

**Title:**

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**Is ERCP-BD or EUS-BD the preferred decompression modality for malignant distal biliary obstruction? A meta-analysis of randomized controlled trials**

*¿Es el ERCP-BD o el EUS-BD la modalidad preferida de descompresión para la obstrucción biliar distal de origen maligno? Metanálisis de ensayos aleatorizados y controlados*

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## ABSTRACT

**Background:** endoscopic retrograde cholangiopancreatography (ERCP)-guided biliary drainage (ERCP-BD) with transpapillary stent placement is the standard palliative treatment for malignant distal biliary obstruction. Endoscopic ultrasound-guided biliary drainage (EUS-BD) has been evaluated for efficacy and safety as an alternative for failed ERCP.

**Purpose:** we aimed to determine whether ERCP-BD or EUS-BD is the preferred treatment modality for decompressing malignant distal biliary obstruction.

**Methods:** we systematically searched for relevant published, prospective, and randomized trials comparing ERCP-BD with EUS-BD in decompressing malignant distal biliary obstruction in databases (i.e., PubMed and Cochrane). Technical success, treatment success, and procedure duration were primary outcome measurements; overall adverse events, post-ERCP pancreatitis (PEP), and stent reintervention rate were the secondary outcomes.

**Results:** three trials with 220 patients met the inclusion criteria. Technical success, treatment success, procedure duration, and overall adverse event rate were similar between ERCP-BD and EUS-BD. However, ERCP-BD had a significantly higher PEP rate than EUS-BD (9.2% vs. 0%), the difference being significant (risk ratio [RR] = 8.5; 95% confidence interval (CI): 1.03-69.91,  $p = 0.05$ ). Similarly, ERCP-BD had a higher stent reintervention rate than EUS-BD (28.4% vs. 4.5%), although the difference was not significant (RR = 1.91; 95% CI: 0.94-3.88,  $p = 0.07$ ).

**Conclusion:** technical success, treatment success, procedure duration, and overall adverse event rate were comparable between ERCP-BD and EUS-BD in decompressing malignant distal biliary obstruction. Nevertheless, EUS-BD had a significantly lower rate of PEP and a lower tendency toward stent reintervention than ERCP-BD. Therefore, EUS-BD might be a suitable alternative to ERCP-BD when performed by experts.

**Keywords:** ERCP-BD. EUS-BD. Adverse events. Malignant distal biliary obstruction. Meta-analysis.

## INTRODUCTION

Obstructive jaundice is one of the most common symptoms in patients with malignant distal

biliary obstruction. Endoscopic retrograde cholangiopancreatography (ERCP) followed by implantation of a transpapillary self-expandable metallic stent (SEMS) has been the preferred treatment modality for the palliation of malignant distal biliary obstruction in patients with an unresectable malignancy (1-3). This modality obtained a success rate greater than 95% with an extremely low adverse event rate (4). However, some adverse events, such as post-ERCP pancreatitis (PEP), cholangitis, and stent dysfunction continue to pose substantial challenges (5,6). ERCP could be precluded when accompanied by duodenal obstruction, a surgically altered anatomy, failed cannulation, and failed wire access across the stricture.

Endoscopic ultrasound-guided biliary drainage (EUS-BD) has gained popularity as an alternative to percutaneous biliary drainage for patients with failed ERCP (7-11). It has several potential advantages over ERCP-guided biliary drainage (ERCP-BD). First, EUS-BD avoids traumatic papillary manipulation, which can lead to acute pancreatitis and post-sphincterotomy bleeding. Second, EUS-BD can access the bile duct when the ampulla cannot be approached endoscopically due to duodenal invasion and altered anatomy from previous surgeries. Third, EUS-BD does not traverse the biliary stricture itself, decreasing the risk of tumor ingrowth and reducing reintervention probability. Fourth, the technical success rate of EUS-BD appears to be higher because the bile duct is accessed under ultrasound-guided direct visualization (12). However, the technique involves complex endoscopic procedures and requires dedicated expertise (13); also, bile leakage-induced biliary peritonitis is a potential adverse event (14-16). Recently, the application of EUS-BD has been limited to failed biliary cannulation during ERCP, altered surgical anatomy, duodenal occlusion, and duodenal stent covering the ampulla (17). Nevertheless, EUS-BD is associated with a shorter procedure duration and reduced adverse events when compared with ERCP-BD, and could represent a preferred treatment modality for patients with distal malignant biliary obstruction (12,18).

In this context, EUS-BD as a potential first-line treatment for malignant distal biliary obstruction has been an issue of concern for researchers. To date, three randomized controlled studies have been conducted to compare the clinical efficacy and safety of EUS-BD versus ERCP-BD in patients with malignant distal biliary obstruction (19-21). However, their results were controversial. Therefore, we aimed to determine whether ERCP-BD or

EUS-BD is to be preferred as treatment modality for the decompression of malignant distal biliary obstruction by using a meta-analysis.

## **METHODS**

### **Protocol and registration**

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (22), and has been registered in PROSPERO (No. CRD42018114407).

### **Data sources**

Two independent investigators systematically identified all previously published prospective randomized trials in English, from January 2008 to November 2018, included in PubMed, Cochrane Library databases, Embase, and MEDLINE, and evaluating EUS-BD and ERCP-BD for malignant biliary obstruction using the following terms: (cholestasis, extrahepatic OR distal biliary obstruction OR malignant biliary obstruction OR malignant distal biliary obstruction) AND (EUS-BD OR EUS-guided transmural biliary drainage OR endoscopic ultrasound-guided biliary drainage OR EUS-guided biliary drainage) AND (ERCP-BD OR ERCP-guided biliary drainage OR ERCP OR endoscopic retrograde cholangio-pancreatography OR endoscopic retrograde cholangiopancreatography) AND (randomized controlled trial OR randomized controlled study OR randomized clinical trial OR randomized clinical study OR randomized trial OR randomized study). We searched for relevant studies following the flowchart shown in figure 1.

### **Inclusion and exclusion criteria**

Seven authors independently screened and discussed the studies to reach a consensus for inclusion and exclusion. The inclusion criterion was randomized control trials comparing ERCP-BD with EUS-BD for the palliation of malignant distal biliary obstruction and published in full English text. Articles were included if they recorded one of the following procedure-related events: technical success, treatment success, procedure duration, PEP, bile peritonitis, bile duct infection, and stent reintervention-related procedure events. The exclusion criteria were as follows: nonhuman studies, insufficient or unspecific data, and

other study types, such as letters, conference abstracts, case reports, and reviews.

### **Data extraction**

Five authors independently extracted data from the included studies. The following data items were extracted: author, title, year of publication, study design, type of stent, technical success, treatment success, procedure duration, overall adverse events, PEP events, bile peritonitis events, and reintervention events for the ERCP-BD group and EUS-BD group. All disagreements were resolved by consensus.

### **Assessment of bias risk**

The quality of the studies was assessed by three authors using the Cochrane Collaboration tool. Factors assessed were as follows: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.

### **Outcome measures**

Our primary outcomes were technical success, treatment success, and procedure duration, whereas the secondary outcomes were overall adverse events, PEP, and reintervention rate. Technical success was defined as the placement of the metal stent across the stricture site by ERCP or through the stomach or the duodenum by EUS. Treatment success was defined as a total serum bilirubin level less than one-quarter of the pretreatment level within 4 weeks. Procedure duration was defined as the time between endoscope positioning for bile duct access and stent deployment. Overall adverse events were comprised of abdominal pain, PEP, bile peritonitis, cholangitis, cholecystitis, pneumoperitoneum, stent migration, and stent occlusion, and they were divided into mild, moderate, and severe by standard criteria (23). In particular, PEP was defined as clinical pancreatitis with a serum amylase level > 3 times the upper limit of normal beyond 24 h after the procedure, and reintervention was defined as any additional endoscopic, percutaneous, or surgical intervention to relieve jaundice after the procedure.

### **Statistical analysis**

A univariate analysis was performed using the  $\chi^2$  test (with Yates correction, when

appropriate). In all cases, values of  $p < 0.05$  were considered statistically significant. All calculations were performed using the SPSS 20 statistical package (IBM Corp., Armonk, NY, USA). All pooled data were analyzed with the Review Manager 5.3 software (Cochrane Informatics and Knowledge Management Department). Dichotomous variables are expressed as risk ratio (RR) with 95% confidence intervals (CI). Continuous variables are expressed as weighted mean differences (WMD) with 95% confidence intervals (CI). The  $I^2$  test and  $p$  value were performed to test heterogeneity, which was considered significant when the result of  $I^2$  was more than 50% and  $p < 0.05$ . The fixed-effects model was used when heterogeneity was not significant; otherwise, a random-effects model was used in this study (24). A funnel plot was generated to assess this study for publication bias.

## RESULTS

As shown in figure 1, 18 publications were identified through the above-mentioned search strategy. After excluding 15 inappropriate studies, three randomized controlled trials were available for analysis (19-21). A total of 220 patients were included in these three trials, of whom 109 were in the ERCP-BD group and 111 were in the EUS-BD group. The quality assessment of these three studies is presented in figure 2, which demonstrates high quality according to study design.

### Characteristics of included studies

As shown in Table 1, Bang's study included 33 patients in the EUS-BD group and 34 patients in the ERCP-BD group (21). Park's study contained 28 and 14 patients undergoing EUS-BD and ERCP-BD, respectively (20). Paik's study contained 64 and 61 patients in the EUS-BD and ERCP-BD groups, respectively (19). For ERCP-BD, biliary sphincterotomy was performed in all studies. In Bang's study, the transmural tract was dilated using a 4 mm × 40 mm balloon dilator during EUS-BD. An 8 mm × 60 mm fully covered SEMS with antimigration function was placed in both groups (21). In Park's study, a 6F cystotome and a hurricane balloon with a 4-mm diameter were introduced along with the guidewire, and the tract was dilated during EUS-BD after the guidewire was passed into the bile duct. A SEMS consisting of an uncovered sleeve part and a fully covered body part with antimigration function was placed in both groups. The diameter of the stent was 10 mm (20). Compared with the previous two

studies, Paik's study was multicentered, and patients were blinded to the procedure. A SEMS was placed in the ERCP-BD group. The metal stents were chosen generally based on tumor involvement of the cystic duct. EUS-BD was performed either as a choledochoduodenostomy or hepaticogastrostomy using a one-step dedicated stent introducer, which functions as a push-type dilator without the need for predilation or use of electrocautery. The preloaded SEMS included in the device could prevent intraperitoneal bile leakage and stent migration (19).

### **Technical success, treatment success, and procedure duration**

As shown in figure 3A, technical success rates were 92.7% (101/109) for ERCP-BD versus 92.8% (103/111) for EUS-BD, with no statistically significant difference (RR = 1; 95% CI: 0.93-1.08,  $p = 0.97$ ). Treatment success was defined as a total serum bilirubin level less than one-quarter of the pretreatment level within 4 weeks in Bang's (21) and Paik's (19) trials. However, it was defined as a decrease in total serum bilirubin level > 50% of the pretreatment level within 4 weeks in Park's (20) trial. The aggregated rate of treatment success, including that in Park's trial, was not significantly different between ERCP-BD and EUS-BD (RR = 1.02; 95% CI: 0.93-1.11,  $p = 0.72$ ) (Fig. 3B), and the result was identical after excluding Park's trial (RR = 1.19; 95% CI: 0.47-3.01,  $p = 0.71$ ) (Fig. 3C). As shown in figure 3D, no significant difference in procedure duration was found (WMD = 0.07; 95% CI: -7.36-7.50,  $p = 0.99$ ).

### **Adverse events**

A total of 29 and 14 overall adverse events were known for ERCP-BD and EUS-BD, respectively. All adverse events were mild to moderate in severity. The incidence of these overall adverse events was not statistically different between ERCP-BD and EUS-BD (RR = 1.64; 95% CI: 0.33-8.26,  $p = 0.55$ ) (Fig. 4A). The rate of overall adverse events tended to be higher with ERCP-BD versus EUS-BD. Thus, we investigated the differences in main adverse events such as PEP, bile peritonitis, and bile duct infection. Results showed that the rate of PEP was significantly higher in ERCP-BD (10/109) than in EUS-BD (0/111) (RR = 8.5; 95% CI: 1.03-69.91,  $p = 0.05$ ) (Fig. 4B). The incidence of bile peritonitis was similar between the two groups (RR = 0.34; 95% CI: 0.04-3.17,  $p = 0.34$ ) (Fig. 4C). The rate of bile duct infection was



higher in ERCP-BD (12/109) than in EUS-BD (5/111), but this difference was not statistically significant (RR = 2.48; 95% CI: 0.90-6.83,  $p = 0.08$ ) (Fig. 4D). Stent reintervention rates were compared. Figure 4E shows that ERCP-BD had a higher tendency toward stent reintervention (31/109) than EUS-BD (15/111); however, there was no statistical difference (RR = 1.91; 95% CI: 0.94-3.88,  $p = 0.07$ ).

### **Publication bias**

No publication biases existed in PEP (Fig. 5A) and stent reintervention rates (Fig. 5B) according to a funnel plot analysis ( $p = 0.19$  and  $p = 0.44$ , respectively).

### **DISCUSSION**

ERCP has been the standard treatment modality for biliary obstruction since the 1990s, and its success rate for malignant distal biliary obstruction ranges from 90% to 95% (18). However, ERCP has limited application in cases of malignant invasion of the duodenum or in the presence of a duodenal stent. In addition, ERCP-BD has some potential drawbacks, including PEP and stent occlusion (25). Since EUS-BD was first reported as “EUS-guided bilioduodenal anastomosis” in 2001, it has been increasingly recognized as an alternative to failed ERCP-BD (26). The efficacy and safety of EUS-BD were reportedly similar to or even better than those of percutaneous transhepatic biliary drainage (PTBD) or ERCP-BD (8,12,18,27,28). However, EUS-BD as a primary treatment modality in decompressing malignant distal biliary obstruction has only been reported in a few studies.

In the current study, a pooled analysis was first performed to evaluate the efficacy and safety of EUS-BD versus ERCP-BD for malignant distal biliary obstruction. Results suggested that no significant differences existed in technical success rate, treatment success rate, procedure duration, and overall adverse events between ERCP-BD and EUS-BD. However, the rate of PEP was significantly lower in EUS-BD than in ERCP-BD. Notably, the rate of PEP in Paik’s study (19) was exceptionally high, and the authors did not use any PEP-related prophylaxis, which is the standard of care nowadays. Therefore, the meta-analysis results regarding PEP must be cautiously interpreted (29). Meanwhile, the incidence of bile peritonitis and bile duct infection was not significantly different between EUS-BD and ERCP-BD. Moreover, the stent reintervention rate with EUS-BD was lower than that with ERCP-

BD. Therefore, EUS-BD might be a suitable alternative to ERCP-BD when performed by experts for patients with malignant distal biliary obstruction. PEP is one of the most concerning adverse events of ERCP-BD, and is associated with significant morbidity, longer hospital stay, and increased financial burden (30-32), although the risk of PEP following transpapillary SEMS placement in patients with pancreatic cancer and distal biliary obstruction is relatively low (6). Considering that EUS-BD avoids traumatic papillary manipulation, it does not increase the risk of PEP, possibly implying significant clinical impacts, including shorter admission duration and lower cost of care. EUS-guided puncture of the biliary tract has the risk of bile leakage, leading to bile peritonitis. Such outcome may limit the use of EUS-BD in clinical practice. However, with the development of new instruments and techniques in EUS-BD, such as the one-step dedicated stent introducer, which avoids the need of predilation or electrocautery use, the procedure would probably reduce the risk of bile peritonitis.

Our results showed that two patients developed bile peritonitis following EUS-BD and no further intervention was required. More importantly, EUS-BD had lower tendency of stent reintervention than ERCP-BD. Stent dysfunction included mainly migration and food impaction with EUS-BD, and tumor ingrowth or overgrowth with ERCP-BD. Recently, an antimigration design has reduced migration risk and potentially even eliminated the need for reintervention (33), but there has been no effective solution for the management of tumor ingrowth or overgrowth. At the same time, further intervention was not required due to the formation of a permanent biliary-enteric fistula at the stent site after EUS-BD; nevertheless, double stenting or EUS-BD is required as an alternative after stent dysfunction in ERCP-BD (20). Most patients with malignant distal biliary obstruction are diagnosed with malignancy of the pancreatic head, and the ability to use the same echoendoscope for both a diagnostic (fine-needle aspiration) and therapeutic (biliary drainage) intervention is likely to improve procedural efficiency and minimize resource utilization (21).

The included studies regarding the EUS-BD procedure were not homogeneous. In the studies by Park and Bang, choledochoduodenostomy was the only EUS-BD technique performed, whereas in the study by Paik, patients underwent either choledochoduodenostomy or hepaticogastrostomy. Although no differences in the rate of treatment success and adverse events were found between the choledochoduodenostomy

and hepaticogastrostomy groups (8,34), further studies and subgroup analyses of the success rate and adverse events of different EUS-BD procedures for drainage of malignant distal biliary obstruction are required when comparing EUS-BD with ERCP-BD as first-line treatment modality.

The present study has some limitations. First, the number of cases was too small to draw a firm conclusion. This small size is also known to have a high risk for type II statistical errors. (35) Second, differences in stent type may affect the outcomes. Third, EUS-BD was usually performed by only a small number of expert endoscopists well trained in both ERCP and EUS, and these published studies originated from tertiary high-volume centers where surgery and radiology backup were available to aid in the management of failed interventions and/or adverse events. General application of the EUS-BD technique is far from universal in contrast to that of ERCP. Whether EUS-BD is comparable or superior to ERCP-BD for the treatment of malignant distal biliary obstruction requires further research.

In conclusion, EUS-BD and ERCP-BD have similar rates of technical success, treatment success, procedure duration, and overall adverse events for the decompression of malignant distal biliary obstruction. However, EUS-BD has advantages in terms of PEP and a lower tendency of stent reintervention as compared with ERCP-BD. Thus, EUS-BD might be a suitable alternative to ERCP-BD when performed by experts, but more studies are needed before concluding that it may be considered a first-line modality for drainage of malignant distal biliary obstruction. There is still a long time before it will be a first-line recommendation in future clinical practice, which probably will imply a paradigm shift in this field.

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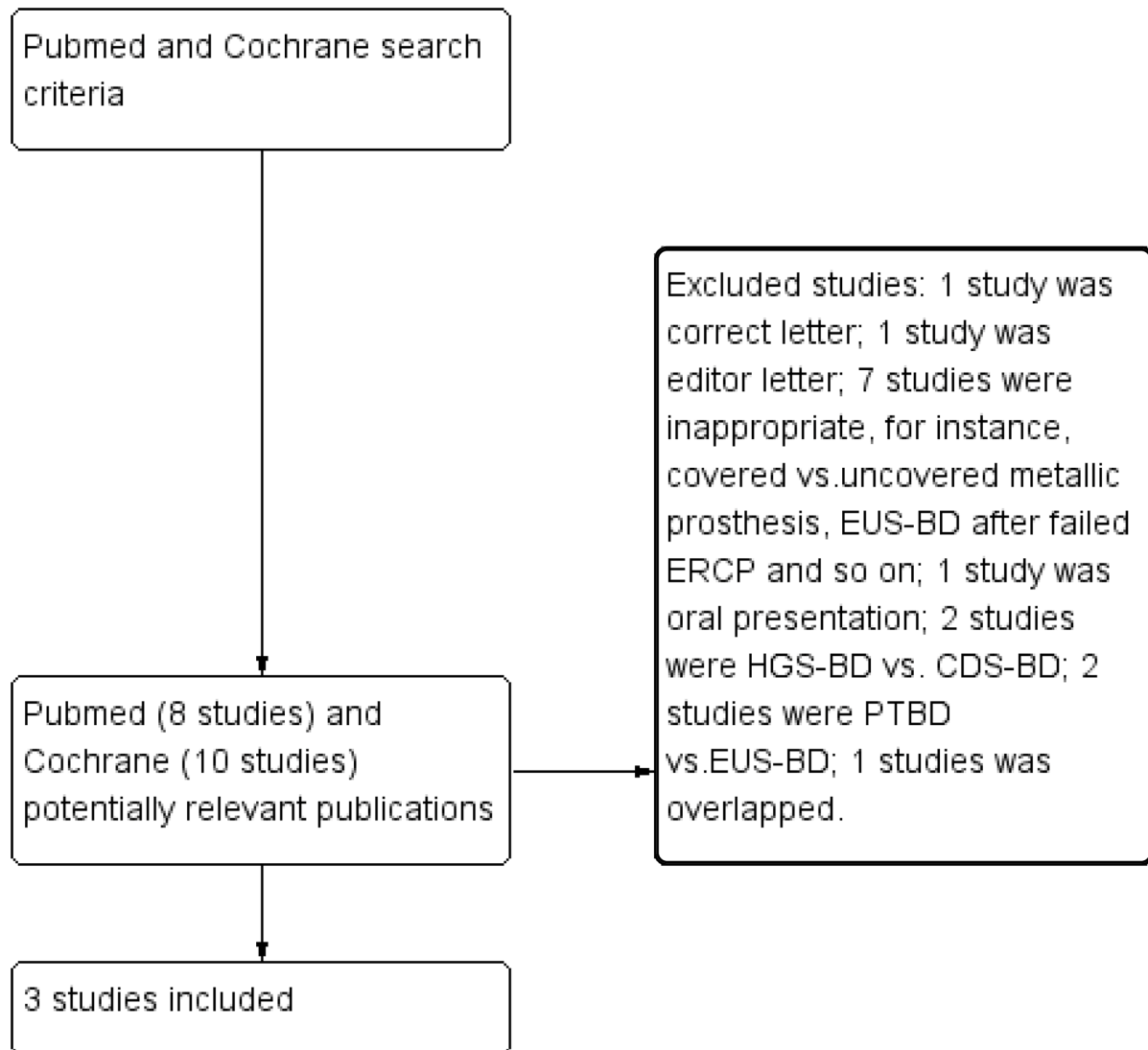


Fig. 1. Flow diagram.



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bang 2018	+	+	+	+	+	+	?
Paik 2018	+	+	+	+	+	+	?
Park 2018	+	+	+	+	+	+	+

Fig. 2. Consensus assessment of bias risk in the included trials. Green, low risk; yellow, unclear risk.

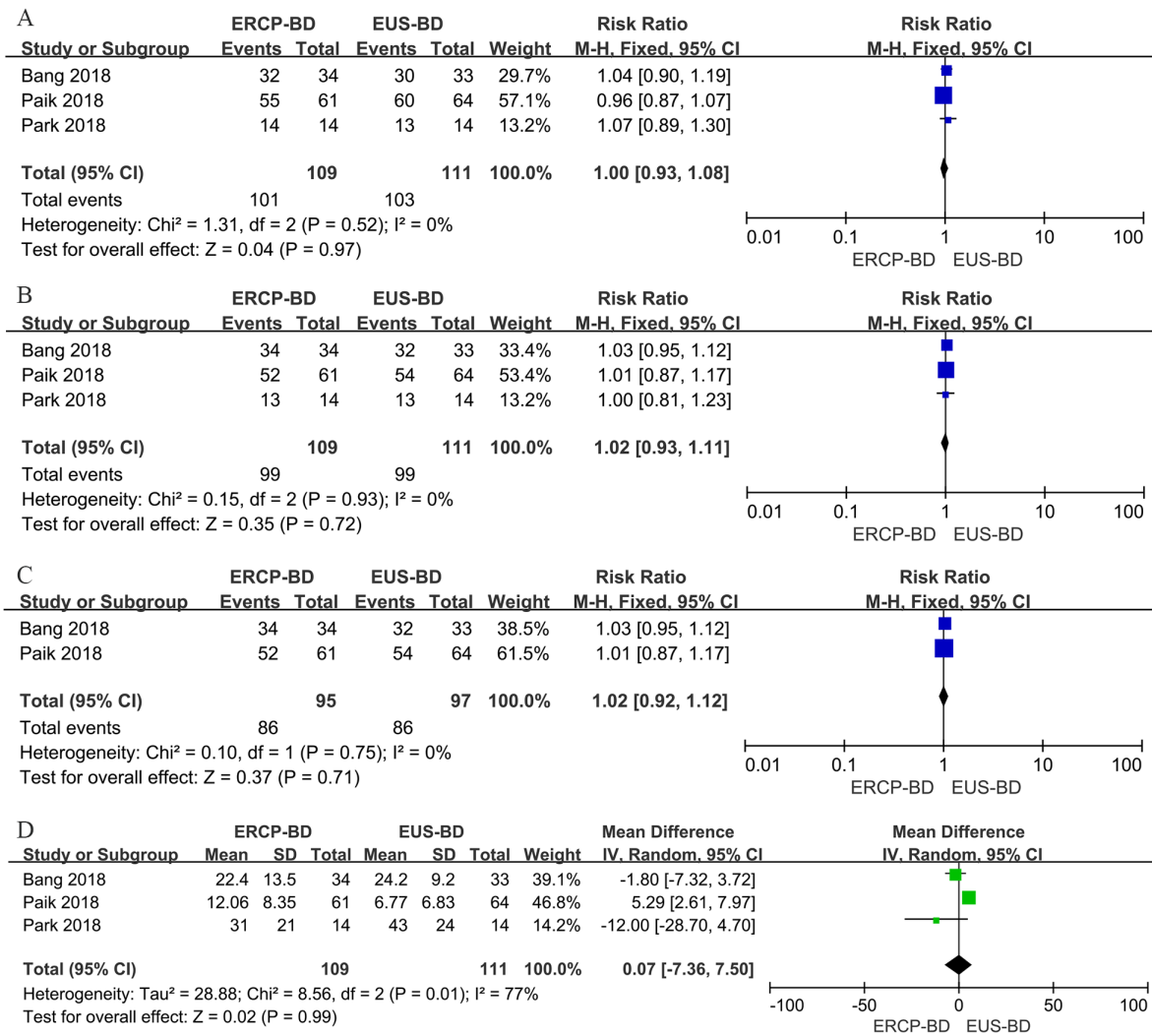


Fig. 3. Technical success and treatment success rates. A. Technical success rates for ERCP-BD and EUS-BD. B. Including Park's trial, treatment success rates for ERCP-BD and EUS-BD. C. Excluding Park's trial, treatment success rates for ERCP-BD and EUS-BD. D. Procedure duration for ERCP-BD and EUS-BD (ERCP: endoscopic retrograde cholangiopancreatography; EUS-BD: endoscopic ultrasound-guided biliary drainage; ERCP-BD: endoscopic retrograde cholangiopancreatography-guided biliary drainage).

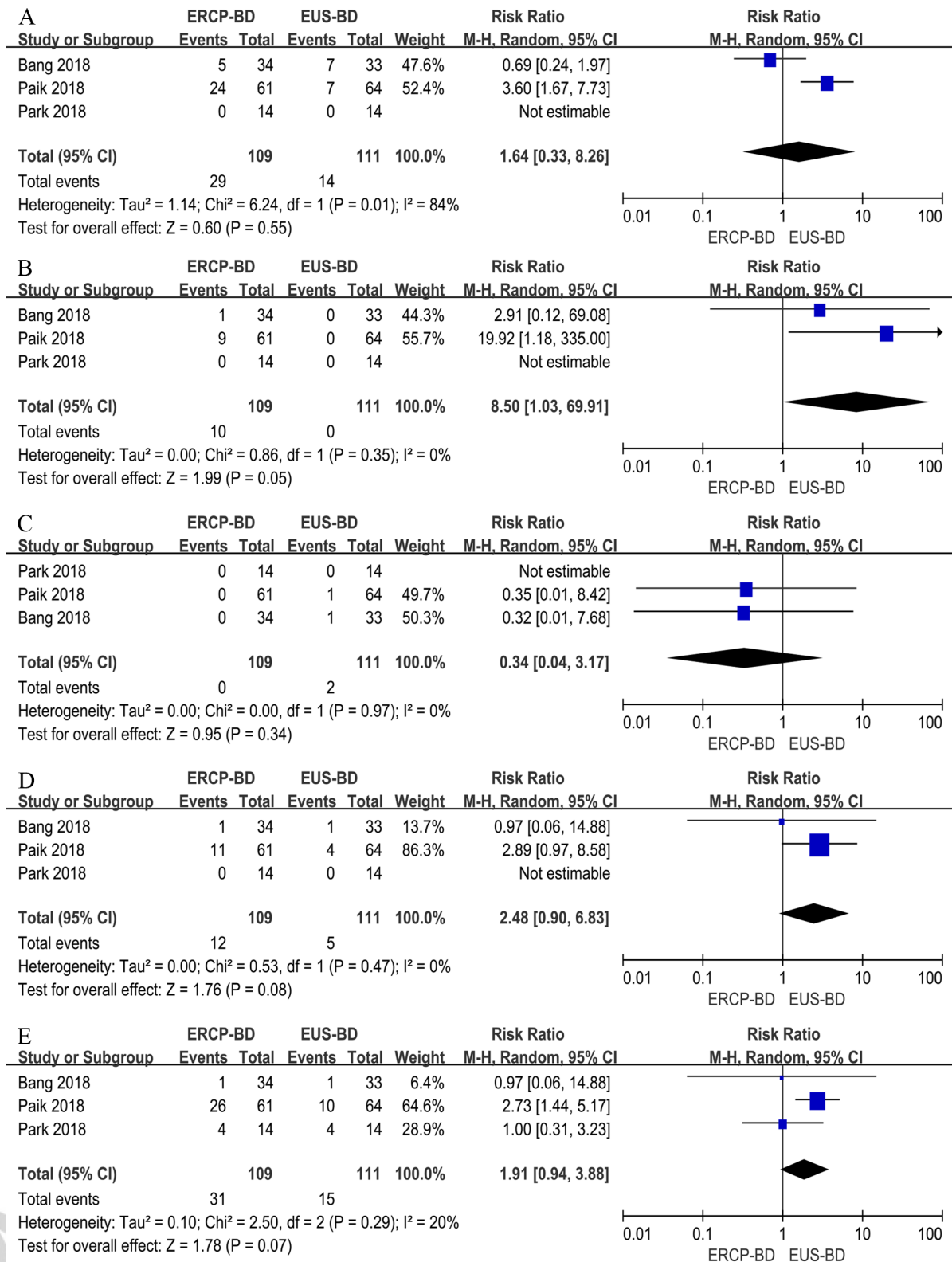


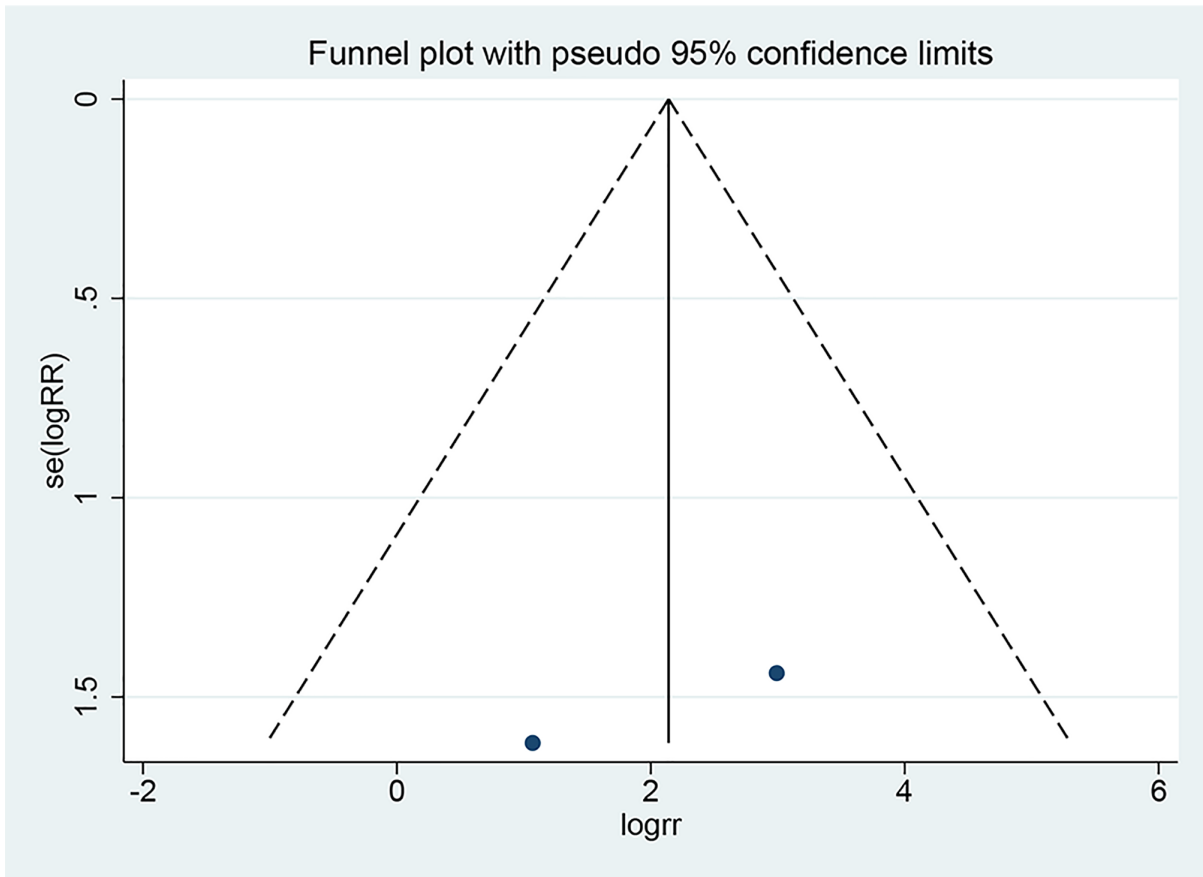
Fig. 4. Adverse events. A. Overall adverse events between ERCP-BD and EUS-BD. B. Rate of PEP in ERCP-BD and EUS-BD. C. Incidence of bile peritonitis in ERCP-BD and EUS-BD. D. Rate of bile duct infection in both groups. E. Stent reintervention rate for ERCP-BD and EUS-BD (ERCP: endoscopic retrograde cholangiopancreatography; EUS-BD: endoscopic ultrasound-

guided biliary drainage; ERCP-BD: endoscopic retrograde cholangiopancreatography-guided biliary drainage).

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A



B

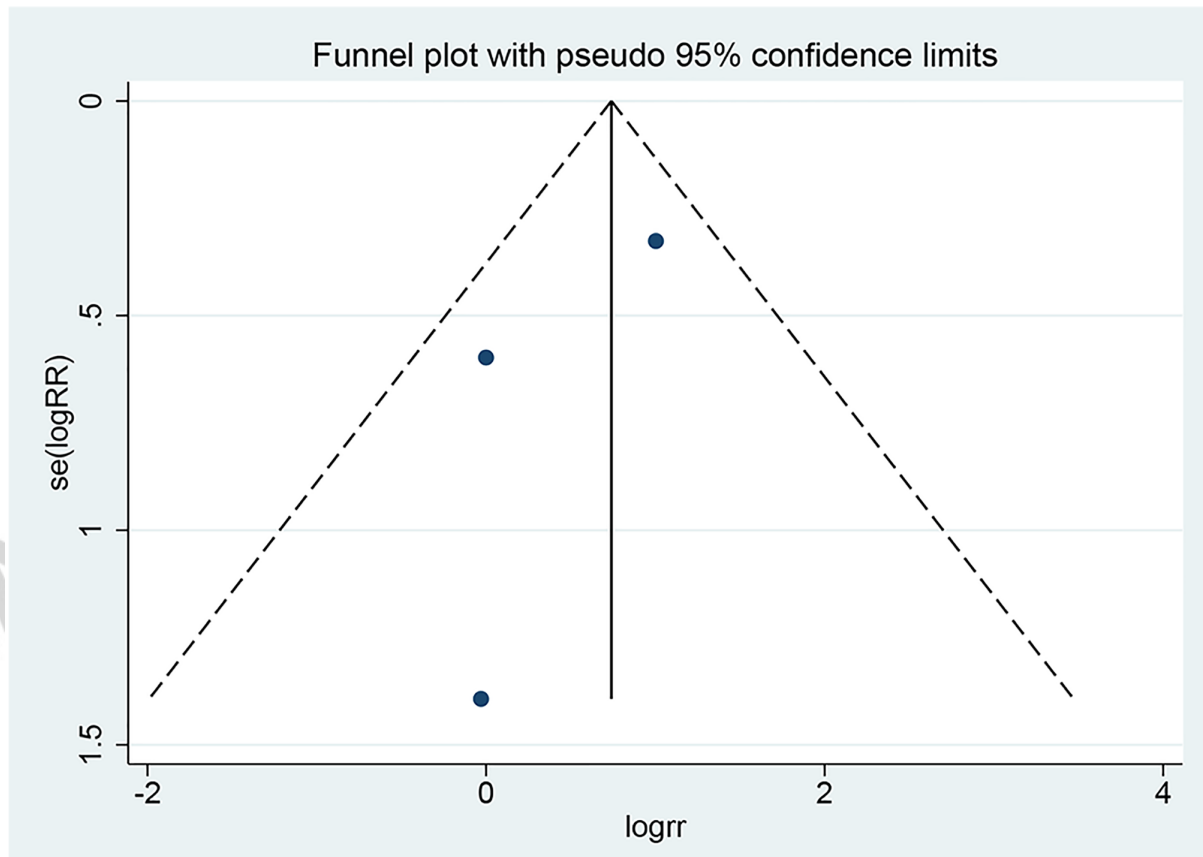


Fig. 5. Publication bias. A. No publication biases in PEP were noted ( $p = 0.19$ ). B. No publication bias was found in stent reintervention rate ( $p = 0.44$ ) (PEP: post-ERCP pancreatitis).

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Table 1. Characteristics of the studies included

	Bang 2018		Paik 2018		Park 2018	
	ERCP-BD (n = 34)	EUS-BD (n = 33)	ERCP-BD (n = 61)	EUS-BD (n = 64)	ERCP-BD (n = 14)	EUS-BD (n = 14)
Route	Trans- papillary	Trans- duodena l	Trans- papillary	Trans- gastric or trans- duodena l	Trans- papillary	Trans- duodenal
Type of stent	8 mm × 60 mm fully covered self- expanda ble metal stent	8 mm × 60 mm fully covered self- expanda ble metal stent	10 mm- diameter uncovere d/covere d metal stent	10 mm- diameter uncovere d/covere d metal stent	10 mm × 60 mm fully covered self- expanda ble metal stent	10 mm × 60 mm fully covered self- expanda ble metal stent
Technical success*	32	30	55	60	14	13
Procedure duration†	22.4 ± 13.5	24.2 ± 9.2	12.06 ± 8.35	6.77 ± 6.83	31 ± 21	24 ± 14
Overall advent events*	5	7	24	7	0	0
PEP*	1	0	9	0	0	0
Bile peritonitis*	0	1	0	1	0	0
Reinterventio n*	1	1	26	10	4	4
Treatment success*	34	32	52	54	13	13

\*No patients; †Mean ± SD (minutes)