

## Review Article

# Percutaneous transhepatic biliary drainage vs. endoscopic biliary drainage in periampullary cancer patients undergoing pancreaticoduodenectomy-a systematic review and meta-analysis

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**Abstract:** Whether percutaneous transhepatic biliary drainage (PTBD) or endoscopic biliary drainage (EBD) is more effective for periampullary cancer (PAC) patients undergoing pancreaticoduodenectomy is not known. The aim of this study was to investigate the safety and efficacy of these two methods as a strategy for the pre-operative management of biliary obstruction. Studies incorporating patients with distal cholangiocarcinoma or pancreatic or ampullary cancer who underwent biliary drainage before pancreaticoduodenectomy were included (EMBASE, Web of Science, and PubMed). Analyses included baseline drainage data, procedure-related complications, post-operative complications, and overall survival. The pooled analyses were performed using RevMan 5.3. Eight studies with a total of 1344 patients were included. Regarding procedure-related complications, a trend towards decreased hyperamylasaemia (OR=0.24, 95% CI [0.12-0.51], P=0.0002) was noted in the PTCD group, and no significant differences in bleeding and cholangitis were observed between the two groups. Regarding the post-operative complications, pancreatic leakage was lower in the PTCD group (OR=0.57, 95% CI [0.33-0.98], P=0.04), and no significant differences were found in the rates of total post-operative complications, wound infection, intra-abdominal infection, bleeding, delayed gastric emptying, or 30-day mortality between the two groups. However, the PTBD group was inferior to the EBD group with respect to long-term outcomes (overall survival HR=1.43, 95% CI [1.18-1.72], P=0.0002). Although the meta-analysis suggests that PTBD exhibits obvious advantages in terms of peri-operative complication rates (pre-operative hyperamylasaemia and post-operative pancreatic fistula rates), EBD results in better survival. Therefore, we advocate using EBD over PTBD for patients undergoing pancreaticoduodenectomy. However, a limitation of the study is that no data from randomized controlled trials were included.

**Keywords:** Drainage, jaundice, pancreaticoduodenectomy, meta-analysis

## Introduction

Most patients with periampullary cancer (PAC), including ampullary carcinoma, pancreatic carcinoma and distal cholangiocarcinoma, have obstructive jaundice at the time of diagnosis, and the only curative treatment for PAC is pancreaticoduodenectomy. Regardless of whether a patient receives a pancreaticoduodenectomy, which is considered the standard treatment, PAC is associated with significant mortality and morbidity [1]. However, a recent meta-analysis showed that among patients with malignant biliary jaundice requiring surgery, patients in the pre-operative biliary drainage

(PBD) group had significantly fewer major adverse effects than those in the direct surgery group [2].

The main therapeutic options for PBD in PAC are percutaneous transhepatic biliary drainage (PTBD) or endoscopic biliary drainage (EBD). EBD can be further subdivided into endoscopic biliary stenting (EBS) and endoscopic nasobiliary drainage (ENBD). Most surgeons consider PTBD an invasive operation; therefore, they are inclined to prefer EBD as a drainage measure. The clinical benefit of PBD in PAC with obstructive jaundice is not well established. It remains unclear whether PTBD or EBD is more effective

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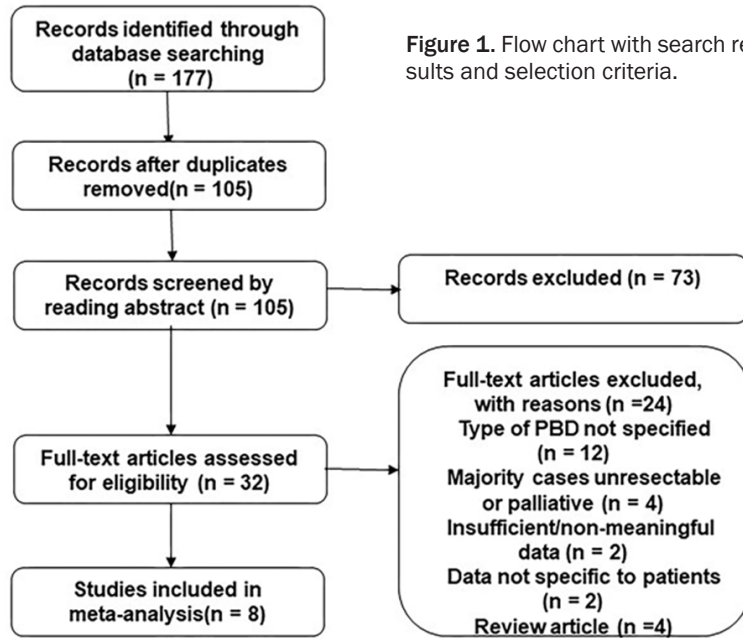


Figure 1. Flow chart with search results and selection criteria.

### Inclusion criteria

The inclusion criteria were as follows: original research based on observational studies or randomized controlled trials (RCTs) in adults; the interventions of interest were PTBD and EBD; the participants of interest were patients undergoing pancreaticoduodenectomy; and an OR with a 95% CI for the risk of pre- and post-operative complications from PBD was provided or could be calculated. Two investigators (Jie Min and Huangbao Li) searched and reviewed all identified studies independently. If the 2 investigators could not reach a consensus about the eligibility of an article, the disagreement was resolved by consulting a third reviewer (Fengqing Zhao).

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### Data extraction and quality assessment

The following data were independently extracted from each study by the 2 investigators: the first author's name, publication year, country, study design, number of participants, pre- and post-operative complications, and overall survival. The Newcastle-Ottawa Scale, an instrument for evaluating the quality of observational studies, was used to assess each of the included studies based on the population selection, study comparability, and outcome of the report. Each study was awarded a score of 1 to 9 points.

### Statistical analysis

The meta-analysis was conducted using RevMan software (version 5.3; Cochrane Collaboration, Copenhagen, Denmark). OR values with 95% CIs were calculated to compare the incidence rates of pre- and post-operative complications between the PTBD group and the EBD group. The values of InHR and SelnHR were calculated as described by Jayne F Tierney [6]. We assessed heterogeneity among the included studies with the Q-test and the  $I^2$  test. An  $I^2 < 50\%$  was considered to represent low heterogeneity, and a fixed-effects model

and safer for the treatment of PAC patients [3, 4]. However, a meta-analysis by Hameed A et al. [5] demonstrated that EBD may be associated with more immediate procedure-related complications in hilar cholangiocarcinoma. Nevertheless, for decades, no systematic examination has been performed to determine which method is more appropriate for treating obstructive jaundice due to PAC in patients undergoing pancreaticoduodenectomy. Therefore, we conducted a meta-analysis to compare the safety and efficacy of PTBD and EBD for PAC treatment in terms of procedure-related, post-operative complications and overall survival.

## Materials and methods

### Search strategy

We identified relevant articles published in English between 2007 and Oct. 2017 by searching EMBASE, PubMed, and Web of Science. The search terms included "pancreaticoduodenectomy", "percutaneous transhepatic biliary drainage", "PTBD", "endoscopic biliary drainage", "EBD", and "ENBD". Reference lists from the identified trials and review articles were manually scanned to identify any other relevant studies. We contacted the original authors to obtain extra information when necessary.

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**Table 1.** Baseline characteristics and quality of the enrolled studies

Study	Country	Study design	Participants		Age (Years)		Males (%)		Outcomes	Total quality score
			PTBD	EBD	PTBD	EBD	PTBD	EBD		
Park, S. Y., et al. (2011)	Korea	RC	34	43	65.9±9.2 <sup>a</sup>	63.7±9.4	77.1%	75.6%	A1, A2, B1, B2, B3, B4, B5, B7	7
Hong, S. K., et al. (2012)	Korea	RC	107	104	65.5±9.0	66.3±8.6	60.8%	68.3%	A1, A2, B3, B1, B2, B3, B4, B5, B6	7
Huang, X., et al. (2015)	China	Prospective	45	55	57.5±10.1	59.0±8.3	68.9%	72.7%	A2, A3, B1, B2, B3, B4, B5, B6, B7	6
Khashab, M. A., et al. (2015)	USA	Prospective	51	22	66.9±12.5	64.9±12.5	56.9%	54.5%	A1, A2, A3	5
Murakami, Y., et al. (2015)	Japan	RC	20	73	<70, 30% <sup>b</sup>	<70, 60.3%	60.0%	46.6%	B1, B8	6
Strom, T. J., et al. (2015)	USA	RC	33	96	67 (44-86) <sup>c</sup>	69 (25-90)	39.4%	55.2%	B2, B3, B4, B5, B7, B8	6
Uemura, K., et al. (2015)	Japan	RC	166	407	67 (27-84)	67 (32-90)	54.2%	54.8%	B1, B2, B3, B4, B7, B8	7
Miura, F., et al. (2017)	Japan	RC	25	63	70.2	70.8	56.0%	76.2%	B1, B4, B7, B8	6

RC = retrospective case-control study; PTBD = percutaneous transhepatic biliary drainage; EBD = endoscopic biliary drainage. a: Average year; b: Grouped by age; c: Median age. A: Procedure-related complications: A1 - Procedure-related complications: Bleeding; A2 - Hyperamylasaemia; A3 - Cholangitis; B: Post-operative complications: B1 - Total post-operative complications; B2 - Wound infection; B3 - Intra-abdominal infection; B4 - Pancreatic leakage; B5 - Bleeding; B6 - Delayed gastric emptying; B7 - 30-day mortality; B8 - Overall survival.

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**Table 2.** Procedure-related and post-operative complications according to PBD type

Complications	No. of studies	PTBD, total (%)	EBD, total (%)	Heterogeneity	Effects model	OR	95% CI	p
Procedure-related complications								
Bleeding	3	12/192	3/169	P=0.81, I <sup>2</sup> =0%	Fixed	2.73	0.85-8.77	0.09
Hyperamylasaemia	4	10/237	37/224	P=0.66, I <sup>2</sup> =0%	Fixed	0.24	0.12-0.51	0.0002
Cholangitis	3	17/203	17/181	P=0.16, I <sup>2</sup> =45%	Fixed	1.00	0.49-2.05	0.99
Post-operative complications								
Total post-operative complications	6	129/397	216/745	P=0.05, I <sup>2</sup> =54%	Random	0.91	0.58-1.44	0.69
Wound infection	5	42/385	59/705	P=0.21, I <sup>2</sup> =32%	Fixed	1.24	0.81-1.91	0.32
Intra-abdominal infection	5	22/385	43/705	P=0.48, I <sup>2</sup> =0%	Fixed	0.73	0.42-1.27	0.26
Pancreatic leakage	6	59/410	123/768	P=0.0001, I <sup>2</sup> =70%	Random	0.57	0.33-0.98	0.04
Subgroup without EBS	4	53/340	73/650	P=0.79, I <sup>2</sup> =0%		1.19	0.80-1.78	0.39
Subgroup with EBS	2	6/70	50/118	P=0.91, I <sup>2</sup> =0%		0.14	0.05-0.36	<0.0001
Bleeding	4	11/219	18/298	P=0.49, I <sup>2</sup> =0%	Fixed	0.82	0.37-1.82	0.63
Delayed gastric emptying	2	5/79	15/98	P=0.37, I <sup>2</sup> =0%	Fixed	0.37	0.13-1.08	0.07
30-day mortality	5	5/303	14/664	P=0.24, I <sup>2</sup> =28%	Fixed	0.81	0.31-2.13	0.67
Overall survival	4	/	/	P=0.46, I <sup>2</sup> =0%	Fixed	HR=1.43	1.18-1.72	0.0002

EBS = endoscopic biliary stenting; PTBD = percutaneous transhepatic biliary drainage, EBD = endoscopic biliary drainage.

was applied. An I<sup>2</sup>>50% was considered to represent high heterogeneity, and a random-effects model was applied. A sensitivity analysis was performed by removing 1 study at a time to assess whether the results were markedly affected by that study. Publication bias was assessed using funnel plots.

### Results

#### Search results and study characteristics

A total of 177 articles were retrieved by searching electronic databases and by manually searching relevant reference lists. After duplicates were identified and excluded, 105 articles remained. We then excluded unrelated reviews, case reports, systematic reviews, and meta-analyses, along with studies that were clearly irrelevant based on their title or abstract. Of these, 8 studies [7-14] including a total of 1344 patients were included in the final analysis. **Figure 1** shows the search results. The sample sizes of the included studies ranged from 73 to 573. In total, 481 patients received PTBD, and 863 patients received EBD. Three studies were conducted in Japan, 1 was conducted in China, 2 were conducted in the USA, and 2 were conducted in South Korea. The characteristics of the included studies are presented in **Table 1**.

#### Incidence of procedure-related hyperamylasaemia

Data from 4 articles [7-10], including 237 cases in the PTBD group and 224 cases in the EBD

group, were used in this meta-analysis. All 4 articles reported that PTBD reduced the incidence of procedure-related hyperamylasaemia when comparing the PTBD and EBD groups. No heterogeneity (P=0.66, I<sup>2</sup>=0%) was found; therefore, we used a fixed-effect model to pool the OR. Overall, the pooled data demonstrated that PTBD was associated with a low incidence of pre-operative hyperamylasaemia (OR=0.24, 95% CI=0.12-0.51, P=0.0002) (**Table 2; Figure 2**).

#### Incidence of post-operative pancreatic fistula

Data from 6 articles [7-9, 12-14], including 410 cases in the PTBD group and 768 cases in the EBD group, were used in this meta-analysis. Two studies [9, 14] reported that EBD increased the incidence of post-operative pancreatic fistula compared with PTBD, but the results from 4 studies [7, 8, 12, 13] showed little significant difference. High heterogeneity (P=0.0001, I<sup>2</sup>=70%) was found; therefore, we used a random-effect model to pool the OR. Overall, the pooled data demonstrated that PTBD was associated with a low incidence of post-operative pancreatic fistula (OR=0.57, 95% CI=0.33-0.98, P=0.04) (**Table 2; Figure 3**).

#### Overall survival

Four studies [11-14] were used to assess overall survival. All 4 studies reported that the PTBD group was inferior to the EBD group with respect to overall survival. No heterogeneity was found (P=0.46, I<sup>2</sup>=0%); therefore, we used a fixed-

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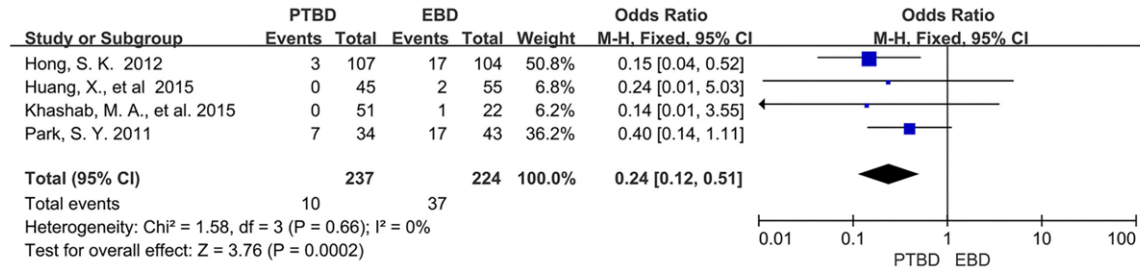


Figure 2. Forest plots of procedure-related hyperamylasaemia. CI, confidence interval.

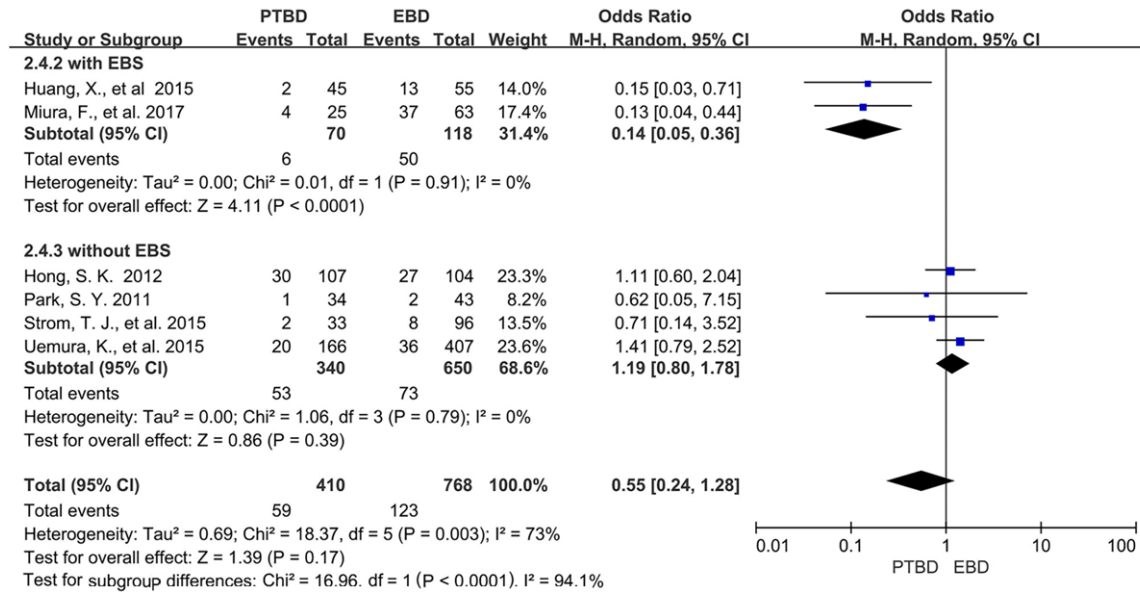


Figure 3. Forest plots of post-operative pancreatic leakage. CI, confidence interval.

effect model to pool the HR. The pooled data demonstrated that PTBD was associated with a worse prognosis (HR=1.43, 95% CI 1.18-1.72, P=0.0002) (Table 2; Figure 4).

### Other complications

Regarding procedure-related complications, no significant differences in bleeding (Figure 5A) or cholangitis (Figure 5B) were observed between the PTBD and EBD groups. Regarding post-operative parameters, no significant differences in the rates of total post-operative complications (Figure 6A), wound infection (Figure 6B), intra-abdominal infection (Figure 6C), bleeding (Figure 6D), delayed gastric emptying (Figure 6E), or 30-day mortality (Figure 6F) were found between the PTBD and EBD groups.

### Subgroup analysis, sensitivity analysis, and assessment of risk of bias

The subgroup analysis showed higher incidence rates of pre-operative pancreatic leakage in the EBD group than in the PTBD group among patients with EBS (OR=0.14, 95% CI=0.05-0.36, P<0.0001) and among patients without EBS (OR=1.19, 95% CI=0.80-1.78, P=0.39) (Table 2). A meta-analysis by Lin H et al. [15] found that ENBD is superior to EBS for treating malignant biliary obstruction in terms of the pre-operative cholangitis rate, the post-operative pancreatic fistula rate, and morbidity. Therefore, EBS may be a source of heterogeneity. The sensitivity analysis suggested that the data in this meta-analysis were relatively stable. Publication bias was small, as shown by the fact that the points on the funnel plots were



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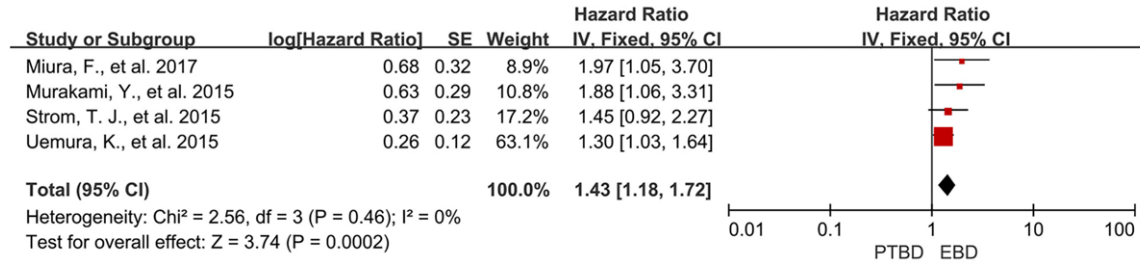


Figure 4. Forest plots of overall survival. CI, confidence interval.

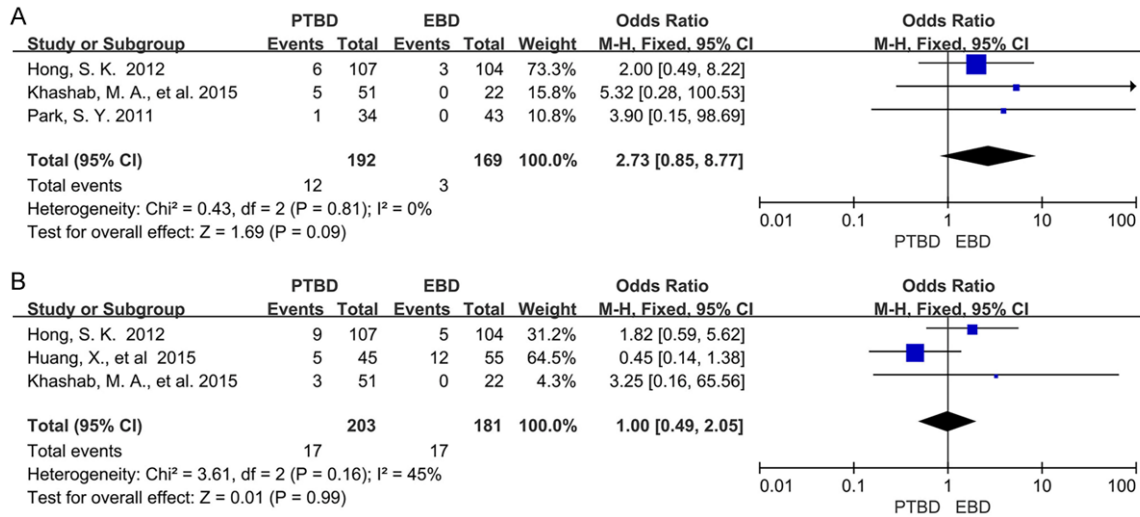


Figure 5. Negative procedure-related complications: (A) Forest plots of procedure-related bleeding; (B) Forest plots of procedure-related cholangitis. CI, confidence interval.

substantially symmetric (Figure 7, illustrating funnel plots for post-operative intra-abdominal infection).

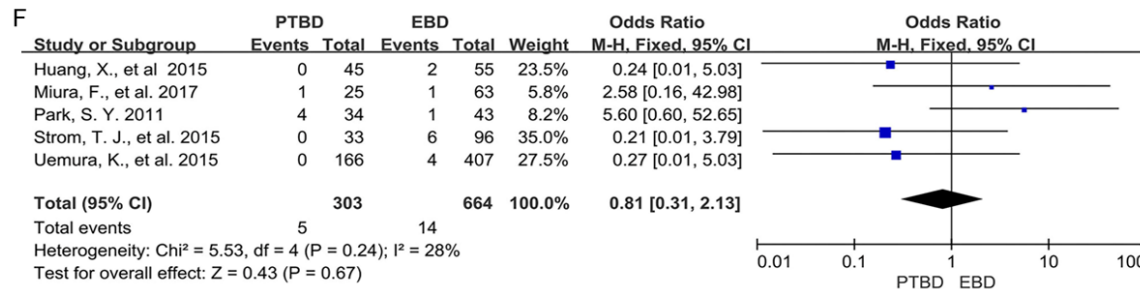
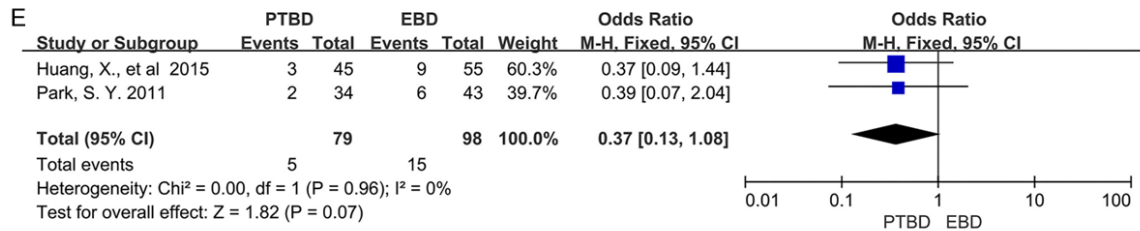
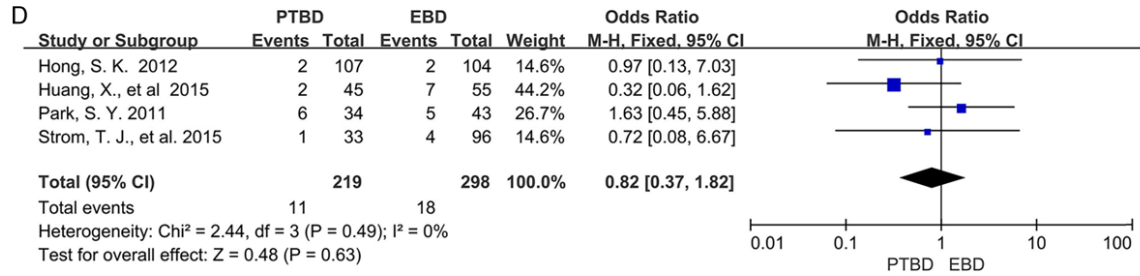
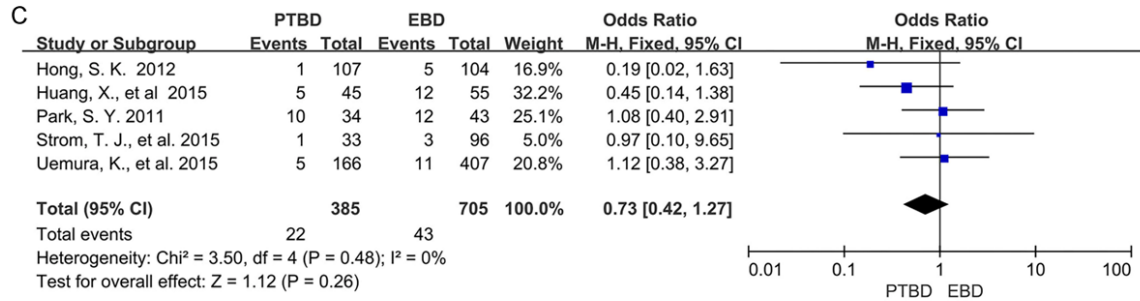
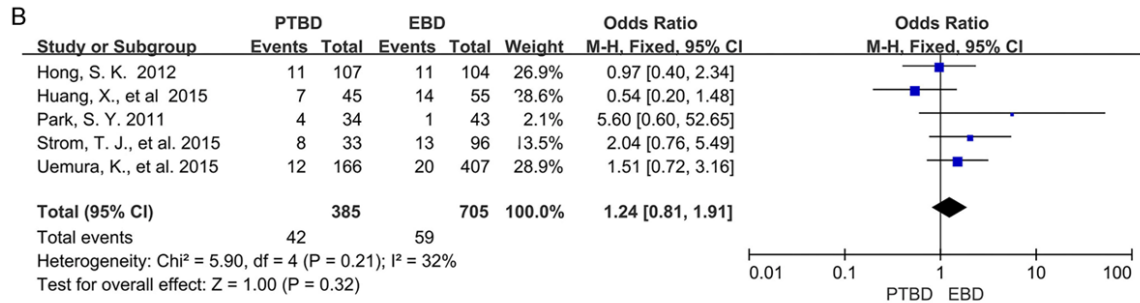
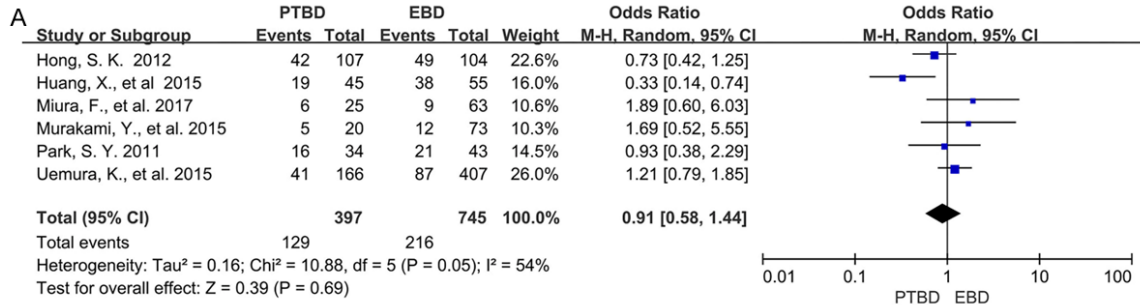
### Discussion

Although the only curative treatment for PAC is radical resection (e.g., pancreaticoduodenectomy), many patients are unable to undergo elective surgery immediately after a diagnosis of cancer due to obstructive jaundice, severe infection, or other reasons. Therefore, drainage is very necessary. The drainage options for PBD in PAC are PTBD and EBD. EBD is beneficial due to its advantages regarding cosmetic appeal and non-invasiveness [16], and EBD is generally believed to be more appropriate than PTBD. However, the rate of therapeutic or technical failure is likely to be higher for EBD than for PTBD [10]; thus, an alternative drainage procedure is needed. Both of these drainage types have advantages and disadvantages.

The present meta-analysis was performed to assess the safety and efficacy of PTBD and EBD.

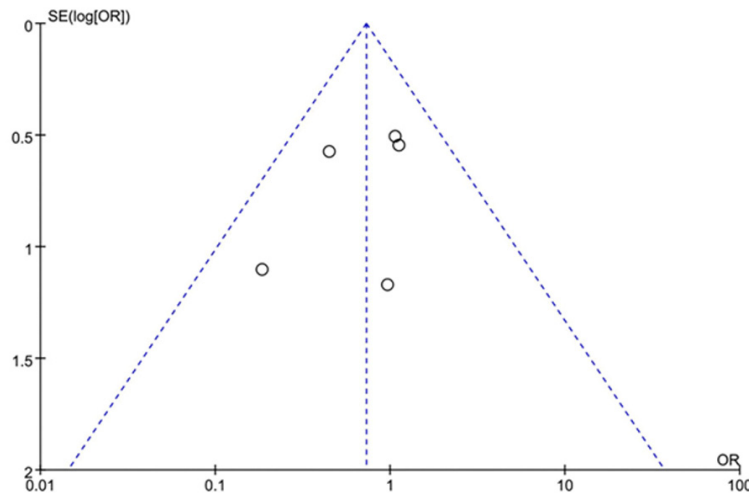
The present meta-analysis demonstrated that PTBD was associated with a lower procedure-related hyperamylasaemia rate ( $\text{OR} = 0.24$ ,  $95\% \text{ CI} = 0.12-0.51$ ,  $P = 0.0002$ ) and a lower post-operative pancreatic fistula rate than EBD ( $\text{OR} = 0.57$ ,  $95\% \text{ CI} = 0.33-0.98$ ,  $P = 0.04$ ). The placement of stents or drainage tubes in the biliary tract could lead to obstruction of the adjacent pancreatic orifice and restrict the outflow of pancreatic fluid, representing a potential risk for hyperamylasaemia or pancreatitis [15]. Perforations, ulcers, and stent dysfunction due to endoscopic sphincterotomy are always associated with pancreatitis and other complications [17]. The stents or drainage tubes used for EBD, which lead to intestinal bacteria retrograde infection, not only result in biliary tract infections and pre-operative chol-

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**Figure 6.** Negative post-operative complications: (A) Forest plots of total post-operative complications; (B) Forest plots of post-operative wound infection; (C) Forest plots of post-operative intra-abdominal infection; (D) Forest plots of post-operative bleeding; (E) Forest plots of post-operative delayed gastric emptying; (F) Forest plots of post-operative 30-day mortality. CI, confidence interval.



**Figure 7.** Funnel plot of post-operative intra-abdominal infection.

angitis but also pose the risk of post-operative infectious complications [18]. In addition, according to the clinical experience of surgeons, oedema often occur in the head of the pancreas and the peri-duodenum in patients who have undergone EBD, which would increase the incidence of peri-operative complications. Therefore, patients in the EBD group are more prone to pancreatic fistula than those in the PTBD group.

Thus, PTBD may likely be more effective and safer than EBD; however, EBD results in increased survival. A literature review using a propensity score-matching analysis found that PTBD is oncologically inferior to EBD, possibly due to catheter-related seeding metastasis [19]. EBD is routed through the bile duct, and PTBD is routed through the percutaneous area and peritoneal cavity; therefore, the leakage of bile-containing exfoliated cancer cells in PTBD is more likely to lead to seeding metastasis. Cytological results in patients with distal cholangiocarcinoma are often positive, which also results in seeding metastasis [19-21]. Although the included studies did not mention seeding metastasis, a meta-analysis of hilar cholangiocarcinoma confirmed that PTBD may increase the risk of PTBD tract seeding metastasis because it confers a poor prognosis, even with subsequent resection of the recurrence [5].

In clinical practice, the choice of drainage scheme is biased; due to their comfort level and the noninvasive nature of EBD, surgeons are more likely to choose this method. Furthermore, as another source of bias, EBD is more demanding in terms of the patient's physical condition; therefore, patients in better physical condition are more likely to be included in the EBD group. Due to the higher surgical skill requirement and the risk of failure, PTBD often becomes an alternative drainage scheme for EBD [8, 10]. In this case, the physical condition of

patients in the PTBD group may be worse than that of patients in the EBD group, possibly explaining the shorter survival of the patients in the PTBD group.

In summary, PTBD shows obvious advantages in terms of peri-operative complication rates involving procedure-related hyperamylasaemia and post-operative pancreatic fistula. However, EBD provides superior survival; therefore, we advocate using EBD over PTBD for patients undergoing pancreaticoduodenectomy.

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### Disclosure of conflict of interest

None.

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