

Endoscopic ultrasound-guided transmural approach versus ERCP-guided transpapillary approach for primary decompression of malignant biliary obstruction: a meta-analysis

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Bibliography

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 Appendix A–E

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ABSTRACT

Background Primary decompression in patients with malignant biliary obstruction can be achieved via endoscopic retrograde cholangiopancreatography (ERCP) with transpapillary stenting, or, more recently, via transmural endoscopic ultrasound-guided biliary drainage (EUS-BD). It is unclear whether either approach is superior in terms of clinical success or adverse events in the primary setting.

Methods A comprehensive systematic electronic search was performed for studies comparing EUS-BD and ERCP as the primary approach with respect to clinical success and any other outcome(s). Pooled relative risks (RRs) and weighted mean differences were obtained as appropriate using DerSimonian and Laird random effects models. Sensitivity analyses were also performed.

Results 5 out of 776 studies with a total of 396 patients were included. Overall clinical success was not significantly different between EUS-BD and ERCP (RR 0.98, 95% confidence interval [CI] 0.93 to 1.03). There was no significant difference in overall adverse events (RR 0.84, 95%CI 0.35 to 2.01), though results suggested that EUS-BD may be associated with a reduced risk of pancreatitis (RR 0.22, 95%CI 0.05 to 1.02). There were no significant differences between EUS-BD and ERCP in terms of procedure time or the risk of stent occlusion.

Conclusions EUS-BD had similar clinical success rates and occlusion rates to ERCP in the primary decompression of malignant biliary obstruction from meta-analysis including a modest number of patients. EUS-BD may be a practical alternative to the ERCP-guided approach in such patients, but further well-designed prospective studies with larger numbers of patients are required to more clearly delineate potential differences in adverse events and cost.

* These authors contributed equally to this work.

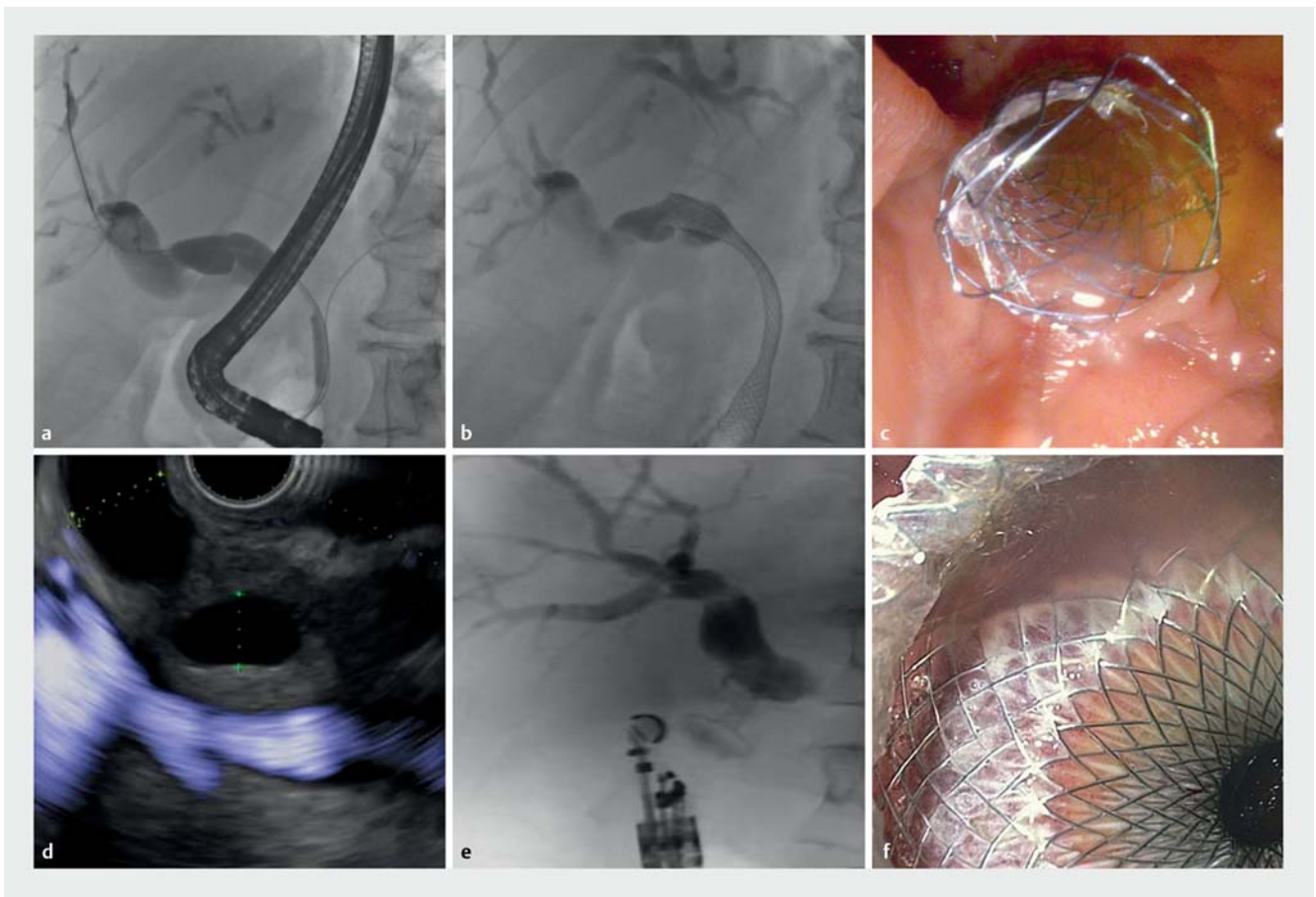
Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is the established method for biliary access, for both diagnostic and therapeutic purposes. Biliary cannulation rates associated with ERCP are generally high, at greater than 90% [1]. However, when faced with malignant biliary obstruction, which can often involve the ampulla, ERCP success rates drop significantly, especially at low-volume centers [2, 3]. Historically, when ERCP fails to achieve drainage in cases of malignant biliary obstruction, percutaneous drainage or surgical bypass have been used as secondary “rescue” therapies. However, these procedures are associated with considerable morbidity and mortality [4–6].

Endoscopic ultrasound (EUS) has become increasingly available as a resource in recent years, with several indications for which EUS is now recommended as a first-line diagnostic or therapeutic modality [7, 8]. EUS can be used to facilitate biliary access through the rendezvous technique, where a guidewire is passed into the bile duct and through the papilla under endosonographic guidance [9]. Alternatively, direct transmural EUS-guided biliary drainage (EUS-BD) is also a well-described tech-

nique for biliary drainage in cases where transpapillary access via ERCP is unsuccessful [10]. Multiple approaches to EUS-BD exist, including choledochoduodenostomy (CDS) and hepato-gastrostomy (HGS) [11, 12]. The optimal approach is decided based on the site of obstruction and the degree of ductal dilation. A recent meta-analysis reported a functional success rate of 92% with EUS-BD, with higher success rates for malignant obstructions compared with benign obstructions [13]. A more recent retrospective series of over 40 patients demonstrated a clinical success rate of 98% for EUS-BD in the secondary decompression of malignant biliary obstruction [14].

Given the mounting evidence for this approach, there is a rapidly growing interest in using EUS-BD as a modality for primary decompression in patients with malignant biliary obstruction, rather than restricting its use to cases where ERCP fails. Representative pictures of both approaches are provided in ► **Fig. 1**. It is plausible that EUS-BD may be more favorable than ERCP in certain instances, as it has the ability to provide direct biliary drainage even in cases of difficult ampullary access or complete distal obstruction. In so doing, one can avoid multiple ampullary cannulation attempts in these patients with challenging anatomy, thus decreasing the rates of post-ERCP pancreatitis,



► **Fig. 1** Endoscopic retrograde cholangiopancreatography (a–c) and endoscopic ultrasound (d–f) approaches to biliary drainage. **a** Cholangiogram showing opacification of the bile duct and a distal biliary stricture. **b** Cholangiogram showing metal stent placement across the stricture with biliary decompression. **c** Endoscopic view of a portion of the deployed metal stent in the duodenum. **d** Sonographic view of the dilated bile duct from the duodenal bulb. **e** Lumen-apposing metal stent deployed into the bile duct through the duodenal bulb. **f** Endoscopic view of a portion of the deployed stent in the duodenum.

which has been confirmed to occur even with guidewire cannulation alone, at rates of greater than 10% when lengthy or multiple cannulations are attempted [15–17].

Few studies have assessed the clinical performance characteristics of EUS-BD compared directly with ERCP in the primary decompression of malignant biliary obstruction. Generally, sample sizes in these studies have been relatively small. Given this potential role for EUS-BD, we conducted a systematic review and meta-analysis to compare relevant outcomes between EUS-BD and ERCP as first-line therapies for decompression of malignant biliary obstruction.

Methods

Overview

Our meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations [18]. A detailed PRISMA Checklist is provided in the online-only Supplementary Materials. The primary objective of this study was to compare the clinical success rate (primary outcome) between EUS-BD and ERCP in the primary decompression of malignant biliary obstruction. The secondary objectives were to compare the technical success rate, occlusion rate, procedure time, total adverse event rate, and individual adverse event rates (secondary outcomes) between EUS-BD and ERCP in the primary decompression of malignant biliary obstruction.

An article was considered eligible for inclusion if it met all of the following criteria: 1) it presented original human data from a clinical trial, prospective or retrospective study; 2) it was a study of adult patients undergoing procedures to provide primary decompression for malignant biliary obstruction; 3) it compared patients undergoing EUS-guided (transmural) drainage vs. ERCP-guided (transpapillary) drainage; and 4) it reported on any clinical outcome(s) or procedural data. Reviews, non-human studies, pediatric studies, studies comparing either approach to another modality alone, studies providing a descriptive analysis of only one approach, studies considering EUS-guided transpapillary drainage (rendezvous procedures), and studies reporting on potential duplicate data were excluded.

Search strategy

A search strategy was co-developed by members of the study team, including a health research librarian. The online databases MEDLINE, Pubmed, EMBASE (Excerpta Medica Database), and CENTRAL (Cochrane Central Registry of Controlled Trials) were comprehensively queried. No date limits were applied from inception of the databases through to 15 November 2018. The detailed search strategy is listed in the Supplementary Materials. A search was also performed of a) the references of all identified relevant published manuscripts and b) abstracts of major gastroenterology meetings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week) between 1 January 2014 and 15 November 2018. Furthermore, the tables of contents of major gastroenterology journals relevant to the field (*Gastroenterology*, *American Journal of Gastroenterology*, *Gastrointestinal Endoscopy*,

Endoscopy, and *Surgical Endoscopy*) were searched from 1 January 2014 to 15 November 2018. Finally, clinical trial registries (clinicaltrials.gov, vacsp.gov, CENTRAL, <http://www.controlled-trials.com/mrct>, and isrctn.com) were searched to identify any ongoing or unpublished trials. All citations were then exported into Rayyan (M Ouzzani, Qatar Computing Research Institute, HBKU, Doha, Qatar) and de-duplication was performed. Two reviewers (K.B., N.F.) independently performed an abstract screen to identify articles for further review. Full-text reviews of these articles were then conducted to generate a final list of included studies. Any disagreements between reviewers were resolved by consensus. Interobserver agreement between the two reviewers with respect to the inclusion of studies was quantified using the Kappa statistic. Attempts were made to contact the authors of any included abstracts for any available additional data.

Data extraction and study quality

A form was created to abstract data from each included study (Supplementary Materials). In cases where a median and interquartile range were reported instead of a mean and standard deviation, we used the median as an approximation of the mean and used the interquartile range divided by 1.35 as an approximation of the standard deviation [19]. Studies underwent independent assessment of quality and bias by two reviewers. Individual components of study quality were assessed according to the Cochrane Risk of Bias Tool for randomized trials [19] and the Newcastle-Ottawa Scale (NOS) for cohort studies [20].

Outcomes

The primary outcome of interest was the clinical success rate. Secondary outcomes of interest included technical success, stent occlusion rate, procedure time, total adverse event rate (early and late), and individual adverse event rates.

Statistical analysis

Measures of effect comparing EUS-BD vs. ERCP (reference group) were estimated and presented in forest plots. Relative risks were estimated for dichotomous outcomes and absolute mean differences were estimated for continuous outcomes. Meta-analysis was performed using a DerSimonian and Laird random effects model. A constant value of 0.5 was added to all cells in cases where there were no events in one of the treatment arms. We used chi-squared tests and I^2 statistics to detect heterogeneity [21]. Publication bias was assessed using funnel plots alongside Begg's and Egger's tests. In order to assess the robustness of the results, the following sensitivity analyses were also performed: 1) randomized trials (RCTs) and observational studies were analyzed separately; 2) each study was removed individually; 3) the constant term added to cells with zero events was varied from 0.1 to 0.9 in increments of 0.1; and 4) a fixed effects model was used instead of a random effects model. All statistical analyses were performed using STATA version 14.2 (StataCorp, College Station, Texas, USA).

Results

Study selection and characteristics

The overall search results are presented in the PRISMA diagram (► **Fig. 2**) [18]. Five studies out of an initial 776 citations were included for the meta-analysis. Of the excluded studies, one [22] compared EUS-BD in secondary decompression with ERCP in primary decompression, another compared EUS-BD to ERCP in the primary setting exclusively in patients with indwelling duodenal stents [23], a third study [24] compared EUS-BD using a transmural approach to EUS-BD using a transpapillary approach, and finally, a conference abstract [25] was excluded because of concerns over potential duplicate patient data.

Pertinent characteristics of the five studies [26–30] included in the meta-analysis are summarized in ► **Table 1**. Four studies were performed in Asia, and one was carried out in the United States. All studies were published within the last 3 years. A total of 396 patients were analyzed (147 had undergone EUS-BD and 249 had undergone an ERCP-guided approach). In the EUS-BD arm, 54.4% of the patients were male, compared with 51.8% in the ERCP arm. Mean age was 67.2 years in the EUS-BD arm and 66.4 years in the ERCP arm. Pancreatic cancer was the most common etiology of malignant biliary obstruction, ranging from 62.4% to 95.5% of the patient populations in individual studies. The next most common etiologies were metastatic pancreatic cancer, cholangiocarcinoma, and ampullary cancer. Overall, 78.2% of the EUS-BD patients underwent CDS and

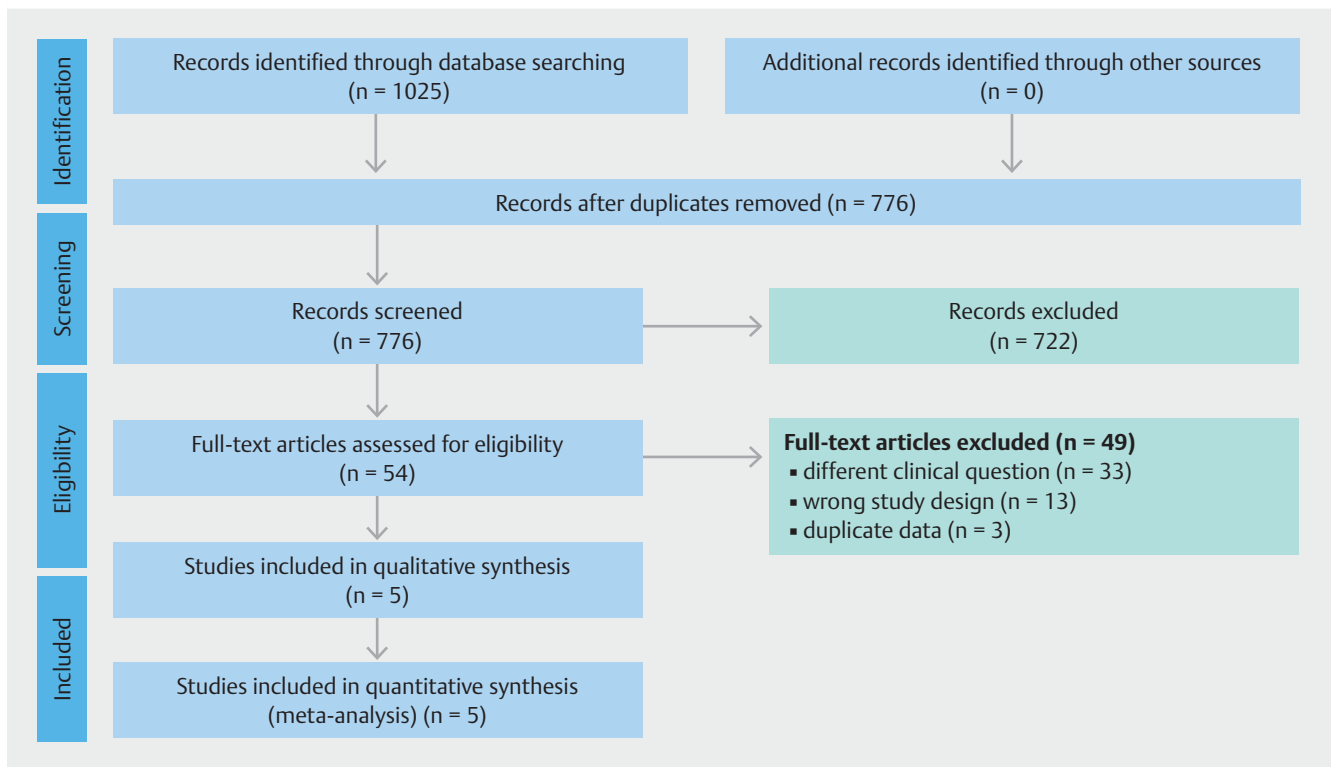
21.8% underwent HGS. Median follow-up ranged from 95 to 298 days within treatment arms.

Assessment of study quality

Study quality assessments of the individual studies using the Cochrane Risk of Bias Tool for randomized trials [19] and the NOS for cohort studies [20] are provided in the Supplementary Materials. Study quality was generally moderate – high for the three RCTs and moderate (mean NOS 5.0) for the two cohort studies. The main source of bias was a lack of blinding in the randomized trials, as is typically expected of studies comparing endoscopic interventions.

Clinical and technical success rates

Study outcomes are summarized in ► **Table 2**. Technical success was defined in studies as successful placement of a stent in the desired location in a single session, with either endoscopic and/or radiographic confirmation. Clinical success was defined in all studies as a relative and/or absolute reduction in bilirubin at 2–4 weeks. There was no overall difference in the pooled relative risk (RR) of clinical success in the EUS-BD group compared with the ERCP group (RR 0.98, 95% confidence interval [CI] 0.93 to 1.03) using a random effects model (► **Fig. 3**). There was a low degree of heterogeneity between the five studies, indicated by an I^2 value of 0.0%. There was also no overall difference in terms of technical success (RR 1.00, 95%CI 0.93 to 1.08) between EUS-BD and ERCP (► **Fig. 3**). The findings with respect to the primary outcome were robust to sensitivity analysis. Specifically, these results remained unchanged when



► **Fig. 2** Study flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

► **Table 1** Summary of characteristics of studies included in the meta-analysis.

Author [ref], year	Study type	Centers, n	Patients (EUS, ERCP), n	Mean age (EUS, ERCP), years	Female (EUS, ERCP), %	Pancreatic cancer etiology (EUS, ERCP), %	Initial bilirubin (EUS/ERCP), mg/dL	Mean or median follow-up (EUS/ERCP), days	Study quality
Paik [26] 2018	RCT	4	125 (64, 61)	66.6 (64.8, 68.4)	46.4 (35.9, 57.4)	62.4 (59.4, 65.6)	8.3/7.7	144/165	Mod – high
Bang [27] 2018	RCT	1	67 (33, 34)	69.3 (69.4, 69.2)	40.3 (48.5, 32.4)	95.5 (100, 91.2)	12.5/12.1	190/174	Mod – high
Park [28] 2018	RCT	1	28 (14, 14)	66.1 (66.8, 65.4)	39.3 (35.7, 42.9)	92.9 (100, 85.7)	7.5/9.9	95/147	Mod
Kawakubo [29] 2016	Retro	1	82 (26, 56)	69.0 (71, 68)	53.7 (69.2, 46.4)	82.9 (96.2, 76.8)	7.5/5.1	298/222	NOS-5
Ridtitid [30] 2016	Retro	1	94 (10, 84)	63.3 (66, 63)	50.0 (50.0, 50.0)	70.2 (60.0, 71.4)	22/18	150/150	NOS-5

EUS, endoscopic ultrasound-guided approach; ERCP, endoscopic retrograde cholangiopancreatography with transpapillary stenting; RCT, randomized controlled trial; retro, retrospective cohort study; mod, moderate quality; NOS, Newcastle-Ottawa Scale for cohort studies [20].

► **Table 2** Summary of outcomes from studies included in the meta-analysis.

Author	Technical success EUS, n/N (%) ERCP, n/N (%)	Clinical success EUS, n/N (%) ERCP, n/N (%)	Procedure time EUS, mean (SD), min ERCP, mean (SD), min	Stent occlusion EUS, n/N (%) ERCP, n/N (%)	Overall adverse events EUS, n/N (%) ERCP, n/N (%)	Pancreatitis EUS, n/N (%) ERCP, n/N (%)
Paik [26]	60/64 (93.8) 55/61 (90.2)	54/64 (84.4) 52/61 (85.2)	5 (3–12) ¹ 11 (7–18) ¹	0/64 (0.0) 3/61 (4.9)	7/64 (10.9) 24/61 (39.3)	0/64 (0.0) 9/61 (14.8)
Bang [27]	30/33 (90.9) 32/34 (94.1)	32/33 (97.0) ² 34/34 (100.0) ²	24.2 (9.2) 22.4 (13.5)	0/33 (0.0) 0/34 (0.0)	7/33 (21.2) 5/34 (14.7)	0/33 (0.0) 1/34 (2.9)
Park [28]	13/14 (92.9) 14/14 (100.0)	13/14 (92.9) 14/14 (100.0)	43 (24) 31 (21)	2/14 (14.3) 4/14 (28.6)	0/14 (0.0) 0/14 (0.0)	0/14 (0.0) 0/14 (0.0)
Kawakubo [29]	N/R	25/26 (96.2) 55/56 (98.2)	19.7 (10.3) 30.2 (13.1)	0/26 (0.0) 5/56 (8.9)	7/26 (26.9) 20/56 (35.7)	0/26 (0.0) 9/56 (16.1)
Ridtitid [30]	10/10 (100.0) 84/84 (100.0)	10/10 (100.0) 79/84 (94.0)	N/R	0/10 (0.0) 14/84 (16.7)	3/10 (30.0) 12/84 (14.3)	0/10 (0.0) 2/84 (2.4)

EUS, endoscopic ultrasound-guided approach; ERCP, endoscopic retrograde cholangiopancreatography with transpapillary stenting; SD, standard deviation; RCT, randomized controlled study; retro, retrospective cohort study; N/R, not reported.

¹ This study reported procedure times in terms of median and interquartile range.

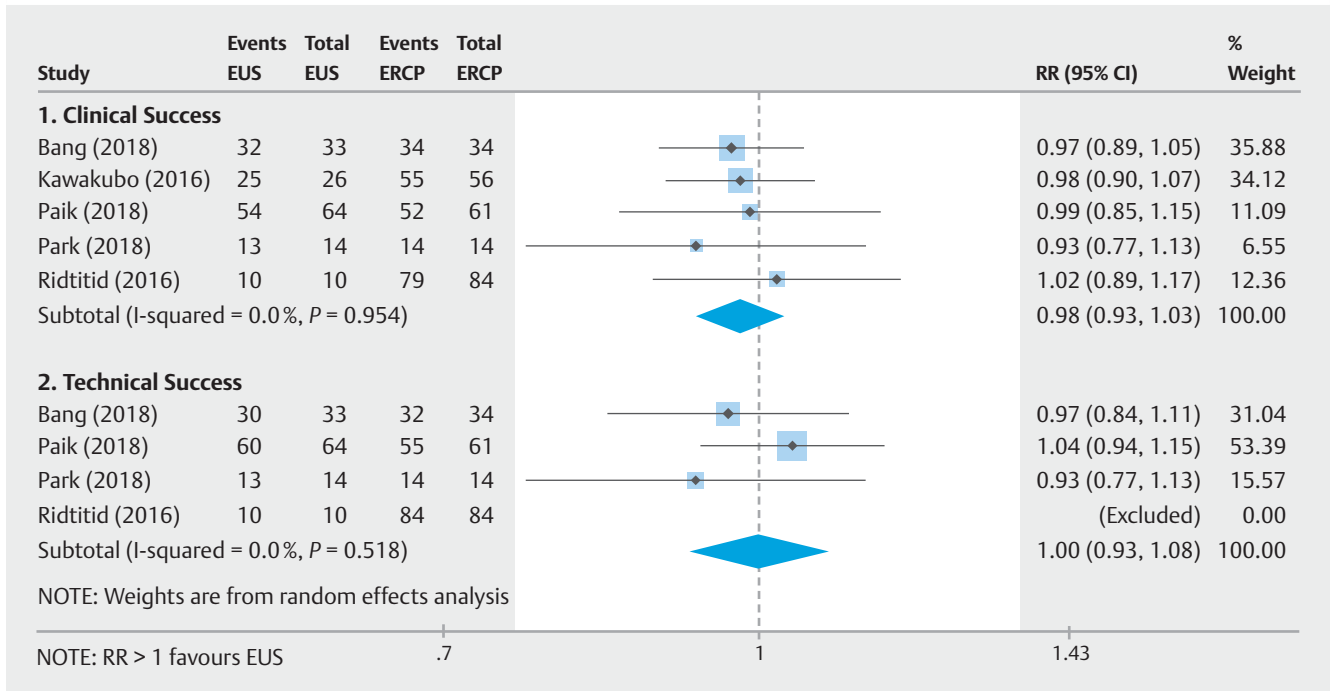
² This study reported the results from an intention-to-treat method, where EUS patients could cross over to ERCP and vice versa – results were unchanged when per-protocol analysis was employed.

1) stratifying by whether or not the assigned treatment was randomized, 2) excluding the studies individually, 3) varying the constant term added to cells with zero events, 4) using a fixed effects model as opposed to a random effects model, and 5) removing the abstract from the analysis. Given the small number of studies in the evidence base and lack of heterogeneity, we did not undertake formal meta-regression or subgroup analysis [19, 31]. Four out of five studies pursued only CDS, ac-

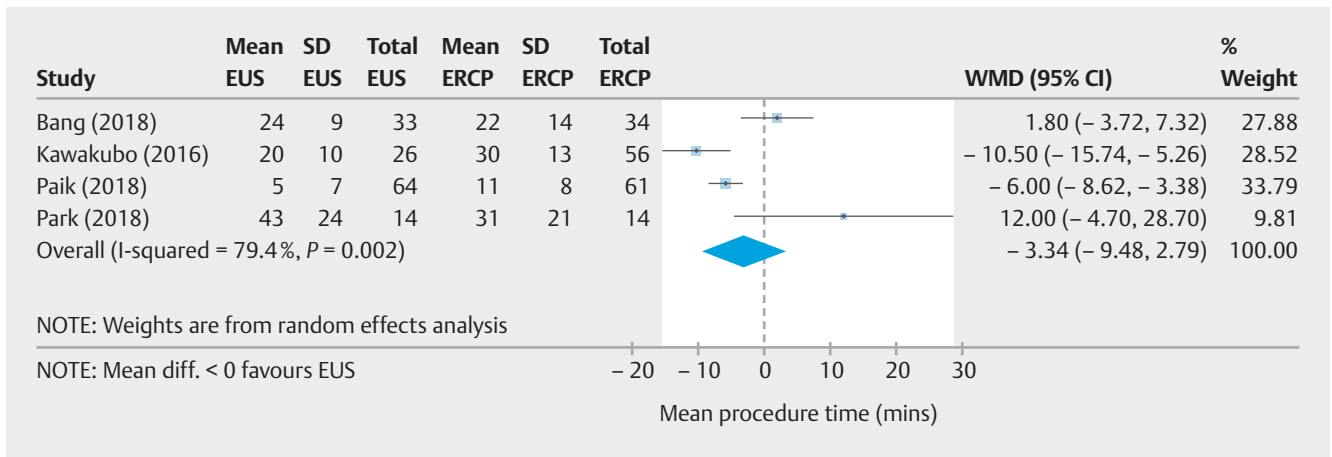
counting for over 75% of the patients in the pooled EUS-BD arm; therefore, we did not compare CDS with HGS.

Procedure time

There was no overall difference between mean procedure time in the EUS-BD group and the ERCP group (► **Fig. 4**), with a mean difference of 3.34 minutes less for EUS-BD (95%CI–9.48 to 2.79). There was a high degree of heterogeneity between the four included studies, indicated by an I^2 value of 79.4%.



► **Fig. 3** Forest plot comparing endoscopic ultrasound (EUS)- and endoscopic retrograde cholangiopancreatography (ERCP)-guided biliary drainage in terms of clinical success and technical success. RR, relative risk; CI, confidence interval.



► **Fig. 4** Forest plot comparing endoscopic ultrasound (EUS)- and endoscopic retrograde cholangiopancreatography (ERCP)-guided biliary drainage in terms of mean procedure time. WMD, weighted mean difference; CI, confidence interval; SD, standard deviation.

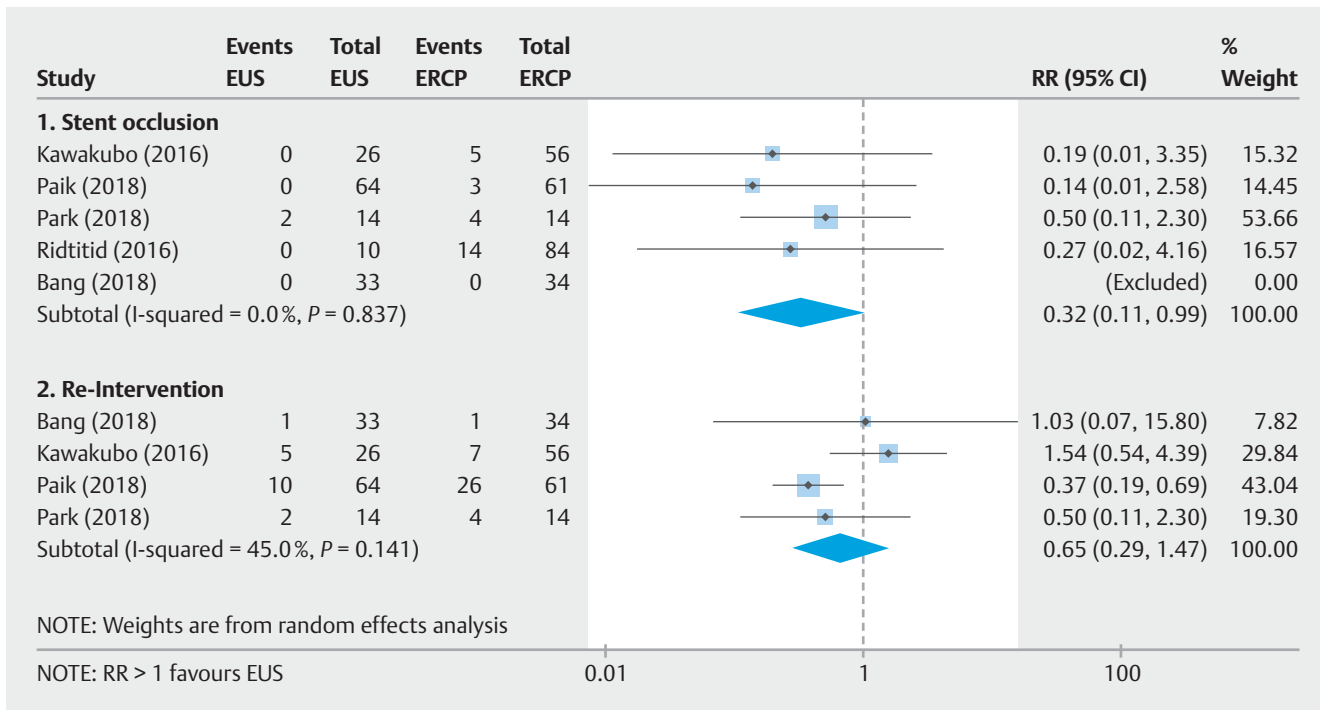
Stent occlusion and re-intervention rates

EUS-BD had a borderline statistically significantly higher risk of stent occlusion relative to ERCP (RR 0.32, 95%CI 0.11 to 0.99), as shown in ► **Fig. 5**. The statistical significance of these findings was not robust following the removal of the included abstract from the analysis (RR 0.33, 95%CI 0.10 to 1.14). There was a low degree of heterogeneity, indicated by an I^2 value of 0.0%. There was no statistically significant difference in the overall rate of re-intervention between EUS-BD and ERCP (► **Fig. 5**), with an RR of 0.65 (95%CI 0.29 to 1.47). There was a moderate degree of heterogeneity, indicated by an I^2 value of

45.0%. Only two studies reported on stent patency duration, and therefore, results of meta-analysis are not reported.

Adverse event rates

There was no difference in the overall (early and late) adverse event rate between EUS-BD and ERCP (► **Fig. 6a**), with a relative risk of 0.84 (95%CI 0.35 to 2.01). There was a high degree of heterogeneity between the five studies, indicated by an I^2 value of 74.3%. Results suggested that the risk of pancreatitis was lower with the EUS-BD approach compared with ERCP, but this finding was not statistically significant (RR 0.22, 95%CI 0.05 to 1.02) (► **Fig. 6a**). After restricting the analysis to the three RCTs,



► **Fig. 5** Forest plot comparing endoscopic ultrasound (EUS)- and endoscopic retrograde cholangiopancreatography (ERCP)-guided biliary drainage in terms of stent occlusion and overall risk of re-intervention. RR, relative risk; CI, confidence interval.

the overall risk of any adverse event (early and late) was similar between the EUS-BD and ERCP (RR 0.61, 95%CI 0.12 to 3.06), but the results specific to pancreatitis became statistically significant (RR 0.12, 95%CI 0.01 to 0.97). Similarly, the removal of the abstract from the analysis did not meaningfully change the effect estimate for any adverse event (RR 0.64, 95%CI 0.26 to 1.58) but it did increase the statistical significance and magnitude of the effect estimate specific to pancreatitis (RR 0.12, 95%CI 0.02 to 0.62).

There was a statistically nonsignificant trend toward an increased risk of cholangitis with the ERCP approach compared with the EUS-BD approach (► **Fig. 6a**). Conversely, there were statistically nonsignificant trends toward increased rates of bile peritonitis, bleeding, and stent migration with the EUS-BD approach (► **Fig. 6b**). In terms of severe adverse events, only two perforations were reported, both of which occurred within the EUS-BD arm of one study [26]. No treatment-related deaths were reported in any of the studies. Given the paucity of events, these outcomes were excluded from the meta-analysis.

Publication bias

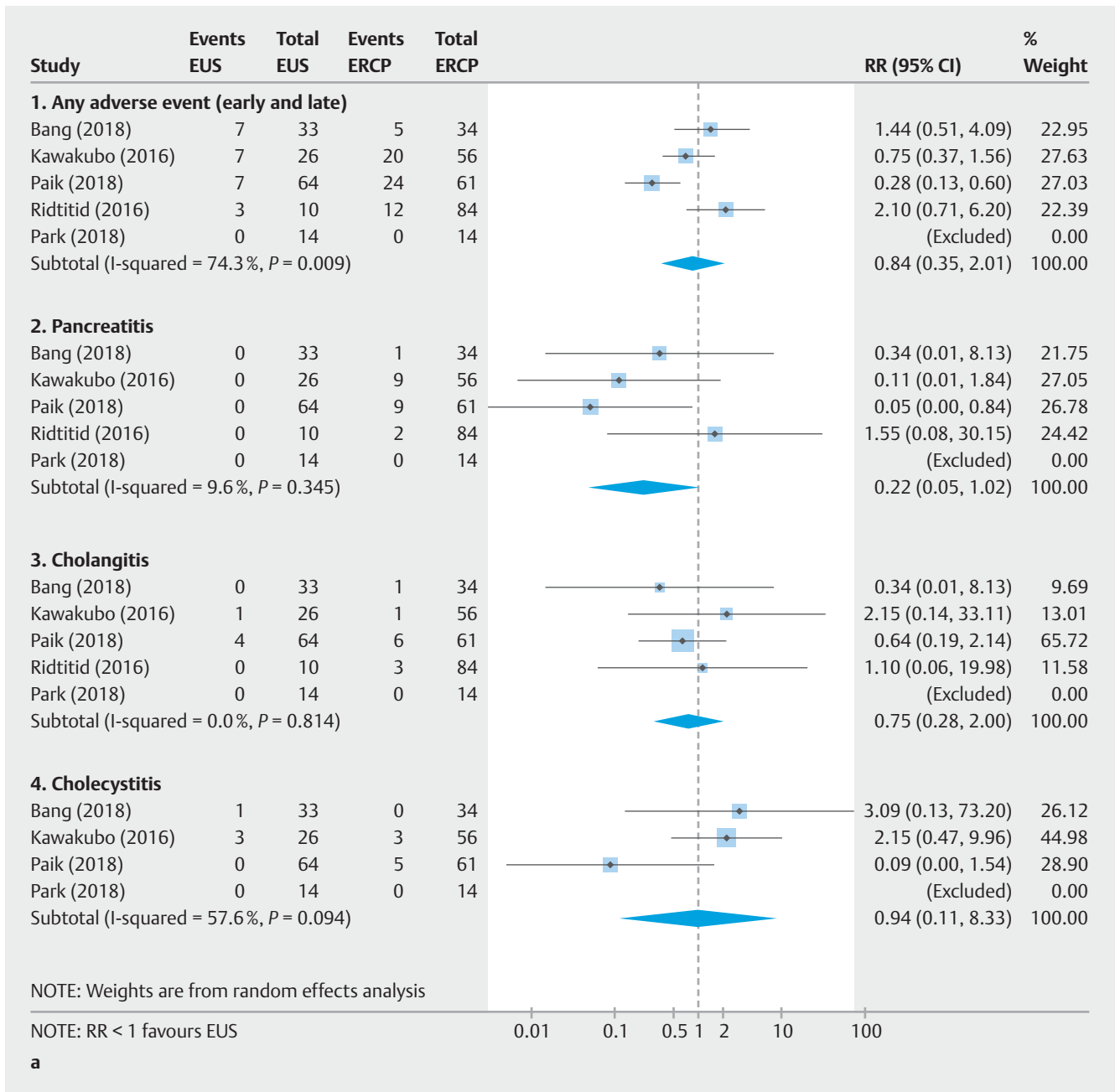
Begg's and Egger's tests yielded no significant evidence of publication bias for the primary outcome of clinical success, with *P* values of 1.00 and 0.96, respectively. A funnel plot (Supplementary Materials) also yielded no clear visual evidence of small study effects for the primary outcome.

Discussion

This systematic review and meta-analysis comparing the outcomes between EUS-BD and ERCP-guided primary drainage of malignant biliary obstruction identified five studies that included a total of 396 patients. Our results suggest that EUS-BD may be as effective as ERCP in the primary decompression of malignant biliary obstruction. Although there was no difference between the approaches in terms of overall adverse events, the results suggested that the EUS-BD approach may have a lower risk of pancreatitis compared with the ERCP-guided approach.

Our meta-analysis has several strengths. The broad search strategy provides a thorough and up-to-date review of the current state of evidence regarding the effectiveness of EUS-BD vs. ERCP in the primary decompression of patients with malignant biliary obstruction. In choosing not to restrict the search to RCTs, our study considers findings from both experimental and observational study designs. We found no evidence of heterogeneity in our primary outcome of clinical success. Our objective assessments revealed moderate – high overall quality among the included RCTs and moderate overall quality among the included observational studies (Supplementary Materials).

Despite its strengths, our study has important limitations. There was a paucity of available studies that addressed our question, and the included studies were generally small, with few observed events for some outcomes, leading to a meta-analysis that was ultimately underpowered to demonstrate treatment differences within potentially important subgroups. Most studies were conducted at a single, high-volume center, which decreases the external validity and applicability of the re-



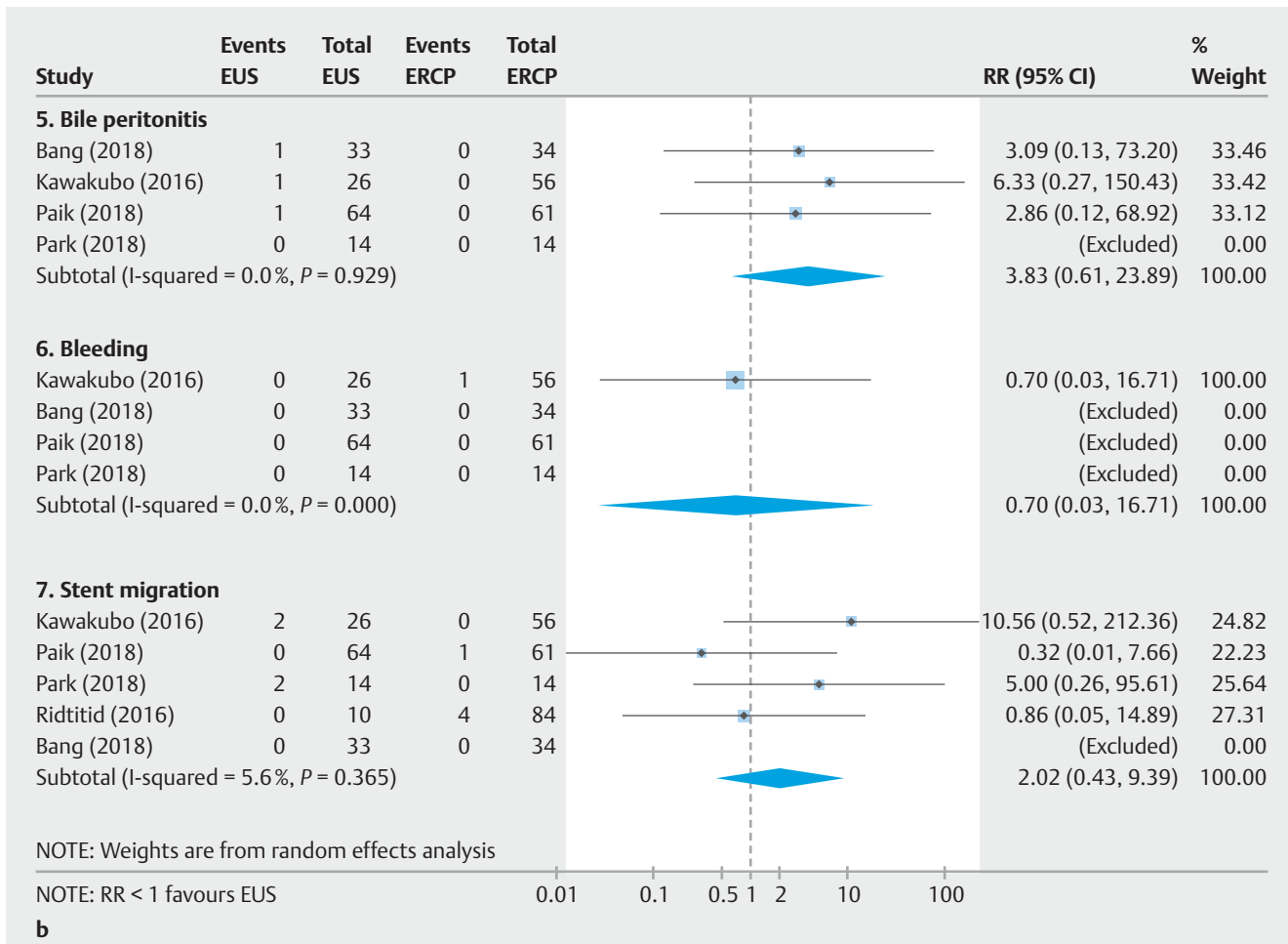
► **Fig. 6** Forest plot comparing endoscopic ultrasound (EUS)- and endoscopic retrograde cholangiopancreatography (ERCP)-guided biliary drainage. **a** Rates of overall adverse events, pancreatitis, cholangitis, and cholecystitis.

Continuation see following page

sults. Differences in study design are likely to have played a role in overall unmeasured methodological heterogeneity. Furthermore, the model of stents used for EUS-BD across studies was variable, adding to further clinical heterogeneity. Indeed, it is unknown what model, or even what type, of stent is optimal for EUS-guided biliary approaches, and whether this varies with a CDS or HGS approach. This should be a focus for well-designed future studies.

Our meta-analysis searched and included grey literature in the form of a conference abstract [30]. Although we ultimately felt that the inclusion of this abstract strengthened our meta-

analysis by increasing the total number of patients studied, in addition to reducing publication bias, we acknowledge the limitations associated with this decision. Specifically, we may have introduced unmeasured heterogeneity to the results due to study methods not being fully described in the abstract. In addition, abstract results often differ from final publication results, and there is a lack of a rigorous peer-review process that applies to abstracts, leading one to question the validity of their results. Attempts to address some of these issues by requesting additional data were unsuccessful. We ensured that all our results were unchanged by excluding the abstract in sensitivity analysis.



► Fig. 6 (Continuation) **b** Rates of bile peritonitis, bleeding, and stent migration. RR, relative risk; CI, confidence interval.

Limitations were also identified within individual studies. These included lack of blinding of patients and endoscopists in the RCTs, and lack of adequate follow-up reporting in the observational studies. Furthermore, there was the potential for selection bias in the observational studies. In one RCT, the competing intervention was used as a rescue modality in the presence of a technical failure. The appropriateness of a traditional intention-to-treat analysis when examining clinical success in this scenario is questionable, though the study results were unchanged when a per-protocol analysis was used. We recommend that future studies employ and report per-protocol analyses to address this issue. Finally, four out of five included studies were conducted in Asia, with a single study having been carried out in the United States. With a relative lack of North American or European studies addressing this question, there is less certainty with respect to the generalizability of these findings.

EUS-BD has been shown to be a safe approach that has comparable effectiveness to percutaneous drainage after failed ERCP, with fewer adverse events [32–35]. Our meta-analysis is the first to address the effectiveness of EUS-BD in the primary decompression of malignant biliary obstruction when compared directly with ERCP. Similar clinical and technical success

rates, procedure times, and re-intervention rates were observed between the two approaches. That being said, it is important to interpret these results within the context of the limitations described above.

Overall early and late adverse event rates were similar between EUS-BD and ERCP, though the number of events was small, leading to a lack of precision for many outcomes. There was a suggestion of an increased risk of pancreatitis with ERCP compared with EUS-BD, as one would expect with a transpapillary approach. However, this potential risk could be offset by nonsignificant trends toward increased bleeding, bile peritonitis, and perforation rates with the EUS-BD approach. Although the initial belief was that occlusion rates were lower with EUS-BD and transmural stenting, we found no evidence of this in our meta-analysis. The reason for this may be due to the fact that, while tumor ingrowth and subsequent stent occlusion appears to be lower with EUS-BD and transmural (compared with transpapillary) stenting, the rate of food-related impaction appears to be higher when CDS is employed [28]. Thus, the overall occlusion rates are likely to be similar between EUS-BD with CDS and ERCP when one considers all types of occlusion, and, in fact, our meta-analysis suggested possible higher rates of oc-

clusion with EUS-BD. Our meta-analysis was unable to differentiate between the performance characteristics of CDS and HGS vs. ERCP in primary decompression, and this should be another focus for future studies.

Overall, when one weighs all possible relevant outcomes, it appears that EUS-BD could potentially be a safe and practical alternative to ERCP in the primary decompression of patients with malignant biliary obstruction. It is important to note that the EUS-BD approach in the primary setting is still at an early stage in terms of limited expertise, procedural volumes, and available evidence. The results of our systematic review and meta-analysis therefore highlight the need for additional high-quality studies directly comparing the two methods in large numbers of patients to identify potential differences in specific adverse events, and to draw comparisons within particular subgroups of interest. At this stage, little is known about the potential variability in EUS-BD success rates between low- and high-volume EUS centers. Success rates are similar between EUS-BD and ERCP based on the results of our meta-analysis, but the performance of larger or multicenter studies that include low-volume EUS centers could alter these results. In addition, future large studies could delineate potential differences between other outcomes such as adverse event rates or procedure times, and could serve to better compare the safety and cost-effectiveness of these two interventions.

The decision on whether to proceed with EUS-BD or ERCP for first-line decompression in this patient population should, at this juncture, be considered cautiously, given that the EUS-BD approach is relatively new in this context. Such a decision ought to be largely based on local expertise, with requisite high EUS experience levels and volumes, given that the adverse event profile associated with the relatively newer EUS-BD approach is arguably of greater consequence. Additionally, the increasing availability of tailored equipment designed solely for the performance of EUS-BD is another important factor. As the EUS-BD approach improves, high-volume experts will eventually disseminate the knowledge to endoscopists at lower-volume centers. Finally, formal cost-effectiveness analyses have not been performed to determine the optimal primary approach in this clinical situation; hence, feasibility and cost should also be considered in future studies and eventual clinical guidelines.

Competing interests

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References

- [1] Domagk D, Oppong KW, Aabakken L et al. Performance measures for ERCP and endoscopic ultrasound: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. *Endoscopy* 2018; 50: 1116–1127
- [2] Donnan E, Bentrem DJ, Komanduri S et al. ERCP in potentially resectable malignant biliary obstruction is frequently unsuccessful when performed outside of a comprehensive pancreaticobiliary center. *J Surg Oncol* 2016; 113: 647–651
- [3] Enochsson L, Swahn F, Arnelo U et al. Nationwide, population-based data from 11,074 ERCP procedures from the Swedish Registry for Gallstone Surgery and ERCP. *Gastrointest Endosc* 2010; 72: 1175–1184
- [4] Nennstiel S, Weber A, Frick G et al. Drainage-related complications in percutaneous transhepatic biliary drainage: an analysis over 10 years. *J Clin Gastroenterol* 2015; 49: 764–770
- [5] Oh HC, Lee SK, Lee TY et al. Analysis of percutaneous transhepatic cholangioscopy-related complications and the risk factors for those complications. *Endoscopy* 2007; 39: 731–736
- [6] Weber A, Gaa J, Rosca B et al. Complications of percutaneous transhepatic biliary drainage in patients with dilated and nondilated intrahepatic bile ducts. *Eur J Radiol* 2009; 72: 412–417
- [7] Gan SI, Rajan E, Adler DG et al. Role of EUS. *Gastrointest Endosc* 2007; 66: 425–434
- [8] Fabbri C, Luigiano C, Lisotti A et al. Endoscopic ultrasound-guided treatments: are we getting evidence based – a systematic review. *World J Gastroenterol* 2014; 20: 8424–8448
- [9] Mallery S, Matlock J, Freeman ML. EUS-guided rendezvous drainage of obstructed biliary and pancreatic ducts: report of 6 cases. *Gastrointest Endosc* 2004; 59: 100–107
- [10] Wiersema MJ, Sandusky D, Carr R et al. Endosonography-guided cholangio-pancreatography. *Gastrointest Endosc* 1996; 43: 102–106
- [11] Khashab MA, Levy MJ, Itoi T et al. EUS-guided biliary drainage. *Gastrointest Endosc* 2015; 82: 993–1001
- [12] Baars JE, Kaffes AJ, Saxena P. EUS-guided biliary drainage: a comprehensive review of the literature. *Endosc Ultrasound* 2018; 7: 4–9
- [13] Wang K, Zhu J, Xing L et al. Assessment of efficacy and safety of EUS-guided biliary drainage: a systematic review. *Gastrointest Endosc* 2016; 83: 1218–1227
- [14] Anderloni A, Fugazza A, Troncone E et al. Single-stage EUS-guided choledochoduodenostomy using a lumen-apposing metal stent for malignant distal biliary obstruction. *Gastrointest Endosc* 2019; 89: 69–76
- [15] Mariani A, Giussani A, Di Leo M et al. Guidewire biliary cannulation does not reduce post-ERCP pancreatitis compared with the contrast injection technique in low-risk and high-risk patients. *Gastrointest Endosc* 2012; 75: 339–346
- [16] Halttunen J, Meisner S, Aabakken L et al. Difficult cannulation as defined by a prospective study of the Scandinavian Association for Digestive Endoscopy (SADE) in 907 ERCPs. *Scand J Gastroenterol* 2014; 49: 752–758
- [17] Bailey AA, Bourke MJ, Williams SJ et al. A prospective randomized trial of cannulation technique in ERCP: effects on technical success and post-ERCP pancreatitis. *Endoscopy* 2008; 40: 296–301
- [18] Moher D, Shamseer L, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1
- [19] Higgins JPT, Altman DG, Sterne JAC et al. (eds) Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (eds). *Cochrane handbook for systematic reviews of interventions* version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011:

- Available from: <http://handbook-5-1.cochrane.org/>, Accessed 7 March 2019
- [20] Wells G, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2018: Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, Accessed 7 March 2019
- [21] Higgins J, Thompson S. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558
- [22] Dhir V, Itoi T, Khashab MA et al. Multicenter comparative evaluation of endoscopic placement of expandable metal stents for malignant distal common bile duct obstruction by ERCP or EUS-guided approach. *Gastrointest Endosc* 2015; 81: 913–923
- [23] Hamada T, Isayama H, Nakai Y et al. Transmural biliary drainage can be an alternative to transpapillary drainage in patients with an indwelling duodenal stent. *Digest Dis Sci* 2014; 59: 1931–1938
- [24] Bapaye A, Mahadik M, Gaadhe R et al. Stent patency of endoscopic ultrasound guided transmural versus transpapillary biliary drainage in malignant biliary obstruction. *J Gastroenterol Hepatol* 2016; 31 : (Suppl. 03): 228
- [25] Piyachaturawat P, Kongkam P, Ridditid W et al. EUS-guided versus percutaneous versus ERCP biliary drainage in patients with malignant biliary obstruction: a case-controlled study from a large referral center. *Gastrointest Endosc* 2017; 85: AB476–AB477
- [26] Paik WH, Lee TH, Park DH et al. EUS-guided biliary drainage versus ERCP for the primary palliation of malignant biliary obstruction: a multicenter randomized clinical trial. *Am J Gastroenterol* 2018; 113: 987–997
- [27] Bang JY, Navaneethan U, Hasan M et al. Stent placement by EUS or ERCP for primary biliary decompression in pancreatic cancer: a randomized trial (with videos). *Gastrointest Endosc* 2018; 88: 9–17
- [28] Park JK, Woo YS, Noh DH et al. Efficacy of EUS-guided and ERCP-guided biliary drainage for malignant biliary obstruction: prospective randomized controlled study. *Gastrointest Endosc* 2018; 88: 277–282
- [29] Kawakubo K, Kawakami H, Kuwatani M et al. Endoscopic ultrasound-guided choledochoduodenostomy vs. transpapillary stenting for distal biliary obstruction. *Endoscopy* 2016; 48: 164–169
- [30] Ridditid W, Kongkam P, Angsuwatcharakorn P et al. Ultimate outcomes of endoscopic transpapillary stenting (ETS) versus EUS-guided choledochoduodenostomy (EUS-CDS) using selfexpandable metallic stent (SEMS) in patients with inoperable malignant distal biliary obstruction. *J Gastroenterol Hepatol* 2016; 31 : (Suppl. 03): 272–273
- [31] Fu R, Gartlehner G, Grant M et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010
- [32] Lee TH, Choi JH, Park doH et al. Similar efficacies of endoscopic ultrasound-guided transmural and percutaneous drainage for malignant distal biliary obstruction. *Clin Gastroenterol Hepatol* 2016; 14: 1011–1019.e1013
- [33] Shah JN, Marson F, Weiler F et al. Single-operator, single-session EUS-guided anterograde cholangiopancreatography in failed ERCP or inaccessible papilla. *Gastrointest Endosc* 2012; 75: 56–64
- [34] Park DH, Jeong SU, Lee BU et al. Prospective evaluation of a treatment algorithm with enhanced guidewire manipulation protocol for EUS-guided biliary drainage after failed ERCP (with video). *Gastrointest Endosc* 2013; 78: 91–101
- [35] Hara K, Yamao K, Hijioka S et al. Prospective clinical study of endoscopic ultrasound-guided choledochoduodenostomy with direct metallic stent placement using a forward-viewing echoendoscope. *Endoscopy* 2013; 45: 392–396