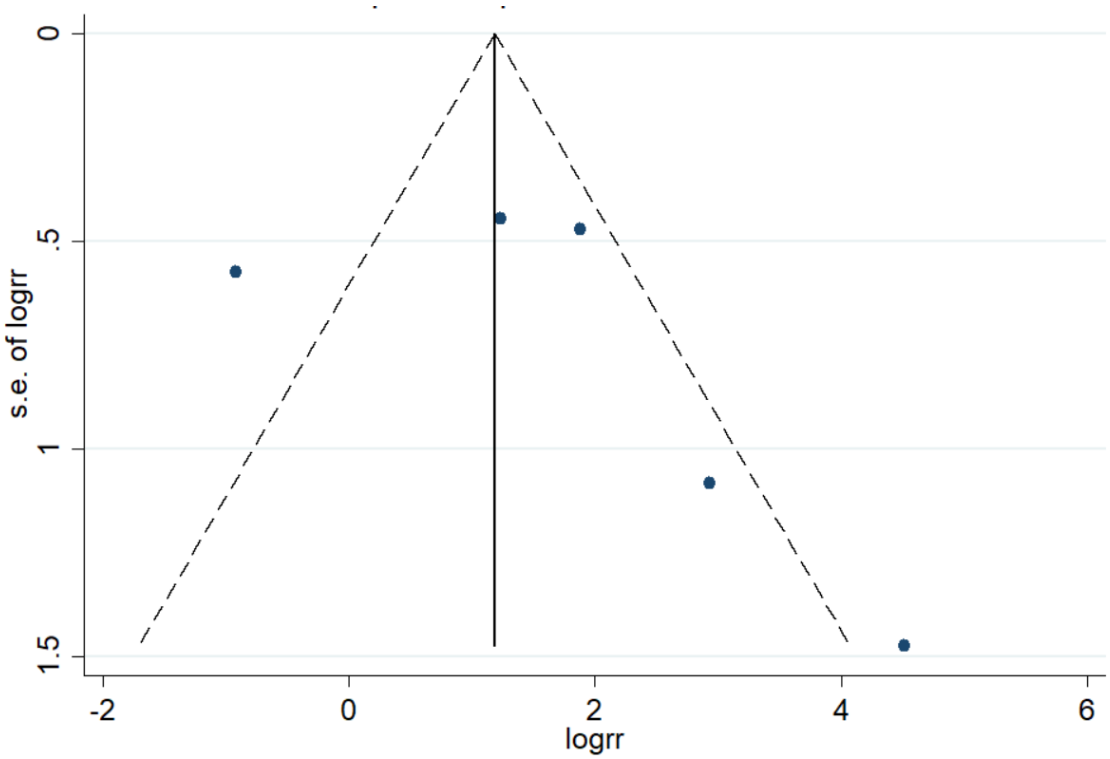
measured to minimize bias?															
5a. Have the authors identified all the important confounding factors?	Can't tell	Yes	Can't tell	Can't tell	Yes	Yes	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Yes
5b. Have they taken the confounding factors into account in the design and/or analysis?	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell
6a. Was the follow-up of subjects complete enough?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6b. Was the follow	Yes	Yes	Can't	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

up of subjects long enough?			tell												

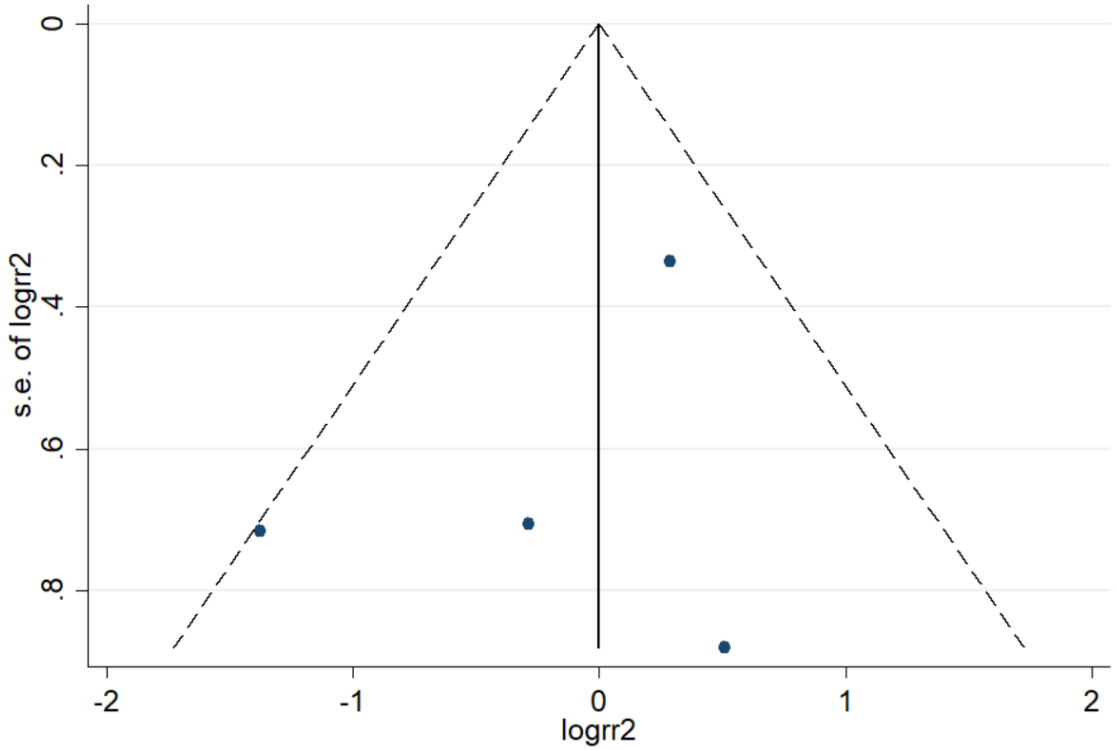
			Can’t tell												
7. Are results precise?	Yes	Yes	Can’t tell	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Do you believe the results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Can the results be applied to the local population?	Can’t tell	Can’t tell	Can’t tell	Can’t tell	Can’t tell	Can’t tell	Can’t tell	Can’t tell	Can’t tell	Can’t tell	Can’ t tell	Can’t tell	Can’t tell	Can’t tell	Can’t tell
10. Are the results of this study consistent with other available evidence?	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Does this study have practical implications?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes



Supplementary Fig. 1. Diagnostic yield. Funnel plot with pseudo-95 % confidence intervals.



Supplementary Fig. 1. Therapeutic yield. Funnel plot with pseudo-95 % confidence intervals.



Supplementary Fig. 2. Rebleeding rate. Funnel plot with pseudo-95 % confidence interval.