

# The safety and efficacy of nasobiliary drainage versus biliary stenting in malignant biliary obstruction

A systematic review and meta-analysis

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#### Abstract

**Background:** Preoperative biliary drainage (PBD) has been widely used to treat patients with malignant biliary obstruction. However, it is still unclear which method of PBD (endoscopic nasobiliary drainage or endoscopic biliary stenting) is more effective. Thus, we carried out a meta-analysis to compare the safety and efficacy of endoscopic nasobiliary drainage (ENBD) and endoscopic biliary stenting (EBS) in malignant biliary obstruction in terms of preoperative and postoperative complications.

**Methods:** We conducted a literature search of EMBASE databases, PubMed, and the Cochrane Library to identify relevant available articles that were published in English, and we then compared ENBD and EBS in malignant biliary obstruction patients. The preoperative cholangitis rate, the preoperative pancreatitis rate, the incidence of stent dysfunction, the postoperative pancreatic fistula rate, and morbidity were analyzed. Odds ratios (ORs) with 95% confidence intervals (Cls) were used to express the pooled effect on dichotomous variables, and the pooled analyses were performed using RevMan 5.3.

**Results:** Seven published studies (n=925 patients) were included in this meta-analysis. We determined that patients with malignant biliary obstruction who received ENBD had reductions in the preoperative cholangitis rate (OR=0.35, 95% CI=0.25–0.51, P < 0.0001), the postoperative pancreatic fistula rate (OR=0.38, 95% CI=0.18–0.82, P=0.01), the incidence of stent dysfunction (OR=0.39, 95% CI=0.28–0.56, P < 0.0001), and morbidity (OR=0.47, 95% CI=0.27–0.82, P=0.008) compared with patients who received EBS.

**Conclusions:** The current meta-analysis suggests that ENBD is better than EBS for malignant biliary obstruction in terms of the preoperative cholangitis rate, the postoperative pancreatic fistula rate, the incidence of stent dysfunction, and morbidity. However, a limitation is that there are no data from randomized controlled trials.

**Abbreviations:** CI = confidence intervals, EBD = endoscopic biliary drainage, EBS = endoscopic biliary stenting, ENBD = endoscopic nasobiliary drainage, HCA = hilar cholangiocarcinoma, MBO = malignant biliary obstruction, PBD = preoperative biliary drainage, POPF = postoperative pancreatic fistula, PTCD = percutaneous transhepatic cholangial drainage, RCTs = randomized controlled trials, OR = odds ratio.

Keywords: endoscopic biliary stenting, endoscopic nasobiliary drainage, malignant biliary obstruction, preoperative biliary drainage

# 1. Introduction

Malignant biliary obstruction (MBO) is invariably attributable to carcinoma of Vater's ampulla, pancreatic carcinoma, hilar

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Ethical approval was not necessary, as this study is a "Systematic Review and Meta-analysis."

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cholangiocarcinoma (HCA), and metastatic disease, and the only curative treatment for MBO is surgical resection. The highest incidence of MBO is in Asia, and it is associated with a poor prognosis for patients, whose median survival is only 1 to 4 years after surgery.<sup>[1]</sup> Regardless of whether a patient receives a pancreaticoduodenectomy or HCA surgery, which has been deemed the standard of care, MBO is associated with significant mortality and morbidity. Moreover, obstructive jaundice resulting from MBO may lead to coagulopathy, liver function decline, and pre- or postoperative cholangitis.<sup>[2]</sup> As the severity of the disease increases, there are more complications, such as renal dysfunction, hepatic failure, and other adverse outcomes.<sup>[3]</sup>

Preoperative biliary drainage, which added a new dimension to the management of MBO, has been widely used on a variety of patients in many clinical centers to resolve jaundice, improve clinical outcomes, and decrease postoperative complications.<sup>[4]</sup> Several studies have indicated that biliary drainage is associated with improvements in the postoperative mortality, morbidity, and resection rate of patients.<sup>[5]</sup> There are three types of PBD endoscopic nasobiliary drainage, endoscopic biliary stenting, and percutaneous transhepatic cholangial drainage (PTCD).

PTCD is not recommended as the initial method of PBD due to the risk of tumor seeding and other adverse events, in addition to

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the discomfort of patients receiving such invasive treatment.<sup>[6]</sup> It is still unclear whether ENBD or EBS is more effective and safe for use in MBO patients. Thus, we carried out a meta-analysis to compare the safety and efficacy of ENBD and EBS in MBO treatment in terms of pre- and postoperative complications.

#### 2. Methods

#### 2.1. Search strategy

We conducted a literature search of the EMBASE, PubMed, and Cochrane Library databases to identify relevant available articles published in English between database inception and May 2016. The search terms included "nasobiliary drainage," "nasobiliary catheter," "nasobiliary drain," and "ENBD" combined with the terms "internal endoscopic biliary drainage," "internal EBD," "endoscopic biliary stenting," "EBS," "endoscopic retrograde biliary drainage," "ERBD," "stent," and "stenting." We also reviewed the reference lists of the included studies for undetected relevant studies. We contacted the original authors to obtain extra information if necessary.

#### 2.2. Inclusion criteria

The inclusion criteria were as follows: original research from observational studies or randomized controlled trials (RCTs) in adults; the interventions of interest were ENBD and EBS; the participants of interest were patients suffering from MBO before surgery; an odds ratio (OR) with a 95% confidence interval (95% CI) for the risk of pre- and postoperative complications from PBD was provided or could be calculated; and the most recent and complete study was included if the data from the same population had been published more than once.

Two investigators searched and reviewed all identified studies independently. If the 2 investigators could not reach a consensus about the eligibility of an article, it was resolved by consulting with a third reviewer.

#### 2.3. Data extraction and quality assessment

The following data were independently extracted from each study by 2 investigators: the first author's name, the publication year, the country where the study was performed, the study design, the size of the drainage tube, the age range or mean age at baseline, the number of participants and deaths, pre- and postoperative complications, and stent or drainage dysfunction.

The Newcastle–Ottawa Scale, an instrument for evaluating the quality of observational studies, was used to assess each of the included studies based on population selection, study comparability and outcome of the report.<sup>[7]</sup> Except for 1 conference abstract that provided the necessary data, each study was awarded a score of 1 point to 9 points.

#### 2.4. Statistical analysis

The meta-analysis was conducted using RevMan software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). ORs with a 95% CI were calculated to compare the incidence of pre- and postoperative complications between the ENBD group and the EBS group. Heterogeneity among the included studies was qualitatively evaluated using a  $\chi$ 2-based Q test. *P* values less than 0.05 showed that there was statistically significant heterogeneity across the studies. The level of heterogeneity between studies was evaluated

using  $I^2$  statistics.  $I^2 < 30\%$  was considered to be low heterogeneity, and a fixed-effects model was applied; 30%  $\leq I^2 \leq 50\%$  was considered to be moderate heterogeneity; and  $I^2 > 50\%$  represented high heterogeneity. A random-effects model was applied when  $I^2 \geq 30\%$ . Sensitivity analysis was performed by removing 1 study at a time to assess whether the results could have been markedly affected by a single study. The publication bias was assessed using funnel plots.

#### 3. Results

#### 3.1. Search results and study characteristics

A total of 612 articles were retrieved by searching electronic databases and manually searching relevant reference lists. After duplicates were identified and excluded, 527 articles remained. We then excluded unrelated reviews, case reports, systematic reviews and meta-analyses, as well as studies that were clearly irrelevant based on their title or abstract; 50 articles remained. Of these, 7 articles<sup>[8–14]</sup> (6 case–control studies and 1 conference abstract) were used in this meta-analysis. The detailed steps of our literature search are shown in Fig. 1. Seven studies with a total of 925 patients were included in the final analysis. The sample sizes of all included studies ranged from 55 to 419. In total, 430 patients (46%) received ENBD, and 495 patients received EBS. Five studies came from Japan, 1 came from China, and 1 came from South Korea. The characteristics of these studies are presented in Table 1.

### 3.2. Incidence of preoperative cholangitis

Data from the  $7^{[8-14]}$  articles including 430 cases in the ENBD group and 495 cases in the EBS group were used in this metaanalysis. Three studies<sup>[8–9,11]</sup> reported that ENBD decreased the incidence of preoperative cholangitis before standard resection or palliative surgery compared with EBS, while no significant association was reported in 4 studies.<sup>[10,12–14]</sup> Moderate heterogeneity ( $I^2$ =31%, P=0.19) was found, so we chose a random-effect model to pool the OR. Overall, the pooled data demonstrated that ENBD was associated with a low incidence of preoperative cholangitis (OR=0.35, 95% CI=0.25–0.51, P<0.0001) in the MBO patients (Fig. 2).

#### 3.3. Incidence of preoperative pancreatitis

Data from 5 articles,<sup>[8–10,12–13]</sup> including 367 cases in the ENBD group and 381 cases in the EBS group, were used in this metaanalysis. All 5 studies reported that there was no significant difference in the incidence of preoperative pancreatitis between the ENBD and EBS groups. No heterogeneity ( $I^2=0\%$ , P=0.91) was found, so we chose a fixed-effect model to pool the OR. Overall, the pooled data demonstrated that neither ENBD nor EBS was associated with a significantly lower incidence of preoperative pancreatitis (OR=0.75, 95% CI=0.44–1.28, P=0.29) in MBO patients (Fig. 3).

# 3.4. Stent dysfunction rate

Five of the 7 studies,<sup>[8,9,12-14]</sup> including 362 cases in the ENBD group and 386 cases in the EBS group, reported a stent dysfunction rate. Three studies<sup>[8,12,13]</sup> reported that ENBD reduced the incidence of preoperative stent dysfunction compared with EBS, but the results from 2 studies,<sup>[9,14]</sup> showed little statistical difference. Low heterogeneity ( $I^2$ =1%, P=0.40) was

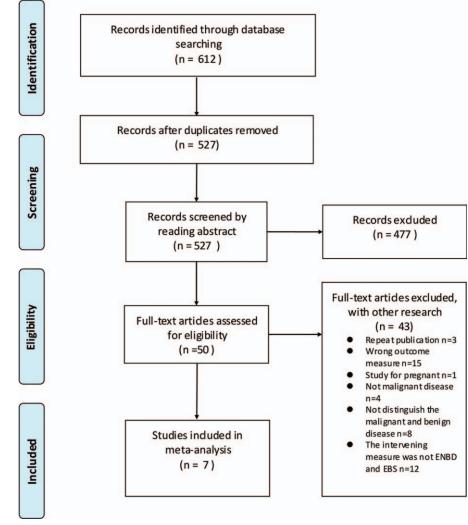


Figure 1. Flow chart for the study selection.

found, so we chose a fixed-effect model to pool the OR. Overall, the pooled data demonstrated that ENBD was associated with a low incidence of stent dysfunction (OR=0.39, 95% CI= 0.28-0.56, P<0.0001) in MBO patients (Fig. 4).

# 3.5. Morbidity

Four studies was used to assess morbidity,<sup>[8-10,14]</sup> which was defined as the incidence of all pre and postoperative complications.

# Although 3 studies<sup>[9,10,14]</sup> showed that ENBD had no significant advantage in terms of morbidity compared with EBS, the pooled results had no heterogeneity $(I^2=0\%, P=0.59)$ and showed that ENBD had a significantly lower incidence of morbidity than EBS (OR=0.47, 95% CI=0.27-0.82, P=0.008) (Fig. 5).

# 3.6. Postoperative Pancreatic Fistula (POPF)

The meta-analysis was used to assess the effect of POPF in 2 trials.<sup>[10,11]</sup> The pancreatic fistula rate was significantly lower in

# Table 1

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			Participants		Sex		The size of tube (Fr)		Age (mean and SD or range)			
Study	Country	Study design	ENBD	EBS	Male	Female	ENBD	EBS	ENBD	EBS	Total quality score	
Kawakami et al <sup>[8]</sup>	Japan	RC	60	20	60	20	5–7	7–8.5	71 (45–81)	70 (59–77)	7	
Sugiyama et al <sup>[9]</sup>	Japan	RC	38	38	19	57	NA	NA	69 (40-85)	68 (49-80)	6	
Huang et al <sup>[10]</sup>	China	RC	18	37	40	15	7	10	$60.6 \pm 8.4$	58.1 ± 8.3	7	
Fujii et al <sup>[11]</sup>	Japan	RC	50	72	76	46	5-7	5	66.5 (39-83)	67 (38-84)	7	
Sasahira et al <sup>[12]</sup>	Japan	RC	166	253	106	60	NA	NA	70 (63–76)	69 (62-75)	7	
Kawakubo et al <sup>[13]</sup>	Japan	RC	85	33	74	44	NA	NA	$69 \pm 9$ for a	all patients	6	
Jo et al <sup>[14]</sup>	South Korea	CA	13	42	NA	NA	NA	NA	NA	NA	NA	

CA=conference abstract, EBS=endscopic billiary stenting, ENBD=endoscopic nasobiliary drainage, NA=data not applicable, RC=retrospective case-control study.

	ENB	D	EBS			<b>Odds Ratio</b>	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.2.1 preoperative ch	olangitis						
Fujii et al 2015	6	50	22	72	7.8%	0.31 [0.12, 0.83]	
Huang et al 2015	4	18	8	37	2.0%	1.04 [0.27, 4.03]	
JO J et al 2015	1	13	7	42	1.5%	0.42 [0.05, 3.74]	
Kawakami et al 2011	12	60	13	20	7.7%	0.13 [0.04, 0.41]	
Kazumichi et al 2016	25	85	12	33	6.0%	0.73 [0.31, 1.70]	
Naoki et al 2016	16	166	69	253	24.4%	0.28 [0.16, 0.51]	
Sugiyamal et al 2013	2	38	5	38	2.3%	0.37 [0.07, 2.02]	
Subtotal (95% CI)		430		495	51.8%	0.35 [0.25, 0.51]	•
Total events	66		136				1000
Heterogeneity: Chi <sup>2</sup> = 8	3.69, df = 6	6 (P = 0)	.19);  2 = 3	31%			
Test for overall effect: 2	Z = 5.57 (F	> < 0.00	0001)				
1.2.2 hilar cholangioc	arcinoma						
Kawakami et al 2011	12	60	13	20	7.7%	0.13 [0.04, 0.41]	
Kazumichi et al 2016	25	85	12	33	6.0%	0.73 [0.31, 1.70]	
Subtotal (95% CI)		145		53	13.7%	0.40 [0.21, 0.75]	•
Total events	37		25			S 8	
Heterogeneity: Chi <sup>2</sup> = 5	5.58, df = 1	1 (P = 0)	.02);  2 =	82%			
Test for overall effect:	Z = 2.82 (F	= 0.00	)5)				
1.2.3 malignant distal	biliary of	ostruct	ion				
Fujii et al 2015	6	50	22	72	7.8%	0.31 [0.12, 0.83]	
Naoki et al 2016	16	166	69	253	24.4%	0.28 [0.16, 0.51]	
Sugiyamal et al 2013	2	38	5	38	2.3%	0.37 [0.07, 2.02]	
Subtotal (95% CI)	(73)	254	Q.7.,	363	34.5%	0.30 [0.18, 0.48]	•
Total events	24		96			N. 588 N.	
Heterogeneity: Chi <sup>2</sup> = 0	0.09, df = 2	2(P = 0)	.96); l <sup>2</sup> =	0%			
Test for overall effect: 2				C. 2020A			
Total (95% CI)		829		911	100.0%	0.34 [0.26, 0.44]	•
Total events	127		257				
Heterogeneity: Chi <sup>2</sup> = 1		11 (P =	and the second	= 26%			
Test for overall effect: 2				_0,0			0.01 0.1 1 10 100
Test for subaroup diffe				(P = 0)	75) $l^2 = 0^6$	2/0	ENBD EBS

Figure 2. Forest plots of preoperative cholangitis rates. Squares indicate study-specific odds ratios (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; and the diamond indicates the summary relative risk estimate with its 95% CI. CI = confidence interval, OR = odds ratio.

the ENBD group than in the EBS group (OR = 0.38, 95% CI = 0.18–0.82, P=0.01) based on the pooled data, which showed no heterogeneity ( $I^2$ =0%, P=0.59) (Fig. 6).

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

Subgroup analysis showed a higher incidence of preoperative cholangitis in the EBS group than in the ENBD group among HCA patients (OR=0.40, 95% CI=0.21-0.75, P=0.005) and malignant distal biliary obstruction patients (OR=0.34, 95% CI = 0.26 - 0.44, P < 0.00001) (Fig. 2). The stent dysfunction rate was also higher in the EBS group than in the ENBD group among HCA patients (OR = 0.26, 95% CI = 0.13-0.50, P < 0.0001) and malignant distal biliary obstruction patients (OR=0.46, 95% CI=0.30-0.71, P=0.0004) (Fig. 4). There was no significant difference in the preoperative pancreatitis rate between ENBD and EBS in HCA patients (OR=0.62, 95% CI=0.24-1.60, P= (0.32) or malignant distal biliary obstruction patients (OR = 0.77, 95% CI=0.40-1.50, P=0.44) (Fig. 3). Sensitivity analysis suggested that the data in this meta-analysis were relatively stable. Funnel plots for the preoperative cholangitis rate, the preoperative pancreatitis rate, the incidence of stent dysfunction, and morbidity were drawn (see Figures, Supplemental Content 1-4, http://links.lww.com/MD/B401, which illustrate funnel plots for preoperative cholangitis rate, preoperative pancreatitis rate, incidence of stent dysfunction, and morbidity). The publication bias was small because the points on the funnel plots were substantially symmetric. A funnel plot for POPF was not made due to the small number of studies.

# 4. Discussion

The management of biliary cancer and pancreatic head cancer is becoming increasingly diversified and effective due to the increased success rate of surgical resection, advances in interventional radiology therapy, and the use of chemotherapy for inoperable cancers.<sup>[15–17]</sup> Nevertheless, the feasibility of surgery or other treatments depends not only on the TNM staging or the size of the tumor but also on the jaundice that arises from biliary obstruction, basic characteristic of patients, and other concomitant disease. If bile duct obstruction cannot be relieved, many patients may not be able to receive further treatment.<sup>[13]</sup> To further improve the therapeutic efficacy for treating MBO, the primary concern for surgeons has been how to achieve the most drainage.

Endoscopic biliary drainage (EBD), which is beneficial due to its advantages in cosmetic appeal<sup>[18]</sup> and noninvasiveness, is generally believed to be more appropriate than PTCD. Although for decades there has been no clear consensus about the safety

	ENB	D	EBS			<b>Odds Ratio</b>	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
2.1.1 preoperative par	ncreatitis						
Huang et al 2015	1	18	1	37	1.0%	2.12 [0.12, 35.93]	
Kawakami et al 2011	2	60	1	20	2.4%	0.66 [0.06, 7.64]	
Kazumichi et al 2016	12	85	7	33	14.1%	0.61 [0.22, 1.72]	
Naoki et al 2016	14	166	26	253	30.7%	0.80 [0.41, 1.59]	
Sugiyamal et al 2013	0	38	1	38	2.4%	0.32 [0.01, 8.22]	
Subtotal (95% CI)		367		381	50.5%	0.75 [0.44, 1.28]	-
Total events	29		36				
Heterogeneity: Chi <sup>2</sup> = 0	.98, df = 4	(P = 0)	.91); l <sup>2</sup> =	0%			
Test for overall effect: 2	Z = 1.07 (F	P = 0.29	))				
2.1.2 hilar cholangioc	arcinoma						
Kawakami et al 2011	2	60	1	20	2.4%	0.66 [0.06, 7.64]	
Kazumichi et al 2016	12	85	7	33	14.1%	0.61 [0.22, 1.72]	
Subtotal (95% CI)		145		53	16.4%	0.62 [0.24, 1.60]	
Total events	14		8				/ //////
Heterogeneity: Chi <sup>2</sup> = 0	0.00, df = 1	(P = 0)	.96); l <sup>2</sup> =	0%			
Test for overall effect: 2	Z = 0.99 (F	P = 0.32	2)				
2.1.3 malignant distal	biliary ob	structi	ion				
Naoki et al 2016	14	166	26	253	30.7%	0.80 [0.41, 1.59]	
Sugiyamal et al 2013	0	38	1	38	2.4%	0.32 [0.01, 8.22]	
Subtotal (95% CI)	35	204		291	33.1%	0.77 [0.40, 1.50]	
Total events	14		27				
Heterogeneity: Chi <sup>2</sup> = 0	).29, df = 1	(P = 0)	.59); l <sup>2</sup> =	0%			
Test for overall effect: 2							
Total (95% CI)		716		725	100.0%	0.73 [0.50, 1.08]	•
Total events	57		71				
Heterogeneity: Chi <sup>2</sup> = 1		P = 0		0%			
Test for overall effect: 2	and the second sec						0.01 0.1 1 10 10
Test for subaroup diffe			1	P = 0	93) $I^2 = 0^9$	2/0	ENBD EBS

Figure 3. Forest plots of preoperative pancreatitis. Squares indicate study-specific odds ratios (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; and the diamond indicates the summary relative risk estimate with its 95% CI. CI=confidence interval, OR=odds ratio.

and efficacy of EBD in MBO, EBD has been widely used in patients who are unable to undergo elective surgery immediately after a diagnosis of cancer due to obstructive jaundice or other reasons. There are 2 types of EBD (ENBD and EBS), and no systematic examination has been performed to determine which is more appropriate for treating MBO. The present meta-analysis was performed to assess the safety and efficacy of ENBD and EBS.

ENBD is an external procedure that drains out the bile and decompresses the biliary obstruction, which is convenient for bile cytology<sup>[19]</sup> and cholangiography, whereas EBS makes diagnosis via the output of bile more difficult. Although discomfort in the throat would prevent ENBD from being an initial drainage method, the major advantage of ENBD is the lower incidence of preoperative cholangitis and other complications. A previous meta-analysis and other RCTs,<sup>[20-23]</sup> which enrolled both benign and MBO participants, reported no significant difference between ENBD and EBS in terms of preoperative cholangitis and other complications, whereas the present meta-analysis demonstrated that ENBD was associated with a lower preoperative cholangitis rate (OR=0.35, 95% CI=0.25-0.51, P< 0.0001) and morbidity (OR=0.47, 95% CI=0.27-0.82, P= 0.008), which was supported by other studies.<sup>[24-26]</sup> The stents used for EBS, which connect the biliary tract and the duodenum, could become clogged due to intestinal microbes and reverse the flow of food when used for distal malignant obstruction. This is not only one of the reasons why biliary tract infections and preoperative cholangitis occur but also a potential risk of postoperative infectious complications.<sup>[11]</sup> Meta-analysis showed that stent dysfunction occurred more often in the EBS group (OR = 0.39, 95% CI=0.28–0.56, P < 0.0001) than in the ENBD group, as well as the causes of dysfunction were stent occlusion in EBS and dislocation in ENBD.<sup>[8]</sup> Therefore, it is not surprising that ENBD is associated with a lower rate of preoperative cholangitis and other infectious complications.

As an internal biliary drainage method, EBS has advantages for hepatic function and immune function by preserving enterohepatic circulation, thereby maintaining metabolism and vitamin absorption.<sup>[12,13]</sup> Another advantage of EBS is the absence of discomfort in the pharynx and nasal cavities compared with ENBD. Son et al<sup>[27]</sup> reported that a short-duration treatment was more appropriate in patients with periampullary cancer and was associated with fewer preoperative complications. The time needed for EBS was always longer than that needed for other PBD methods, which lead to prolonged hospital stays and an increased probability of infection.<sup>[10]</sup> In addition, meta-analysis revealed that the pancreatic fistula rate was significantly higher in the EBS group than in the ENBD group (OR=0.38, 95% CI=0.18-0.82, P=0.01). Fujii et al<sup>[11]</sup> found that EBS was an independent predictive factor of pancreatic fistula, and POPF was found to be a reason for abdominal and surgical site infections.<sup>[28,29]</sup> Although this observation may result from the biases of pooling small-sample studies, it would affect the choice of surgeon.

Furthermore, the incidence of preoperative pancreatitis was higher in the EBS group than in the ENBD group even though the present meta-analysis and other studies showed no significant difference.<sup>[8,9,12,13]</sup> In a high-volume prospective study, Wilcox

	ENB	D	EBS	5		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl	
3.1.1 stent dysfunctio	n							
JO J et al 2015	1	13	7	42	1.5%	0.42 [0.05, 3.74]		
Kawakami et al 2011	15	60	13	20	7.2%	0.18 [0.06, 0.53]		
Kazumichi et al 2016	28	85	20	33	9.5%	0.32 [0.14, 0.73]		
Naoki et al 2016	30	166	88	253	28.2%	0.41 [0.26, 0.66]		
Sugiyamal et al 2013	10	38	12	38	4.4%	0.77 [0.29, 2.09]		
Subtotal (95% CI)		362		386	50.8%	0.39 [0.28, 0.56]	◆	
Total events	84		140				2 C 1	
Heterogeneity: Chi <sup>2</sup> = 4	.06, df = 4	(P = 0)	.40);  2 =	1%				
Test for overall effect: 2	Z = 5.18 (F	> < 0.00	0001)					
3.1.2 hilar cholangioc	arcinoma							
Kawakami et al 2011	15	60	13	20	7.2%	0.18 [0.06, 0.53]	n n <u></u> n	
Kazumichi et al 2016	28	85	20	33	9.5%	0.32 [0.14, 0.73]		
Subtotal (95% CI)		145		53	16.7%	0.26 [0.13, 0.50]	◆	
Total events	43		33					
Heterogeneity: Chi <sup>2</sup> = 0	.68, df = 1	(P = 0)	.41);  2 = 1	0%				
Test for overall effect: 2	Z = 4.02 (F	> < 0.00	001)					
3.1.3 malignant distal	biliary ob	ostructi	on					
Naoki et al 2016	30	166	88	253	28.2%	0.41 [0.26, 0.66]		
Sugiyamal et al 2013	10	38	12	38	4.4%	0.77 [0.29, 2.09]		
Subtotal (95% CI)		204		291	32.5%	0.46 [0.30, 0.71]	▲	
Total events	40		100				2.1	
Heterogeneity: Chi <sup>2</sup> = 1		(P = 0)		20%				
Test for overall effect: 2	and the second second							
Total (95% CI)		711		730	100.0%	0.39 [0.31, 0.51]	•	
Total events	167		273					
Heterogeneity: Chi <sup>2</sup> = 8		B(P = 0)	Second Second	1%				
Test for overall effect: 2		•					0.01 0.1 1 10	100
Test for subaroup differ	Sector Sector			(P = 0)	$(35) I^2 = 4$	5%	ENBD EBS	

Figure 4. Forest plots of stent dysfunction rates. Squares indicate study-specific odds ratios (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; and the diamond indicates the summary relative risk estimate with its 95% CI. CI=confidence interval, OR=odds ratio.

	ENB	D	EBS	5		<b>Odds Ratio</b>			Odds	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, Fixed, 95% Cl				
Huang et al 2015	11	18	27	37	18.8%	0.58 [0.18, 1.92]			-	_		
JO J et al 2015	2	13	18	42	19.7%	0.24 [0.05, 1.23]				-		
Kawakami et al 2011	23	60	13	20	32.8%	0.33 [0.12, 0.96]		-	-			
Sugiyamal et al 2013	13	38	16	38	28.7%	0.71 [0.28, 1.81]			-	-		
Total (95% CI)		129		137	100.0%	0.47 [0.27, 0.82]			٠			
Total events	49		74									
Heterogeneity: Chi <sup>2</sup> = 1	.94, df = 3	B(P=0)	.59); l <sup>2</sup> = 1	0%				1			10	100
Test for overall effect: 2	Z = 2.65 (F	P = 0.00	0.01	0.1	ENBD	EBS	10	100				

Figure 5. Forest plots of morbidity. Squares indicate study-specific odds ratios (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; and the diamond indicates the summary relative risk estimate with its 95% CI. CI = confidence interval, OR = odds ratio.

	ENB	D	EBS	5		Odds Ratio		Odd	s Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I	M-H, Fix	ed, 95%	CI	
Fujii et al 2015	8	50	26	72	76.6%	0.34 [0.14, 0.83]		_			
Huang et al 2015	3	18	10	37	23.4%	0.54 [0.13, 2.27]		-			
Total (95% CI)		68		109	100.0%	0.38 [0.18, 0.82]		+			
Total events	11		36								
Heterogeneity: Chi <sup>2</sup> =	0.30, df =	1 (P = (		- 01			10	100			
Test for overall effect:	Z = 2.47 (	P = 0.0	0.01	0.1 ENBD	EBS	10	100				

Figure 6. Forest plots of postoperative pancreatic fistula. Squares indicate study-specific odds ratios (the size of the square reflects the study-specific statistical weight); horizontal lines indicate 95% CIs; and the diamond indicates the summary relative risk estimate with its 95% CI. CI = confidence interval, OR = odds ratio.

et al<sup>[30]</sup> showed that EBS was one of the factors associated with pancreatitis. The placement of stents, especially large-bore stents, would lead to the obstruction of the adjacent pancreatic orifice and restrict the outflow of the pancreatic juice, which could be a potential risk for pancreatitis. In addition, an endoscopic sphincterotomy is routinely performed when placing large-bore plastic stents or self-expandable metal stents. Perforations, ulcers, and stent dysfunction due to endoscopic sphincterotomy are always associated with pancreatitis and other complications.<sup>[31]</sup> Nevertheless, the question of whether endoscopic sphincterotomies could lead to a higher incidence of pancreatitis is still debated when this procedure is also used in ENBD.

There were several limitations of this meta-analysis that should be taken into consideration when interpreting our results. First, we did not assess the impact of different types or stents and whether the procedure of endoscopic sphincterotomy was used in the procedure of drainage. Second, the number of included studies and the subgroup analysis were insufficient, and the study design was retrospective and lacked randomized controls. Third, because of limited information, the participants were all from Asia. Fourthly, self-expandable metal stents, which were not used in our enrolled studies, are reported to be associated with fewer complications and lower occlusion rates than plastic stents.<sup>[32–34]</sup> Finally, there could be a publication bias, which may influence the authenticity of our results.

# 5. Conclusions

Patients with MBO who are treated with ENBD have lower rates of preoperative cholangitis, postoperative pancreatic fistula, stent dysfunction, and morbidity than patients who are treated with EBS. The current meta-analysis suggests that ENBD is better than EBS for treating patients with MBO in terms of the preoperative cholangitis rate, the postoperative pancreatic fistula rate, the incidence of stent dysfunction, and morbidity. However, the method of biliary drainage in MBO is variable and depends upon various factors, such as the patient's clinical status and comfort, disease status, and the availability of technology and expertise, which should be taken into full consideration when interpreting our results. In addition, we still need further multicenter RCTs to prove our observations.

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