Internal drainage versus external drainage in palliation of malignant biliary obstruction: a meta-analysis and systematic review

Xiaopeng Tian[1,2], Zixuan Zhang[1], Wen Li[1,3]

[1]Medical School of Chinese PLA, Beijing, China
[2]Department of Gastroenterology, Xingtai People's Hospital, Xingtai, Hebei, China
[3]Department of Gastroenterology and Hepatology, Chinese PLA General Hospital, Beijing, China

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Corresponding author:
Wen Li
Department
of Gastroenterology
and Hepatology
Chinese PLA General Hospital
Medical School of Chinese PLA
28 Fuxing Road
Beijing 100853, China
Phone: +86 10 55499107
E-mail: liwen2000@yahoo.com

Abstract

Introduction: Preoperative biliary drainage has been widely used to treat patients with malignant biliary obstruction. However, it is still unclear which method is more effective: internal drainage or external drainage. Thus, we carried out a meta-analysis to compare the safety and efficacy of the two drainage methods in treatment of malignant biliary obstruction in terms of preoperative and postoperative complications.
Material and methods: We conducted a literature search of Medline, EMBASE, PubMed, Ovid journals and the Cochrane Library, and compared internal drainage and external drainage in malignant biliary obstruction patients. The pre- and postoperative complications, stent dysfunction rate and mortality were analyzed.
Results: Ten published studies (n = 1464 patients) were included in this meta-analysis. We found that patients with malignant biliary obstruction who received external drainage showed reductions in the preoperative cholangitis rate (OR = 0.33, 95% CI: 0.24–0.44, p < 0.00001), the incidence of stent dysfunction (OR = 0.41, 95% CI: 0.30–0.57, p < 0.00001), and total morbidity (OR = 0.34, 95% CI: 0.23–0.50, p < 0.00001) compared with patients who received internal drainage.
Conclusions: The current meta-analysis indicates that external drainage is better than internal drainage for malignant biliary obstruction in terms of the preoperative cholangitis rate, the incidence of stent dysfunction and total morbidity, etc. However, the findings need to be confirmed by randomized controlled trials.

Key words: malignant biliary obstruction, preoperative biliary drainage, internal drainage, external drainage, meta-analysis.

Introduction

Malignant biliary obstruction (MBO) is a common disease in the clinic that may be caused by the compression and invasion of malignant tumors or metastatic lymph nodes to biliary ducts. Common malignant tumors include primary carcinoma of the bile duct, gallbladder carcinoma, liver cancer, carcinoma of the head of the pancreas, ampullary carcinoma and other metastatic cancers. MBO has a poor prognosis, and its 5-year survival rate is estimated to be less than 5% [1]. Surgery should be the first choice of treatment for such patients, and the traditional method is to carry out tumor resection combined with choledochojejunostomy. However, those patients usually have severe jaundice when visiting the hospital. Some of them are suffering from severe cholangitis on the basis of jaundice, indicating a serious state of illness and poor systemic condition, which may result in an extremely low resection rate. In addition, patients may suffer relatively high postoperative complications and mortality. Even worse, some of the patients cannot tolerate palliative biliary tract decompression. With respect to the above, preoperative biliary drainage has been widely accepted in clinical practice and is used to decrease the severity of jaundice, thereby improving the prognosis of patients [2]. However, preoperative biliary drainage is still controversial in clinical practice [3, 4]. One of the major problems is that preoperative biliary drainage may lead to biliary drainage-related complications such as cholangitis, pancreatitis, hemorrhage, or perforation. Moreover, biliary drainage-related complications may introduce postoperative complications. Therefore, the selection and application of an appropriate method for drainage that is safer and more effective is an urgent problem to be solved. At present, there are two commonly used drainage methods: external drainage and internal drainage. External drainage mainly consists of percutaneous transhepatic biliary drainage (PTBD) and endoscopic nasobiliary drainage (ENBD), while internal drainage is predominantly endoscopic bile duct stenting (EBS). So far, it remains unclear whether internal drainage or external drainage is more appropriate for preoperative biliary drainage. Therefore, the present study was conducted to evaluate and compare the efficacy and safety of the two drainage methods in MBO treatment in terms of preoperative and postoperative complications, so as to provide a potential basis for clinical treatment options.

Material and methods

Search strategy

Two researchers conducted a literature search of the Medline, EMBASE, PubMed, Ovid journals and Cochrane Library databases to identify relevant available articles published in English between January 1980 and May 2017. The search strategy involved keyword search and subject headings retrieval. The search terms included "external drainage" or "nasobiliary drainage", "ENBD" or "percutaneous transhepatic biliary drainage", "PTBD" combined with the terms "internal drainage" or "endoscopic biliary stenting", "EBS", "endoscopic retrograde biliary drainage", "ERBD". A preliminary selection was conducted by screening titles and abstracts of the retrieved literature. Documents that met the inclusion criteria were then checked carefully in full detail to finally determine whether or not to incorporate them. To avoid missing useful information, we also reviewed the reference lists of the included studies for undetected relevant studies and contacted the original authors to obtain extra information if necessary.

Inclusion criteria

The inclusion criteria were as follows: included studies focused on the assessment of preoperative biliary drainage in patients with malignant biliary obstruction; the drainage methods were external drainage (PTBD or ENBD) and internal drainage (EBS); the outcomes included pre- and post-operative complications; original research from observational studies or randomized controlled trials. 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 a third reviewer.

Exclusion criteria

Subjects included in the study were patients with benign obstructive jaundice, or patients who were unable to undergo surgical treatment; the drainage method was only external drainage or internal drainage; repeated reports; the design was flawed, and the quality of the study was poor.

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 study design, the size of the drainage tube, the age range or mean age at baseline, pre- and postoperative complications, stent/tube dysfunction and mortality. Stent/tube dysfunction (occlusion or dislocation) is defined as the recurrence of biliary obstruction and jaundice and/or evidence of cholestasis confirmed by ultrasonography (US) or computed tomography (CT), requiring biliary re-intervention. The Newcastle-Ottawa Scale, an instrument for evaluating the quality of observational studies, was used to assess each of the included studies [5]. Each study was awarded a score of 1 point to 9 points (Table I).

Statistical analysis

When included studies were comparable, meta-analysis was performed, otherwise systematic review was conducted only. Dichotomous data are presented as the odds ratio (OR) with 95% confidence interval (CI). The heterogeneity among studies was tested using a χ^2-based Q test. If there was no significant heterogeneity ($p > 0.10$), the fixed effect model was applied for follow-up

Table I. Baseline characteristics and quality of included studies

Study	Study design	Participants			Sex		Size of tube (Fr)			Age (mean and SD or range)			Total quality score
		External drainage		Internal drainage	Male	Female	External drainage		Internal drainage	External drainage		Internal drainage	
		ENBD	PTBD	EBS			ENBD	PTBD	EBS	ENBD	PTBD	EBS	
Jung *et al.* [9]	RC	13	43	42	60	38	7	7–10	7–10	58.9 (42–77)	65 (40–82)	61.1 (29–80)	7
Sugiyama *et al.* [10]	RC	38	0	38	19	57	NA	–	NA	69 (40–85)	–	68 (49–80)	6
Huang *et al.* [11]	RC	18	45	37	71	29	7	10	10	60.6 ±8.4	57.5 ±10.1	58.1 ±8.3	7
Fujii *et al.* [12]	RC	50	0	72	76	46	5–7	–	5	66.5 (39–83)	–	67 (38–84)	7
Kishi *et al.* [13]	RC	28	99	44	135	36	NA	NA	NA	65 (44–80)	65 (31–82)	65 (43–86)	7
Sasahira *et al.* [14]	RC	166	0	253	106	60	NA	–	NA	70 (63–76)	–	69 (62–75)	7
Kawakami *et al.* [15]	RC	60	48	20	60	20	5–7	7–10	7–8.5	71 (45–81)	71 (45–81)	70 (59–77)	7
Kawakubo *et al.* [16]	RC	85	0	33	74	44	NA	–	NA	69 ±9 for all patients			6
Kitahata *et al.* [17]	RC	10	50	67	NA	NA	7	7	NA	70 ±9		68 ±8	6
Hashimoto *et al.* [18]	RC	21	0	84	NA	NA	6 or 7.2	–	6–10	NA	–	NA	6

ENBD – endoscopic nasobiliary drainage, PTBD – percutaneous transhepatic biliary drainage, EBS – endoscopic biliary stenting, NA – data not applicable, RC – retrospective case-control study.

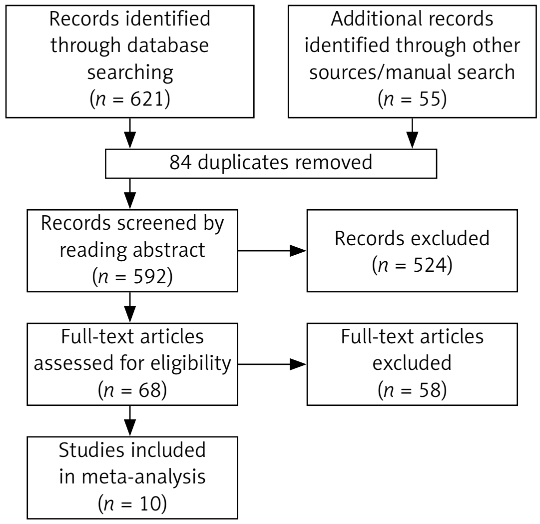

Figure 1. Flow chart for study selection

analysis; if there was significant heterogeneity ($p \leq 0.10$), the random effects model was applied [6]. The level of heterogeneity between studies was evaluated using I^2 statistics. $I^2 < 30\%$ was considered to be low heterogeneity, while $I^2 > 50\%$ represented high heterogeneity. Sensitivity analysis was performed by removing 1 study at a time to assess whether the results would be markedly affected by a single study. Funnel plots were constructed to evaluate potential publication bias [7, 8]. The meta-analysis was performed on RevMan 5.3 (The Cochrane Collaboration, Oxford, UK) software provided by the Cochrane Collaboration.

Results

Search results and study characteristics

The last retrieval time was May 30, 2017. A total of 676 articles were retrieved by searching electronic databases and manually searching relevant reference lists. After duplicates were identified and excluded, 592 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. As a result, 68 articles remained. After reading the full text, 10 articles [9–18] involving a total of 1464 patients were included in the meta-analysis. The detailed steps of our document retrieval are shown in Figure 1. In total, 774 patients received external drainage, and 690 patients received internal drainage. All included articles are case-control studies. The characteristics of these studies are presented in Table I.

Incidence of preoperative cholangitis

Nine of the 10 studies [9–17], including 753 cases in the external drainage group and 606 cases in the internal drainage group, investigated preop-

Study or subgroup	External drainage Events	External drainage Total	Internal drainage Events	Internal drainage Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Kawakami 2011	17	108	13	20	12.5	0.10 (0.04–0.29)
Sugiyama 2013	2	38	5	38	3.2	0.37 (0.07–2.02)
Kitahata 2014	1	60	15	67	9.4	0.06 (0.01–0.46)
Fujii 2015	6	50	22	72	10.7	0.31 (0.12–0.83)
Huang 2015	9	63	8	37	5.8	0.60 (0.21–1.73)
Jung 2015	9	56	12	42	7.8	0.48 (0.18–1.27)
Kazumichi 2016	25	85	12	33	8.2	0.73 (0.31–1.70)
Kishi 2016	13	127	10	44	9.0	0.39 (0.16–0.96)
Naoki 2016	16	166	69	253	33.4	0.28 (0.16–0.51)
Total (95% CI)		**753**		**606**	**100.0**	**0.33 (0.24–0.44)**
Total events	98		166			

Heterogeneity: $\chi^2 = 13.18$, $df = 8$ ($p = 0.11$); $I^2 = 39\%$

Test for overall effect: $Z = 7.14$ ($p < 0.00001$)

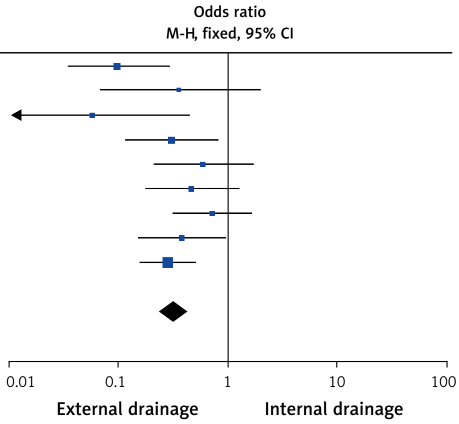

Figure 2. Forest plot of preoperative cholangitis rates

Study or subgroup	External drainage Events	External drainage Total	Internal drainage Events	Internal drainage Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Kawakami 2011	23	108	13	20	15.1	0.15 (0.05–0.41)
Sugiyama 2013	10	38	12	38	7.7	0.77 (0.29–2.09)
Jung 2015	9	56	7	42	5.9	0.96 (0.33–2.82)
Naoki 2016	30	166	88	253	50.0	0.41 (0.26–0.66)
Kazumichi 2016	28	85	20	33	16.9	0.32 (0.14–0.73)
Hashimoto 2016	1	21	13	84	4.3	0.27 (0.03–2.22)
Total (95% CI)		**474**		**470**	**100.0**	**0.41 (0.30–0.57)**
Total events	101		153			

Heterogeneity: $\chi^2 = 8.32$, $df = 5$ ($p = 0.14$); $I^2 = 40\%$

Test for overall effect: $Z = 5.28$ ($p < 0.00001$)

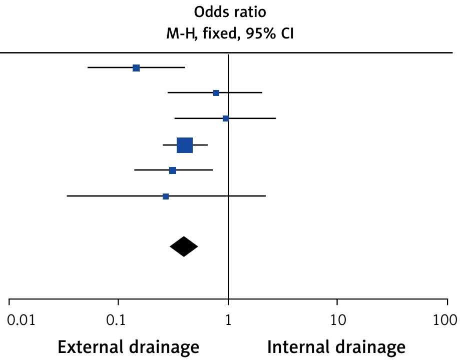

Figure 3. Forest plots of stent/tube dysfunction rate

Study or subgroup	External drainage Events	External drainage Total	Internal drainage Events	Internal drainage Total	Weight (%)	Odds ratio M-H–fixed–95% CI
Kawakami 2011	38	108	13	20	16.1	0.29 (0.11–0.79)
Sugiyama 2013	13	38	16	38	11.9	0.71 (0.28–1.81)
Kitahata 2014	15	60	43	67	34.4	0.19 (0.09–0.40)
Jung 2015	14	56	18	42	17.4	0.44 (0.19–1.05)
Huang 2015	30	63	27	37	20.1	0.34 (0.14–0.81)
Total (95% CI)		**325**		**204**	**100.0**	**0.34 (0.23–0.50)**
Total events	110		117			

Heterogeneity: $\chi^2 = 5.28$–$df = 4$ ($p = 0.26$); $I^2 = 24\%$

Test for overall effect: $Z = 5.44$ ($p < 0.00001$)

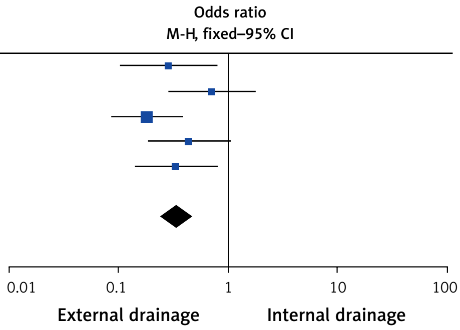

Figure 4. Forest plots of overall morbidity

erative cholangitis. The heterogeneity among the studies was not statistically significant ($I^2 = 39\%$, $p = 0.11$), so we chose a fixed-effect model to pool the OR. Overall, the pooled data demonstrated that external drainage was associated with a low incidence of preoperative cholangitis (OR = 0.33, 95% CI: 0.24–0.44, $p < 0.00001$) in the MBO patients (Figure 2).

Stent/tube dysfunction rate

Six of the 10 studies [9, 10, 14–16, 18], including 474 cases in the external drainage group and 470 cases in the internal drainage group, reported a stent/tube dysfunction rate. Heterogeneity among studies was not statistically significant ($I^2 = 40\%$, $p = 0.14$), so we chose a fixed-effect model to pool the OR. Overall, the pooled data demonstrated that external drainage was associated with a low incidence of stent/tube dysfunction (OR = 0.41, 95% CI: 0.30–0.57, $p < 0.00001$) in MBO patients (Figure 3).

Overall morbidity

Five of the 10 studies assessed overall morbidity [9–11, 15, 17], which is defined as the incidence of all pre- and postoperative complications. Heterogeneity among them was not statistically significant ($I^2 = 24\%$, $p = 0.26$). The pooled results

Study or subgroup	External drainage Events	External drainage Total	Internal drainage Events	Internal drainage Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Kawakami 2011	3	100	1	20	14.0	0.54 (0.05–5.50)
Kitahata 2014	1	60	3	67	23.8	0.36 (0.04–3.57)
Jung 2015	5	56	4	42	35.6	0.93 (0.23–3.70)
Fujii 2015	0	50	0	72		Not estimable
Huang 2015	0	63	2	37	26.6	0.11 (0.01–2.39)
Total (95% CI)		**287**		**166**	**100.0**	**0.52 (0.20–1.35)**
Total events	9		10			

Heterogeneity: $\chi^2 = 1.75$, $df = 3$ ($p = 0.63$); $I^2 = 0\%$

Test for overall effect: $Z = 1.34$ ($p = 0.18$)

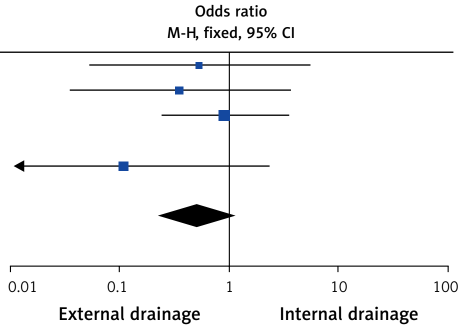

Figure 5. Forest plots of overall mortality

Study or subgroup	External drainage Events	External drainage Total	Internal drainage Events	Internal drainage Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Kitahata 2014	7	60	14	67	28.4	0.50 (0.19–1.34)
Huang 2015	5	63	10	37	28.2	0.23 (0.07–0.75)
Fujii 2015	8	50	26	72	43.5	0.34 (0.14–0.83)
Total (95% CI)		**173**		**176**	**100.0**	**0.35 (0.20–0.63)**
Total events	20		50			

Heterogeneity: $\chi^2 = 0.98$, $df = 2$ ($p = 0.61$); $I^2 = 0\%$

Test for overall effect: $Z = 3.54$ ($p = 0.0004$)

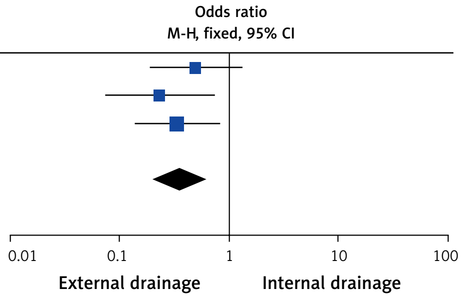

Figure 6. Forest plots of POPF

Study or subgroup	External drainage Events	External drainage Total	Internal drainage Events	Internal drainage Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Kitahata 2014	1	60	1	67	10.9	1.12 (0.07–18.28)
Huang 2015	4	63	2	37	27.8	1.19 (0.21–6.81)
Jung 2015	5	56	5	42	61.3	0.73 (0.20–2.69)
Total (95% CI)		**179**		**146**	**100.0**	**0.90 (0.34–2.38)**
Total events	10		8			

Heterogeneity: $\chi^2 = 0.22$, $df = 2$ ($p = 0.89$); $I^2 = 0\%$

Test for overall effect: $Z = 0.22$ ($p = 0.83$)

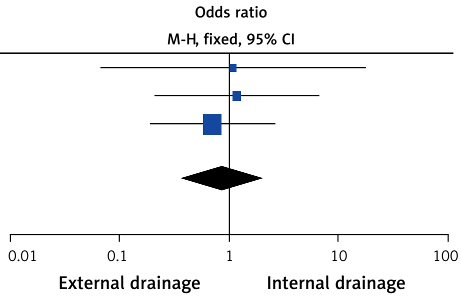

Figure 7. Forest plots of biliary leakage

showed that external drainage had a significantly lower incidence of morbidity than internal drainage (OR = 0.34, 95% CI: 0.23–0.50, $p < 0.00001$) (Figure 4).

Mortality

Five of the 10 studies [9, 11, 12, 15, 17] assessed mortality. No heterogeneity among them ($I^2 = 0\%$, $p = 0.63$) was found, so we chose a fixed-effect model to pool the OR. Overall, the pooled data demonstrated that neither external drainage nor internal drainage was associated with significantly lower mortality (OR = 0.52, 95% CI: 0.20–1.35, $p = 0.18$) in MBO patients (Figure 5).

Postoperative pancreatic fistula

Three of the 10 studies assessed the effect of postoperative pancreatic fistula (POPF) [11, 12, 17]. The pancreatic fistula rate was significantly lower in the external drainage group than in the internal drainage group (OR = 0.35, 95% CI: 0.2–0.63, $p = 0.0004$) based on the pooled data, which showed no heterogeneity ($I^2 = 0\%$, $p = 0.61$) (Figure 6).

Postoperative biliary leakage

Three of the 10 studies investigated biliary leakage [7, 9, 15]. No heterogeneity ($I^2 = 0\%$, $p = 0.89$) was found, so we chose a fixed-effect model to pool the OR. Overall, the pooled data demonstrated that neither external drainage nor internal drainage was associated with a significantly lower incidence of biliary leakage (OR = 0.90, 95% CI: 0.34–2.38, $p = 0.83$) in MBO patients (Figure 7).

Intra-abdominal abscess

Four of the 10 studies assessed the effect of intra-abdominal abscess [9, 11, 12, 17]. Neither exter-

Study or subgroup	External drainage		Internal drainage		Weight (%)	Odds ratio M-H, fixed, 95% CI
	Events	Total	Events	Total		
Kitahata 2014	7	60	9	67	25.1	0.85 (0.30–2.45)
Jung 2015	3	56	2	42	7.2	1.13 (0.19–7.10)
Fujii 2015	3	50	15	72	38.7	0.24 (0.07–0.89)
Huang 2015	9	63	8	37	28.9	0.60 (0.21–1.73)
Total (95% CI)		**229**		**218**	**100.0**	**0.56 (0.31–1.02)**
Total events	22		34			

Heterogeneity: χ^2 = 2.78, df = 3 (p = 0.43); I^2 = 0%

Test for overall effect: Z = 0.1.90 (p = 0.06)

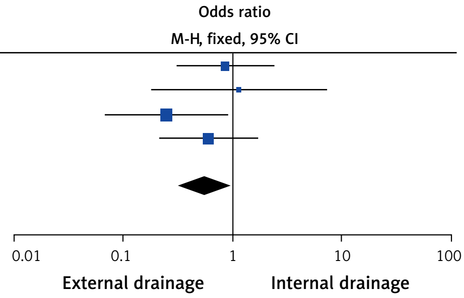

Figure 8. Forest plots of intra-abdominal abscess

Study or subgroup	External drainage		Internal drainage		Weight (%)	Odds ratio M-H, fixed, 95% CI
	Events	Total	Events	Total		
Kitahata 2014	1	60	4	67	35.2	0.27 (0.03–2.46)
Huang 2015	2	63	2	37	23.1	0.57 (0.08–4.25)
Jung 2015	2	56	4	42	41.7	0.35 (0.06–2.02)
Total (95% CI)		**179**		**146**	**100.0**	**0.37 (0.12–1.14)**
Total events	5		10			

Heterogeneity: χ^2 = 0.27, df = 2 (p = 0.87); I^2 = 0%

Test for overall effect: Z = 1.73 (p = 0.08)

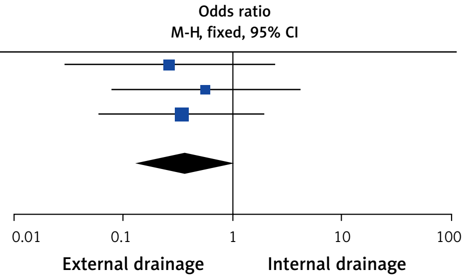

Figure 9. Forest plots of sepsis

Study or subgroup	External drainage		Internal drainage		Weight (%)	Odds ratio M-H–fixed–95% CI
	Events	Total	Events	Total		
1.1.1. Hilar cholangiocarcinoma						
Kawakami 2011	17	108	13	20	16.8	0.10 (0.04–0.29)
Kazumichi 2016	25	85	12	33	11.1	0.73 (0.31–1.70)
Subtotal (95% CI)		**193**		**53**	**27.9**	**0.35 (0.19–0.66)**
Total events	42		25			
Heterogeneity: χ^2 = 8.24, df = 1 (p = 0.004); I^2 = 88%						
Test for overall effect: Z = 3.27 (p = 0.001)						
1.1.2. Malignant distal biliary obstruction						
Kitahata 2014	1	60	15	67	12.7	0.06 (0.01–0.46)
Fujii 2015	6	50	22	72	14.4	0.31 (0.12–0.83)
Naoki 2016	16	166	69	253	45.0	0.28 (0.16–0.51)
Subtotal (95% CI)		**276**		**392**	**72.1**	**0.25 (0.15–0.40)**
Total events	23		106			
Heterogeneity: χ^2 = 2.27, df = 2 (p = 0.32); I^2 = 12%						
Test for overall effect: Z = 5.63 (p = 0.00001)						
Total (95% CI)		**469**		**445**	**100.0**	**0.28 (0.19–0.41)**
Total events	65		131			

Heterogeneity: χ^2 = 10.77, df = 4 (p = 0.03); I^2 = 63%

Test for overall effect: Z = 6.57 (p < 0.00001)

Test for subdroun differences: χ^2 = 0.70, df = 1 (p = 0.40), I^2 = 0%

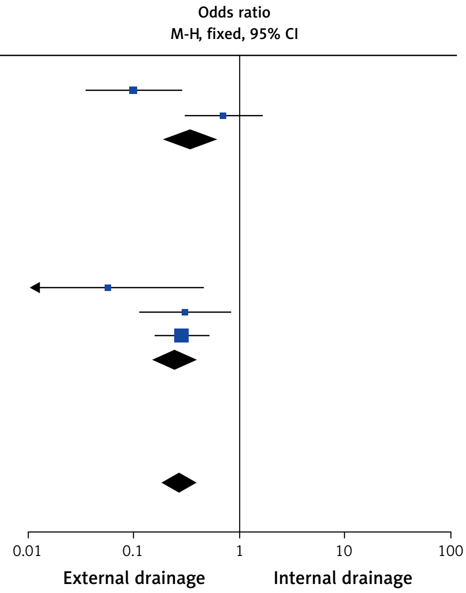

Figure 10. Forest plots of subgroup analysis of preoperative cholangitis

nal drainage nor internal drainage was associated with a significantly lower incidence of intra-abdominal abscess (OR = 0.56, 95% CI: 0.31–1.02, p = 0.06) based on the pooled data, which showed no heterogeneity (I^2 = 0%, p = 0.43) (Figure 8).

Postoperative sepsis

Three of the 10 studies researched sepsis [9, 11, 17]. No heterogeneity (I^2 = 0%, p = 0.87) was found, so we chose a fixed-effect model to pool the OR. Overall, the pooled data demonstrated that neither external drainage nor internal drainage was associated with a significantly lower incidence of sepsis (OR = 0.37, 95% CI: 0.12–1.14, p = 0.08) in MBO patients (Figure 9).

Subgroup analysis and sensitivity analysis

Subgroup analysis showed a higher incidence of preoperative cholangitis in the internal drainage group than in the external drainage group among hilar cholangiocarcinoma (HCA) patients (OR = 0.35, 95% CI: 0.19–0.66, p = 0.001) and malignant distal biliary obstruction patients (OR = 0.25, 95% CI: 0.15–0.40, p < 0.00001) (Figure 10).

Study or subgroup	External drainage Events	External drainage Total	Internal drainage Events	Internal drainage Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
1.3.1. Hilar cholangiocarcinoma						
Kawakami 2011	23	108	13	20	16.8	0.15 (0.05–0.41)
Kazumichi 2016	28	85	20	33	18.8	0.32 (0.14–0.73)
Subtotal (95% CI)		**193**		**53**	**35.7**	**0.24 (0.12–0.45)**
Total events	51		33			
Heterogeneity: χ^2 = 1.35, *df* = 1 (*p* = 0.24); I^2 = 26%						
Test for overall effect: *Z* = 4.37 (*p* < 0.0001)						
1.3.2. Malignant distal biliary obstruction						
Sugiyama 2013	10	38	12	38	8.6	0.77 (0.29–2.09)
Naoki 2016	30	166	88	253	55.7	0.41 (0.26–0.66)
Subtotal (95% CI)		**204**		**291**	**64.3**	**0.46 (0.30–0.71)**
Total events	40		100			
Heterogeneity: χ^2 = 1.24, *df* = 1 (*p* = 0.26) I^2 = 20% 23						
Test for overall effect: *Z* = 3.57 (*p* = 0.0004)						
Total (95% CI)		**397**		**344**	**100.0**	**0.38 (0.27–0.54)**
Total events	91		133			
Heterogeneity: χ^2 = 5.60, *df* = 3 (*p* = 0.13); I^2 = 46%						
Test for overall effect: *Z* = 5.32 (*p* < 0.00001)						
Test for subaroun differences: χ^2 = 2.86, df = 1 (*p* = 0.09), I^2 = 65.0%						

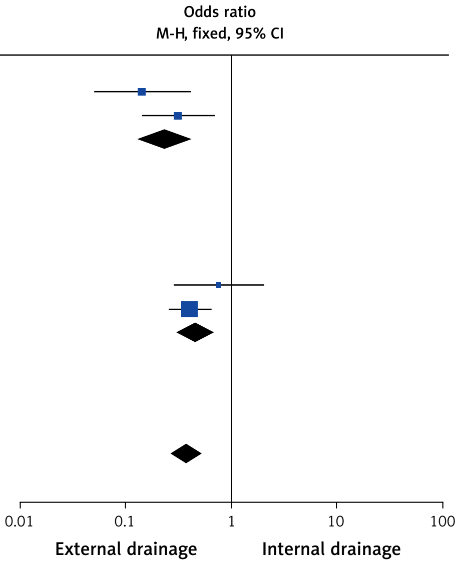

Figure 11. Forest plots of subgroup analysis of stent/tube dysfunction rate

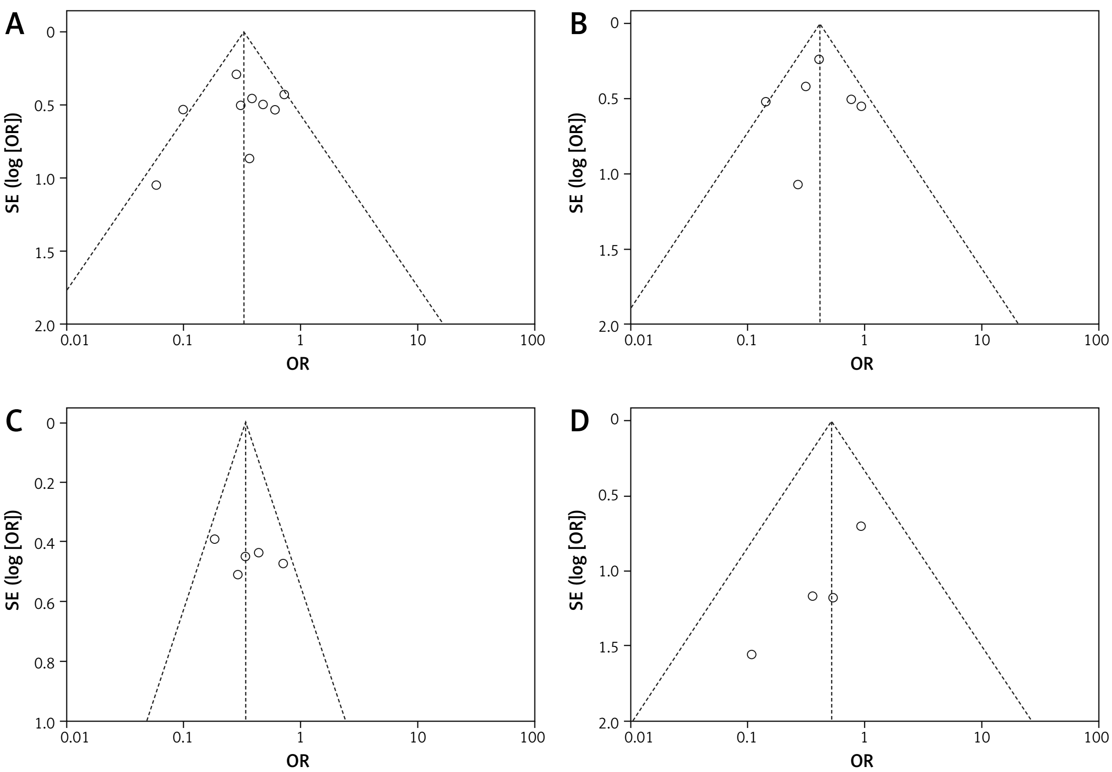

Figure 12. Funnel plot assessing for publication bias. **A** – preoperative cholangitis rate, **B** – stent/tube dysfunction rate, **C** – overall morbidity, **D** – mortality

The stent/tube dysfunction rate was also higher in the internal drainage group than in the external drainage group among HCA patients (OR = 0.24, 95% CI: 0.12–0.45, p < 0.001) and malignant distal biliary obstruction patients (OR = 0.46, 95% CI: 0.30–0.71, p = 0.0004) (Figure 11). Sensitivity analysis suggested that the data in this meta-analysis were relatively stable.

Assessment of risk of bias

Funnel plots for the preoperative cholangitis rate, the incidence of stent/tube dysfunction, overall morbidity and mortality were drawn (Figure 12). The publication bias was small because the points on the funnel plots were substantially symmetric. Funnel plots for POPF, biliary leak-

Study or subgroup	ENBD Events	ENBD Total	EBS Events	EBS Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Kawakami 2011	12	60	13	20	13.7	0.13 (0.04–0.41)
Sugiyama 2013	2	30	5	38	4.1	0.37 (0.07–2.02)
Huang 2015	4	18	8	37	3.6	1.04 (0.27–4.03)
Fujii 2015	6	50	22	72	13.9	0.31 (0.12–0.83)
Jung 2015	2	13	12	42	4.2	0.45 (0.09–2.36)
Kishi 2016	1	28	10	44	6.6	0.13 (0.02–1.05)
Kazumichi 2016	25	85	12	33	10.7	0.73 (0.31–1.70)
Naoki 2016	16	166	69	253	43.3	0.28 (0.16–0.51)
Total (95% CI)		**458**		**539**	**100**	**0.34 (0.24–0.49)**
Total events	68		151			

Heterogeneity: $\chi^2 = 9.69$, $df = 7$ ($p = 0.21$); $I^2 = 28\%$
Test for overall effect: $Z = 5.93$ ($p < 0.00001$)

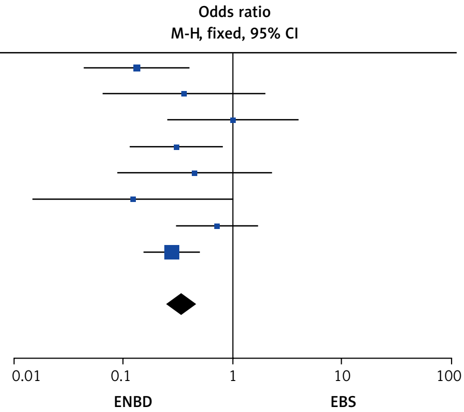

Figure 13. Forest plot of preoperative cholangitis in patients who underwent endoscopic internal and external drainage

Study or subgroup	ENBD Events	ENBD Total	EBS Events	EBS Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Kawakami 2011	15	60	13	20	13.6	0.18 (0.06–0.53)
Sugiyama 2013	10	38	12	38	8.2	0.77 (0.29–2.09)
Jung 2015	1	13	7	42	2.8	0.42 (0.05–3.74)
Hashimoto 2016	1	21	13	84	4.6	0.27 (0.03–2.22)
Kazumichi 2016	28	85	20	33	17.9	0.32 (0.14–0.73)
Naoki 2016	30	166	88	253	52.9	0.41 (0.26–0.66)
Total (95% CI)		**383**		**470**	**100.0**	**0.39 (0.27–0.55)**
Total events	85		153			

Heterogeneity: $\chi^2 = 4.17$, $df = 5$ ($p = 0.53$); $I^2 = 0\%$
Test for overall effect: $Z = 5.34$ ($p < 0.00001$)

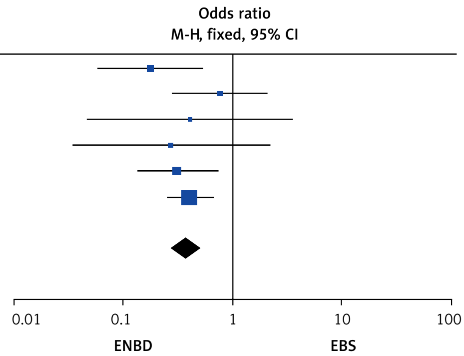

Figure 14. Forest plot of stent/tube dysfunction rate in patients who underwent endoscopic internal and external drainage

Study or subgroup	ENBD Events	ENBD Total	EBS Events	EBS Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Kawakami 2011	2	60	1	20	4.2	0.66 (0.06–7.64)
Sugiyama 2013	0	38	1	38	4.3	0.32 (0.01–8.22)
Jung 2015	0	13	6	42	9.0	0.21 (0.01–3.95)
Huang 2015	1	18	1	37	1.8	2.12 (0.12–35.93)
Kazumichi 2016	12	85	7	33	25.4	0.61 (0.22–1.72)
Naoki 2016	14	166	26	253	55.2	0.80 (0.41–1.59)
Total (95% CI)		**380**		**423**	**100.0**	**0.70 (0.41–1.18)**
Total events	29		42			

Heterogeneity: $\chi^2 = 1.69$, $df = 5$ ($p = 0.89$); $I^2 = 0\%$
Test for overall effect: $Z = 1.35$ ($p = 0.18$)

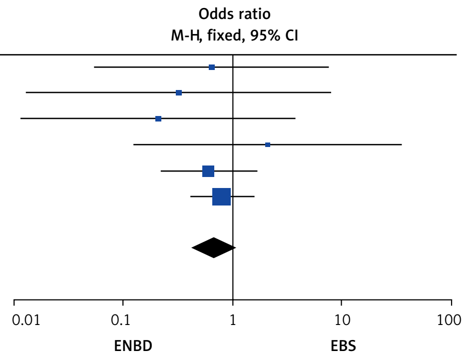

Figure 15. Forest plot of preoperative pancreatitis in patients who underwent endoscopic internal and external drainage

age, intra-abdominal abscess and sepsis were not made due to the small number of studies.

The comparison of different ways of drainage in the endoscope

A comparison was made separately between endoscopic internal and external drainage (EBS and ENBD), and the results indicated that ENBD was associated with a lower incidence of preoperative cholangitis (OR = 0.34, 95% CI: 0.24–0.49, $p < 0.00001$) in the MBO patients (Figure 13). The stent/tube dysfunction rate was also lower in the ENBD group than in the EBS group (OR = 0.39, 95% CI: 0.27–0.55, $p < 0.00001$) (Figure 14). Neither ENBD nor EBS was associated with a significantly lower incidence of preoperative pancreatitis (OR = 0.70, 95% CI: 0.41–1.18, $p = 0.18$) in MBO patients (Figure 15). ENBD had a significantly lower incidence of morbidity than EBS (OR = 0.47, 95% CI: 0.27–0.82, $p = 0.008$) (Figure 16). Neither ENBD nor EBS was associated with a significantly lower mortality (OR = 0.26, 95% CI: 0.04–1.6, $p = 0.15$) (Figure 17).

Study or subgroup	ENBD		EBS		Weight	Odds ratio
	Events	Total	Events	Total	(%)	M-H, fixed, 95% CI
Kawakami 2011	23	60	13	20	32.8	0.33 (0.12–0.96)
Sugiyama 2013	13	38	16	38	28.7	0.71 (0.28–1.81)
Huang 2015	11	18	27	37	18.8	0.58 (0.18–1.92)
Jung 2015	2	13	18	42	19.7	0.24 (0.05–1.23)
Total (95% CI)		**129**		**137**	**100.0**	**0.47 (0.27–0.82)**
Total events	49		74			

Heterogeneity: $\chi^2 = 1.94$, $df = 3$ ($p = 0.59$); $I^2 = 0\%$

Test for overall effect: $Z = 2.65$ ($p = 0.008$)

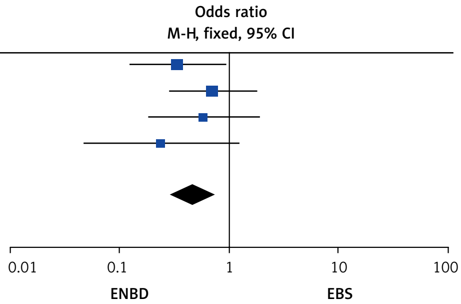

Figure 16. Forest plot of morbidity in patients who underwent endoscopic internal and external drainage

Study or subgroup	ENBD		EBS		Weight	Odds ratio
	Events	Total	Events	Total	(%)	M-H, fixed, 95% CI
Kawakami 2011	0	60	1	20	37.1	0.11 (0.00–2.75)
Huang 2015	0	18	2	37	27.2	0.38 (0.02–8.42)
Fujii 2015	0	50	0	72		Not estimable
Jung 2015	0	13	4	42	35.7	0.32 (0.02–6.28)
Total (95% CI)		**141**		**171**	**100.0**	**0.26 (0.04–1.60)**
Total events	0		7			

Heterogeneity: $\chi^2 = 0.36$, $df = 2$ ($p = 0.83$); $I^2 = 0\%$

Test for overall effect: $Z = 1.46$ ($p = 0.15$)

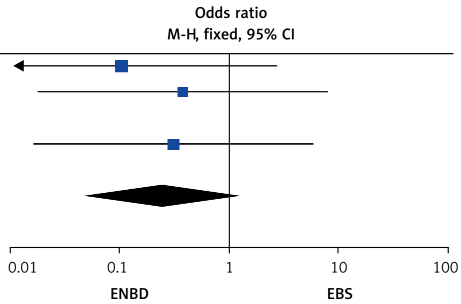

Figure 17. Forest plot of mortality in patients who underwent endoscopic internal and external drainage

Discussion

With the progress of technology, the success rate of surgical resection for malignant tumors of the biliary tract and pancreas head has become increasingly high. 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 characteristics of patients, and other concomitant disease. According to the statistics, the postoperative mortality and postoperative morbidity of patients with malignant obstructive jaundice was 5% to 27% and ~50%, respectively [19, 20]. In consideration of the situation, a large number of studies have been carried out to explore the major risk factors causing the high mortality and morbidity. It has been reported that hyperbilirubinemia (serum bilirubin ≥ 170 mmol/l) in patients who underwent obstructive jaundice surgery might increase their postoperative morbidity and mortality [21–23]. The reasons may be that hyperbilirubinemia would lead to impairment of liver function, decreased clearance of endotoxin, coagulation disorders, decreased immune function, and an impaired gastrointestinal mucosal barrier [24–27]. As an attempt to reduce these complications, preoperative biliary drainage was pursued in these patients. The aim was to restore normal physiology by improving the biliary drainage.

The EBS, PTBD and ENBD are the common drainage methods currently applied in the clinic. However, there is still no randomized controlled trial to evaluate which method is most ideal for preoperative drainage of malignant obstructive jaundice. This is the first meta-analysis to analyze whether internal drainage or external drainage is better for preoperative biliary drainage in patients with MBO. EBS has the advantages in cosmetic appeal and noninvasiveness [28], and, as a method of internal biliary drainage, it is more in compliance with human physiological needs, which may contribute to the improvement of nutritional status, reduction of endotoxemia, enhancement of the protective effect of the gastrointestinal mucosal barrier and improvement of the immune function [3]. Nevertheless, it has been reported that EBS may prolong hospital stay and increase postoperative morbidity and mortality compared with external drainage [29, 30]. On the other hand, PTBD has a relatively low incidence of postoperative complications, and a higher rate of success than bile duct decompression with EBS for advanced hepatic hilar carcinoma [31]. As for ENBD, its advantage is that bile duct cytology and cholangiography can be performed simultaneously. However, external drainage has some disadvantages. For example, drains for external drainage may be dislodged or pulled out by patients when they are unconscious. Furthermore, PTBD is an invasive technique that involves catheterization into the parenchyma of the liver, which may increase the tumor spread to 5–20% [32, 33], while ENBD may lead to patient discomfort or cosmetic problems because of the presence of the tube through the nasopharynx.

In the present meta-analysis, the results showed that patients with malignant obstructive jaundice who received external drainage (PTBD or ENBD) had reductions in the preoperative cholangitis rate (OR = 0.33, 95% CI: 0.24–0.44, $p < 0.00001$), overall morbidity (OR = 0.34, 95% CI: 0.23–0.50, $p < 0.00001$) and postoperative complications in terms of pancreatic fistula (OR = 0.35, 95% CI: 0.2–0.63, $p = 0.0004$) and intra-abdominal abscess (OR = 0.56, 95% CI: 0.31–1.02, $p = 0.06$) than those who received internal drainage (EBS). 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 [12]. This meta-analysis showed that stent dysfunction occurred more often in the internal group (OR = 0.39, 95% CI: 0.28–0.56, $p < 0.0001$) than in the external group, and that the causes of dysfunction were stent occlusion in EBS and dislocation in ENBD or PTBD [15]. Stent occlusion was reported to cause more than half the incidence of preoperative cholangitis [34]. Furthermore, some previous studies have confirmed that occurrence of preoperative cholangitis significantly increased postoperative complications including pancreatic fistula and delayed gastric emptying [35, 36]. Therefore, internal drainage, which was associated with more preoperative cholangitis, significantly increased the incidence of morbidity compared with external drainage. However, there was no significant difference in in-hospital mortality between external drainage and internal drainage (OR = 0.52, 95% CI: 0.20–1.35, $p = 0.18$). In addition, subgroup analyses were conducted. The results also showed that in both HCA patients and those with malignant distal biliary obstruction, the incidence of preoperative cholangitis and the rate of stent dysfunction with internal drainage were higher than those with external drainage. Other aspects, such as overall morbidity, were not further analyzed due to the limited number of selected articles. Therefore, the results of the subgroup analyses suggest that the location and type of tumor do not affect our conclusion that external drainage is better than internal drainage for malignant biliary obstruction in terms of the incidence of preoperative cholangitis and the rate of stent dysfunction.

At the same time, a single comparison was also made between the two methods of endoscopic internal and external drainage (EBS and ENBD), and the results also suggested that patients with malignant obstructive jaundice who received ENBD had a lower preoperative cholangitis rate (OR = 0.34, 95% CI: 0.24–0.49, $p < 0.00001$), stent/tube dysfunction rate (OR = 0.39, 95% CI: 0.27–0.55, $p < 0.00001$) and overall morbidity (OR = 0.47, 95% CI: 0.27–0.82, $p = 0.008$) than those who received EBS. In addition, the incidence of preoperative pancreatitis (OR = 0.70, 95% CI: 0.41–1.18, $p = 0.18$) was higher in the EBS group than in the ENBD group even though the meta-analysis showed no significant difference. A prospective study [37] showed that EBS was one of the factors that cause pancreatitis. Stent placement, especially a large-bore stent, would cause the obstruction of the adjacent pancreatic orifice, and limit the outflow of pancreatic juice, which may be a potential risk factor to induce pancreatitis. In addition, an endoscopic sphincterotomy is usually performed when large-bore plastic stents are placed. Perforations, ulcers, and stent dysfunction caused by endoscopic sphincterotomy are always associated with pancreatitis and other complications.

In conclusion, external drainage is superior to internal drainage for malignant biliary obstruction in controlling preoperative and postoperative complications according to this meta-analysis. However, long-term external drainage can lead to insufficient bile in the intestines, thus weakening inhibition of intestinal bacteria and causing endotoxemia [23]. It may also cause malnutrition because of lipid malabsorption and fluid balance disorders because of bile loss. These problems of external drainage may be solved by internal drainage. In humans, it is well known that the increased intestinal permeability caused by obstructive jaundice is recovered after internal biliary drainage [38, 39]. Internal drainage is more physiological than external drainage, as the enterohepatic circulation of bile is maintained. The benefits of internal drainage have been demonstrated in a series of animal experiments conducted by our team concerning internal and external drainage for the management of obstructive jaundice [40–42]. Our results indicated that internal drainage was superior to external drainage in restoring the damaged intestinal barrier, inhibiting bacterial translocation and reducing expression of inflammatory factors. Nevertheless, the advantages of internal drainage relative to external drainage were not demonstrated in the current meta-analysis or in the included studies. One of the possible reasons is that, due to the limited clinical drainage technique, plastic stents were predominantly used in the involved patients who underwent internal drainage. Plastic stents are inexpensive and easy to operate for repeated placement; however, their major disadvantage is that they may lead to recurrence of jaundice and increase the incidence of cholangitis [43–45]. Compared with plastic stents, metal stents have a larger diameter when expanded, and the expansion time is notably longer [46–48]. Wasan *et al.* [49] showed that metal stents could reduce the occurrence of cholangitis and intraoperative and postoperative complications. Moreover, covered metallic stents may not only protect against tumor ingrowth but also minimize bacterial adherence and sludge formation that cause biliary infections [50, 51]. However, the high price has limited the widespread use of metal stents in clinical practice. Therefore, research and literature on the use of metal stents in internal drainage is insufficient.

In addition to the absence of metal stents included as a comparative study, other limitations should also be taken into account in the meta-analysis. Firstly, the studies were all retrospective studies lacking randomized controlled trials. Secondly, the number of studies included and subgroup analysis were inadequate. Thirdly, different studies defined the complications differently, and the evaluation criteria were different, which might affect the final analysis. With respect to the above, large-scale, large-sample, multi-centered and randomized controlled trials will be needed to further validate the results.

Conflict of interest

The authors declare no conflict of interest.

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