T-Tube Use After Laparoscopic Common Bile Duct Exploration

Cuinan Jiang, MSc, Xiuhao Zhao, MSc, Shi Cheng, MD

ABSTRACT

Background and Objectives: Laparoscopic common bile duct exploration (LCBDE) has been verified to be an effective technique in treating choledocholithiasis, and T-tube insertion has been widely performed after LCBDE. With growing doubts regarding the effectiveness and safety of T-tube drainage (TTD), it has been suggested to replace such with primary duct closure (PDC). This metaanalysis aimed to evaluate the short- and long-term effectiveness and safety of PDC compared with TTD after LCBDE.

Methods: The PubMed, Science Citation Index, and Cochrane Central Register of Controlled Trials databases were used to accomplish a systematic literature search for randomized controlled trials and pro-/retrospective cohort studies that compared PDC alone or PDC combined with biliary drainage stenting (PDC+BD) with TTD after LCBDE. A subgroup analysis was established to compare PDC+BD with TTD. RevMan 5.3 was used for the statistical analysis.

Results: A total of 2552 patients from 26 studies were included. The pooled odds ratio supported PDC, which yielded lower postoperative overall morbidity and incidence of bile leak and bile peritonitis and shorter surgical time and postoperative hospital stay when compared with TTD. In the subgroup analysis, PDC+BD showed significantly better results in terms of postoperative overall

DOI: 10.4293/JSLS.2018.00077

morbidity, incidence of bile leak and bile peritonitis, surgical time, and postoperative hospital stay than did TTD. PDC and PDC+BD showed no difference in the incidence of recurrent stones and biliary stricture during the longterm follow-up period compared with TTD.

Conclusion: PDC alone or PDC+BD is superior to TTD as a duct-closure method after LCBDE.

Key Words: Laparoscopic common bile duct exploration, Primary duct closure, T-tube drainage, Biliary drainage.

INTRODUCTION

Common bile duct (CBD) stones are a biliary disease requiring surgical intervention. They can form initially in situ, which is mainly attributed to infection and bile stasis, and may also originate secondary to gallbladder stones or intrahepatic bile duct stones¹; approximately 10%–20% of patients with symptomatic gallstones have CBD stones.² Patients presenting with CBD stones are likely to develop biliary colic, obstructive jaundice, cholangitis, or biliary pancreatitis or may stay in the asymptomatic state.

Various techniques for treating CBD stones are feasible and effective. Presently, the popular techniques include laparoscopic cholecystectomy (LC) + laparoscopic common bile duct exploration (LCBDE; single-stage) and LC + pre-/postoperative endoscopic retrograde cholangiopancreatography or that combined with endoscopic sphincterotomy (EST) (two-stage). Both options are effective in detecting and extracting CBD stones²⁻⁴; however, LC+LCBDE shows advantages in terms of its lower rate of technique failure, fewer number of procedures, shorter hospital stay, and lower hospital charges.5-7 LCBDE can be performed via either the transductal or transcystic approach, although the latter has less biliary complications; its application is subject to some restrictions; and its success depends on whether the choledochoscope is able to enter the CBD, cystic duct anatomy (diameter, shape, and position of the cystic-CBD junction), and CBD stones (location, size, and number).8,9

Department of General Surgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China (Mr. Jiang, Mr. Zhai, Dr. Cheng).

Disclosures: None reported.

Conflicts of Interest: All authors declare no conflict of interest regarding the publication of this article.

Informed consent: Dr. Cheng declares that written informed consent was obtained from the patient/s for publication of this study/report and any accompanying images.

Address correspondence to: Shi Cheng, MD, Department of General Surgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China. Telephone: +86.13691004036, +86.010-67096586, Fax: +86.010-67096586, E-mail: chengshi20150411@163.com.

[@] 2019 by JSLS, Journal of the Society of Laparoendoscopic Surgeons. Published by the Society of Laparoendoscopic Surgeons, Inc.

T-tube drainage (TTD) has been widely used for CBD closure when LCBDE was performed via the transductal approach; its functions include biliary tract decompression to prevent further bile leaks, postoperative cholangiography when necessary, and removal of retained stones using a choledochoscope.¹⁰ However, the use of a T tube usually contributes to several postoperative complications with a morbidity of 4%-16.4%^{11,12}; the most frequent among such complications is bile leak due to T-tube removal, which is the cause of bile peritonitis, mainly because of an incomplete trans-T-tube sinus-tract formation. The other related problems include CBD obstruction due to T-tube twisting, hydroelectrolytic imbalance as a result of uncontrolled drainage of bile, T-tubesite cellulitis, discomfort and inconvenience to patients with an indwelling T tube, and longer hospital stay due to delayed postoperative recovery.10,13,14 To avoid these complications associated with T-tube use occurring in LCBDE patients, applying primary duct closure (PDC) alone or PDC combined with internal or external biliary drainage (IBD or EBD, respectively) (antegrade biliary stent, spontaneously removed biliary stent, C-tube, and transcystic biliary decompression) for CBD closure after LCBDE was recommended by some surgeons; further, several clinical trials and meta-analyses have provided supportive views on the use of PDC or PDC combined with other biliary drainage (PDC+BD) techniques, when compared with the use of TTD; the former yielded lower postoperative morbidity and incidence of postoperative biliary peritonitis, shorter surgical time and hospital stay, and lower hospital expenses.^{15,16}

However, previous meta-analyses^{15–17} that focused on this field contained relatively small sample sizes, and up to only 4 randomized controlled trials were included; it was unreasonable to confuse the bile leak occurring when the T tube was indwelling with that occurring after the T tube was removed; furthermore, retained stones should also not be recognized as a postoperative complication but a cure failure (according to the modified Clavien classification¹⁸). The above-mentioned deficiencies were common in previous meta-analyses on this topic. In addition, the complications that emerged during follow-up periods, such as biliary stricture and recurrent stones, were not analyzed in detail. Thus, we conducted this meta-analysis based on a larger cohort of 2552 patients to evaluate the potential advantages or limitations of PDC alone or PDC+BD compared with TTD in a more reasonable and comprehensive approach.

METHODS

Data Sources and Search Strategies

A literature search was conducted using the PubMed (October 1976 to May 2018), Cochrane Central Register of Controlled Trials (1983–2017), and Science Citation Index (October 1976 to May 2018) databases to select studies comparing PDC/PDC+BD with TTD. We utilized the following search terms for retrieval: T tube, PDC, or primary closure or primary suture, LCBDE, and choledocholithiasis. Further, similar articles recommended by the databases were taken into account, and relevant articles from the reference lists were retrieved by manual search.

Study Selection

Clinical trials (randomized controlled trials, retrospective cohort studies, and prospective cohort studies) were included in this meta-analysis for the purpose of comparing PDC/PDC+BD with TTD after LCBDE. If more than one publication reported the results of a single study, the most recent article and that with more complete data were selected for the meta-analysis. There was no restriction in the language of the articles.

Irrelevant studies, noncontrol studies, review articles, nonhuman studies, unpublished materials and abstracts, letters, and case reports were excluded.

The inclusion criteria for the studies were as follows:

- 1. Patients diagnosed with choledocholithiasis or CBD stones
- 2. Illustrated demographic and clinical features of the patients
- 3. Patients without absolute contraindication for laparoscopic surgery
- 4. Patients without severe acute cholangitis, ampullary stenosis with multiple intrahepatic stones, suspected biliary neoplasia, liver cirrhosis, or hemorrhagic tendency
- Reported at least one of the following outcomes: 1) postoperative overall morbidity; 2) biliary-specific complications (bile leak, bile peritonitis, and CBD obstruction); 3) surgical time; 4) length of postoperative hospital stay; 5) recurrent stones; and 6) postoperative biliary stricture

Preliminary screening and full-article assessment were performed independently by two reviewers (JC and ZX).

Disagreements were resolved through mutual discussion or evaluated by a third reviewer (CS).

Data Extraction and Study Quality Assessment

Two review authors (JC and ZX) independently extracted the data from the included studies and checked the extracted data together. Disagreements on the extracted data were resolved by consulting relevant knowledge. The clinical outcomes extracted included as follows: 1) characteristics of the studies (study type, number of patients assigned to each technique group, T-tube type, T-tube removal time, and follow-up period); 2) number of patients who experienced postoperative overall complications, bile leak, bile peritonitis, CBD obstruction, postoperative pancreatitis, recurrent stones, biliary stricture, and other complications; and 3) surgical time and length of postoperative hospital stay.

We used the Cochrane Collaboration Risk of Bias Tool¹⁹ to assess the risk of bias for the randomized controlled trials; the quality of the retrospective cohort studies and prospective cohort studies was assessed in accordance with the recommendations suggested by the Newcastle-Ottawa quality assessment tool.²⁰

Statistical Analysis

The software RevMan 5.3 was applied for the statistical analysis. The heterogeneity among the studies was examined using χ^2 test. When the I² value was \leq 50%, the heterogeneity could be accepted. If the *P* value of the heterogeneity test was greater than .10, it was considered that homogeneity existed among the studies. The fixed-effect model (Mantel-Haenszel method) was used to calculate the summary statistics; when substantial heterogeneity ($P \leq .01$; I² > 50%) was detected, the random-effect model (DerSimonian and Laird method) was used for the analysis.

Dichotomous variables were analyzed using odds ratios (ORs) with 95% confidence intervals (CIs) and continuous variables using weighted mean differences with 95% CIs. Peto ORs were applied for very low incidence outcome analyses to minimize bias. If $P \leq .05$, and the 95% CI did not contain the value 1, the OR/Peto OR was considered to indicate a significant difference; if the $P \leq .05$, and the 95% CI did not contain the value 0, the weighted mean differences was considered to indicate a significant difference.

RESULTS

Study Search and Description

A total of 369 articles were identified through the electronic database search (368 articles) and manual search (one article); the manually retrieved study²¹ was identified from the reference list of one of the other relevant articles.²² After reviewing the titles and abstracts of these obtained articles, 339 were excluded because they were irrelevant studies, noncontrol studies, systematic reviews, animal studies, or studies that focused on open common bile duct exploration (CBDE). The full texts of the 30 remaining studies were then assessed. Finally, 26 studies9,12,21,23-45 were eligible for this meta-analysis. Seven were randomized controlled trials,9,21,23,24,38,42,43 and the other 19 were retrospective cohort studies or prospective cohort studies. Sixteen studies9,12,21,23,26,28,30,33,34,37-41,43,44 compared LCBDE+PDC with LCBDE+TTD. Eight studies24,25,28,29,32,36,42,45 compared LCBDE+PDC+IBD with LCBDE+TTD; three studies27,31,35 compared LCBDE+ PDC+EBD with LCBDE+TTD; and one study²⁸ compared three bile duct closure methods following LCBDE (Table 1). The descriptions of the various IBD and EBD technical processes are listed in Table 2. A total of 2552 patients were included in this meta-analysis.

Quality Assessment

The quality of the seven randomized controlled trials was assessed using the Cochrane Collaboration Risk of Bias Tool; the final judgment of all the randomized controlled trials was "unclear risk of bias." The quality of the 15 retrospective cohort studies and 4 prospective cohort studies was assessed using the Newcastle-Ottawa quality assessment tool; all the retrospective cohort studies and prospective cohort studies could be awarded 4–7 stars.

Postoperative Overall Morbidity

In the 16 studies^{9,12,21,23,26,28,30,33,34,37–41,43,44} that compared LCBDE+PDC with LCBDE+TTD, 74 patients (7.5%) in the PDC group and 106 patients (12.8%) in the TTD group developed postoperative complications; the PDC group showed a significantly lower overall morbidity than did the TTD group (OR = 0.55, 95% CI = 0.39–0.76, P = .0004; no heterogeneity was found; I² = 0%; P = .91) (**Figure 1A**). Thirty-three of the 106 patients developed postoperative complications due to T-tube removal or accidental dislodgement in the TTD group^{9,12,21,23,26,28,30,33,34,38,39,43} (**Table 2**).

		Char	d Studies				
	Number of	of Patient	Intervention	n			
Study	Study Group	Control Group	Study Group	Control Group	T-tube Type and Removal Time	Follow-up	
Martin et al ¹² (RCS)	55	61	PDC	TTD	NA; Clamped at 7d,removed at 21d	Unclear	
Cai et al ³⁹ (RCS)	134	100	PDC	TTD	NA; 12w after operation	median 26m	
Dong et al ³⁸ (RCT)	97	90	PDC	TTD	14–20Fr latex rubber T-tube; 3–4w after operation	median 12m	
El-Geidie et al ⁹ (RCT)	61	61	PDC	TTD	14–16Fr latex rubber T-tube; 10d after operation	at 2w and 2m	
Ha et al ⁴¹ (PCS)	12	26	PDC	TTD	NA; 14d after operation	every 3m	
Parra-Membrives et al ²⁸ (RCS)	36	52	PDC	TTD	10–16Fr rubber T-tube; 1m after operation	1m and 6m after operation	
Shakya et al ²¹ (RCT)	20	20	PDC	TTD	12/14Fr; 11d after operation	Unclear	
Wang et ³⁰ (PCS)	132	108	PDC	TTD	6 and 8 mm in diameter; 12w after operation	12w after discharge or T-tube removal	
Jameel et al ⁴⁴ (PCS)	48	10	PDC	TTD	NA; 3–4w after discharge	6w after discharge	
Liu et al ³⁴ (RCS)	49	12	PDC	TTD	NA; unclear	1y after operation	
Wen et al ²⁶ (RCS)	52	33	PDC	TTD	16–20Fr latex rubber T-tube; 4w after operation	Unclear	
Yi et al ³⁷ (RCS)	91	51	PDC	TTD	16Fr; 2w after operation	median 48.8m	
Zhang HW et al ³³ (RCS)	93	92	PDC	TTD	NA; 14d after operation	median 40m	
Zhang K et al ⁴⁰ (RCS)	25	25	PDC	TTD	NA; 4–6w after operation	6w after operation, median 18m	
Zhang LD et al ²³ (RCT)	40	40	PDC	TTD	14–20Fr latex rubber T-tube; 3–4w after operation	25m average	
Zhang WJ et al ⁴³ (RCT)	47	46	PDC	TTD	14–20Fr latex rubber T-tube; 3–5w after operation	3–24m after discharge	
Griniatsos et al ²⁹ (RCS)	21	32	PDC+IBD	TTD	NA; 16d after operation (14–17d)	unclear	
Kim and Lee et al ³⁶ (RCS)	50	36	PDC+IBD	TTD	NA; 32 \pm 7.5d after operation	unclear	
Lyon et al ⁴⁵ (PCS)	82	34	PDC+IBD	TTD	NA; 4–5w after operation	unclear	
Mangla et al ²⁴ (RCT)	31	29	PDC+IBD	TTD	NA; 11d after operation	unclear	

Table 1. Continued											
	Number	of Patient	Intervention	1							
Study	Study Control Group Group			Control Group	T-tube Type and Removal Time	Follow-up					
Martinez-Beana et al ³² (RCS)	28	47	PDC+IBD	TTD	8–14Fr latex Kehr tube; 1m after operation	unclear					
Tang et al ²⁵ (RCS)	35	28	PDC+IBD	TTD	16Fr, 2w after operation	every 3m after discharge					
Xu et al ⁴² (RCT)	22	25	PDC+IBD	TTD	NA, 14–21d after operation	unclear					
Parra-Membrives et al ²⁸ (RCS)	58	52	PDC+IBD	TTD	10–16Fr rubber T-tube; 1m after operation	1m and 6m after operation					
Huang et al ³⁵ (RCS)	10	40	PDC+EBD	TTD	16–20Fr rubber T-tube; 8d after operation	median 35.4m					
Kanamaru et al ³¹ (RCS)	30	15	PDC+EBD	TTD	NA; 3–4w after operation	unclear					
Wei et al ²⁷ (RCS)	30	52	PDC+EBD	TTD	12–16Fr latex rubber T-tube; 3–4w after operation	3–40w					

d: days; w: weeks; m: months; PDC: primary duct closure; TTD: T-tube drainage; IBD: internal biliary drainage; EBD: external biliary drainage; RCT: randomized controlled trial; RCS: retrospective cohort study; PCS: prospective cohort study; NA: not available.

In the 11 studies^{24,25,27–29,31,32,35,36,42,45} included in the subgroup analysis, 45 patients (11.3%) in the LCBDE+ PDC+BD group and 71 patients (18.2%) in the LCBDE+ TTD group developed postoperative complications; the PDC+BD group showed a significantly lower overall morbidity than did the TTD group (OR = 0.58, 95% CI = 0.38–0.89, P = .01; the heterogeneity could be accepted; I² = 31%; P = .15) (**Figure 1B**). Twenty-six patients^{27–29,32,36,45} in the TTD group developed complications associated with T tube use (**Table 2**).

Bile Leak

In 16 studies, 9,12,21,23,26,28,30,33,34,37–41,43,44 46 patients (4.6%) in the PDC group and 59 patients (7.1%) in the TTD group had bile leak. The result tended to favor the PDC group, which showed a lower incidence of bile leak; however, no significant difference was found (OR = 0.68, 95% CI = 0.45–1.03, P = .07; no heterogeneity was found; I² = 0%; P = .99) (**Figure 2A**). Twenty patients^{21,23,26,28,30,33,34,38,39,43} in the TTD group experienced bile leak as a result of planned T-tube removal, removal by mistake, or accidental dislodgement. When we excluded the 20 bile-leak cases and compared the patients with bile leak occurring when the T tube was in situ with the PDC group patients, no difference in the incidence of bile leak was found (OR = 1.04, 95% CI = 0.67–1.61, P = .86; no heterogeneity was found; I² = 0%, P = .97) (**Figure 2C**).

In the 11 studies^{24,25,27–29,31,32,35,36,42,45} included in the subgroup analysis, 23 patients (5.8%) in the PDC+BD group and 40 patients (10.3%) in the TTD group had bile leak. The PDC+BD group showed a significantly lower incidence of bile leak than did the TTD group (OR = 0.57, 95% CI = 0.33–0.96, P = .04; no heterogeneity was found; I² = 0%, P = .49) (**Figure 2B**). Eighteen patients^{27–29,32,36,45} in the TTD group had bile leak as a result of planned T-tube removal or accidental dislodgement; when these patients were excluded and compared, the result showed no difference between them (OR = 1.09, 95% CI = 0.60–1.98, P = .77; no heterogeneity was found; I² = 0%, P = .73) (**Figure 2D**).

Bile Peritonitis

Seventeen patients^{9,12,23,26,28,30,38,39,43} in the TTD group and none in the PDC group had bile peritonitis; the result showed a significant difference (OR = 0.2, 95% CI = 0.07-0.55, P = .002; no heterogeneity was found; I² = 0%, P = 1.00) (**Figure 3A**). Of these 17 patients,^{23,26,28,30,38,39,43} nine patients had bile peritonitis due to T-tube removal

	Tal Complications A	ble 2. ssociated with	TTD
PDC vs TTD	T-tube accidental dislodgement	8	A total of eight patients had T-tube accidenta dislodgement, two of whom developed bile leak and bile peritonitis. Three patients were treated with reoperation for T-tube replacement, while the treatment in the other five patients was not mentioned.
	Complications due to T-tube removal	23	There were 18 patients who had bile leak after T-tube removal, 10 of whom developed bile peritonitis; the five remaining patients developed other complications following T- tube removal.
	T-tube twisting	2	Two patients developed CBD obstruction due to T-tube twisting.
	Total	33	
PDC+BD vs TTD	T-tube accidental dislodgement	4	Four patients had T-tube accidental dislodgement, one of whom experienced bile leak and bile peritonitis. One patient received reoperation for T-tube replacement.
	Complications due to T-tube removal	22	Seventeen patients experienced bile leak afte T-tube removal, 11 of whom developed bile peritonitis; the five remaining patients developed other complications following T- tube removal.
	T-tube twisting	0	
	Total	26	

and three patients, T-tube accidental dislodgement. We excluded 12 patients and compared the findings, and the Peto OR was applied owing to the low incidence; the result favored the PDC group, which also showed a significant difference (OR = 0.14, 95% CI = 0.02-0.82, P = .03; no heterogeneity was found; $I^2 = 0\%$, P = .96) (**Figure 3C**).

In the seven studies^{27–29,32,35,36,45} included in the subgroup analysis, one patient in the PDC+BD group and 14 patients in the TTD group experienced bile peritonitis; the result favored the PDC+BD group, which showed a significant difference (OR = 0.26, 95% CI = 0.09–0.77, P =.01; no heterogeneity was found; I² = 0%, P = .82) (**Figure 3B**). Twelve patients^{27–29,32,36,45} in the TTD group developed bile peritonitis due to T-tube removal or T-tube accidental dislodgement; we then excluded these patients and analyzed the findings, and the Peto OR was applied owing to the low incidence. The result tended to favor the PDC+BD group but showed no significant difference (Peto OR = 0.23, 95% CI = 0.01–5.30, P = .36; no heterogeneity was found; I² = 0%, P = .92) (**Figure 3D**).

CBD Obstruction

Two patients in the PDC group (one had a stitch occluding the bile duct, and one had ampullary edema) and 2 patients (T-tube twisting) in the TTD group had CBD obstruction after surgery; the result had no significant difference between the two groups^{12,23,43} (Peto OR = 1.05, 95% CI = 0.15–7.48, P = .96; the heterogeneity could be accepted; I² = 53%, P = .12) (**Figure 4A**).

Tang et al²⁵ reported CBD obstruction cases due to stent blockage in the PDC+BD group, but provided no detailed data, no CBD obstruction was noted in the TTD group.

Postoperative Pancreatitis

In 3 studies, 23,38,43 3 patients in the PDC group and one patient in the TTD group had postoperative pancreatitis; the result tended to favor the TTD group. However, no significant difference was discovered (Peto OR = 2.67,

a.Postoperative overall morbidity in PDC versus TTD

Study or Subgroup	PDC Events		TTD Events	Total	Weight	Odds Ratio M-H, Fixed, 95% Cl	Odds Ratio M-H, Fixed, 95% Cl
ai HH 2012	6	134	6	100	7.1%	0.73 [0.23, 2.35]	
Dong ZT 2014	9	97	12	90	12.2%	0.66 [0.27, 1.66]	
I-Geidie 2010	1	61	5	61	5.3%	0.19 [0.02, 1.65]	
la JP 2004	1	12	3	26	1.9%	0.70 [0.06, 7.49]	
ameel 2008	7	48	2	10	3.0%	0.68 [0.12, 3.91]	
iu WS 2017	7	49	3	12	4.5%	0.50 [0.11, 2.31]	
Aartin 1998	5	55	10	61	9.3%	0.51 [0.16, 1.60]	
arra-Membrives 2017	9	36	25	52	16.5%	0.36 [0.14, 0.91]	
Shakya 2017	1	20	3	20	3.1%	0.30 [0.03, 3.15]	
Vang Cy 2013	4	132	7	108	8.0%	0.45 [0.13, 1.58]	
Ven SQ 2017	5	52	2	33	2.4%	1.65 [0.30, 9.04]	
'i HJ 2015	3	91	1	51	1.3%	1.70 [0.17, 16.83]	
hang HW 2014	2	93	1	92	1.1%	2.00 [0.18, 22.45]	
hang K 2016	2	25	1	25	1.0%	2.09 [0.18, 24.61]	
hang LD 2008	6	40	11	40	10.1%	0.47 [0.15, 1.41]	
(hang WJ 2015	6	47	14	46	13.3%	0.33 [0.12, 0.97]	
otal (95% CI)		992		827	100.0%	0.55 [0.39, 0.76]	•
otal events	74		106			• • •	
Heterogeneity: Chi ² = 8.3	1, df = 15	(P = 0.9)	91); I ² = 0	%			0.01 0.1 1 10 10
est for overall effect: Z =	3.53 (P =	0.0004	5)				0.01 0.1 1 10 10 Favours (PDC) Favours (TTD)
Postoperative overall morbidi	lity in PDC+	BD vers	us TTD				
	PDC+		TTD			Odds Ratio	Odds Ratio
study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Friniatsos 2005	0	21	6	32	8.8%	0.09 [0.01, 1.78]	4 .
luang SM 2010	2	10	4	40	2.2%	2.25 [0.35, 14.49]	
(anamaru 2007	4	30	2	15	4.0%	1.00 [0.16, 6.19]	
(im and Lee 2004	5	50	4	36	7.2%	0.89 [0.22, 3.57]	
yon 2014	0	82	4	34	10.9%	0.04 [0.00, 0.79]	
1angla 2012	2	31	4	29	6.7%	0.43 [0.07, 2.56]	
faritinez-Baena 2013	6	28	11	47	11.2%	0.89 [0.29, 2.76]	
	16	58	25	52	33.0%	0.41 [0.19, 0.91]	
arra-Membrives 2017							
ang CN 2006	10	35	4	28	5.5%	2.40 [0.66, 8.70]	
Vei Q 2004	0	30	6	52	8.2%	0.12 [0.01, 2.16]	
		00	1	25	2.4%	0.36 [0.01, 9.37]	
(u YK 2016	0	22					
(u YK 2016 Total (95% CI)	0				100.0%	0.58 (0.38, 0.89)	•
otal (95% CI)		397			100.0%	0.58 [0.38, 0.89]	•
	45	397	71	390	100.0%	0.58 [0.38, 0.89]	◆
fotal (95% CI) fotal events leterogeneity: Chi ² = 14. fest for overall effect: Z =	45 59, df = 10 2.52 (P =	397 0 (P = 0 0.01)	71	390	100.0%	0.58 [0.38, 0.89]	0.01 0.1 1 10 10 Favours [PDC+BD] Favours [TTD]
otal (95% CI) otal events leterogeneity: Chi² = 14.:	45 59, df = 10 2.52 (P =	397) (P = 0 0.01))	71	390 31%	100.0%	0.58 [0.38, 0.89] Odds Ratio	
Total (95% CI) Total events Heterogeneity: Chi [≈] = 14. Test for overall effect: Z = Other complications in PDC	45 59, df = 10 2.52 (P = Versus TTL PDC	397 0 (P = 0 0.01) 0	71 1.15); I² = TTD	390 31%		Odds Ratio	Favours (PDC+BD) Favours (TTD) Odds Ratio
Total (95% CI) Total events Heterogeneity: Chi≆ = 14.1 Test for overall effect: Z = Other complications in PDC	45 59, df = 10 2.52 (P = Versus TTL PDC Events	397 0 (P = 0 0.01) 0 	71 1.15); I² = TTD Events	390 31% Total	Weight	Odds Ratio M-H, Fixed, 95% Cl	Favours (PDC+BD) Favours (TTD)
Total (95% CI) Total events Heterogeneity: Chi ² = 14. Test for overall effect: Z = Other complications in PDC Study or Subgroup Cai HH 2012	45 59, df = 10 2.52 (P = 2 versus TTL PDC Events 0	397 0 (P = 0 0.01) 0 <u></u>	71 1.15); I ^z = TTD <u>Events</u> 1	390 31% <u>Total</u> 100	Weight 3.6%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.25 [0.01, 6.12]	Favours (PDC+BD) Favours (TTD) Odds Ratio
otal (95% CI) Total events leterogeneity: Chi ² = 14.: est for overall effect: Z = Other complications in PDC tudy or Subgroup cai HH 2012 Dong ZT 2014	45 59, df = 10 2.52 (P = PDC Events 0 3	397 0 (P = 0 0.01) 0 <u>Total</u> 134 97	71 1.15); I ^z = TTD <u>Events</u> 1 6	390 31% <u>Total</u> 100 90	Weight 3.6% 12.7%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.25 [0.01, 6.12] 0.45 [0.11, 1.84]	Favours (PDC+BD) Favours (TTD) Odds Ratio
otal (95% CI) otal events leterogeneity: Chi ² = 14.1 est for overall effect: Z = Other complications in PDC study or Subgroup cai HH 2012 bong ZT 2014 i-Geidie 2010	45 59, df = 10 2.52 (P = 2.52 (P = 2.52 (P = 2.52 (P = 2.52 (P = 2	397 0 (P = 0 0.01) 0 <u>Total</u> 134 97 61	71 1.15); I [≥] = TTD <u>Events</u> 1 6 3	390 31% <u>Total</u> 100 90 61	Weight 3.6% 12.7% 7.3%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.25 (0.01, 6.12) 0.45 (0.11, 1.84) 0.14 (0.01, 2.69)	Favours (PDC+BD) Favours (TTD) Odds Ratio
otal (95% CI) otal events leterogeneity: Chi [≆] = 14.: est for overall effect: Z = Other complications in PDC tudy or Subgroup cai HH 2012 ong ZT 2014 I-Geidie 2010 la JP 2004	45 59, df = 10 2.52 (P = 2.52 (P = 2.52 (P = 90 90 1 3 0 1	397 0 (P = 0 0.01) 7 <u>Total</u> 134 97 61 12	71 1.15); I ² = TTD <u>Events</u> 1 6 3 2	390 31% <u>Total</u> 100 90 61 26	Weight 3.6% 12.7% 7.3% 2.4%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35]	Favours (PDC+BD) Favours (TTD) Odds Ratio
otal (95% CI) total events leterogeneity: Chi ² = 14.: test for overall effect: Z = Other complications in PDC tudy or Subgroup tai HH 2012 tong ZT 2014 l-Geidie 2010 la JP 2004 ameel 2008	45 59, df = 10 2.52 (P = 2.52 (P = 2.52 (P = 0 3 0 1 4	397 0 (P = 0 0.01) Total 134 97 61 12 48	71 0.15); I ² = TTD Events 1 6 3 2 2	390 31% <u>Total</u> 100 90 61 26 10	Weight 3.6% 12.7% 7.3% 2.4% 6.4%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33]	Favours (PDC+BD) Favours (TTD) Odds Ratio
otal (95% CI) otal events leterogeneity: Chi ² = 14.: est for overall effect: Z = Other complications in PDC tudy or Subgroup ai HH 2012 ong ZT 2014 I-Geidie 2010 la JP 2004 ameel 2008 iu WS 2017	45 59, df = 10 2.52 (P = 2.52 (P = 2	397 0 (P = 0 0.01) Total 134 97 61 12 48 49	71 1.15); I [≥] = TTD Events 1 6 3 2 2 2 2	390 31% <u>Total</u> 100 90 61 26 10 12	Weight 3.6% 12.7% 7.3% 6.4% 6.1%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36]	Favours (PDC+BD) Favours (ITD) Odds Ratio
otal (95% CI) otal events leterogeneity: Chi ² = 14.: est for overall effect: Z = Other complications in PDC tudy or Subgroup tai HH 2012 ong ZT 2014 I-Geidie 2010 la JP 2004 ameel 2008 iu WS 2017	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0	397 0 (P = 0 0.01) 7 134 97 61 12 48 49 55	71 1.15); I [≥] = TTD Events 1 6 3 2 2 2 5	390 31% 100 90 61 26 10 12 61	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33]	Favours (PDC+BD) Favours (TTD) Odds Ratio
otal (95% CI) otal events leterogeneity: Chi ² = 14.: est for overall effect: Z = Other complications in PDC tudy or Subgroup ai HH 2012 ong ZT 2014 I-Geidie 2010 la JP 2004 armeel 2008 la WS 2017 lartin 1998	45 59, df = 10 2.52 (P = 2.52 (P = 2	397 0 (P = 0 0.01) Total 134 97 61 12 48 49	71 1.15); I [≥] = TTD Events 1 6 3 2 2 2 2	390 31% <u>Total</u> 100 90 61 26 10 12	Weight 3.6% 12.7% 7.3% 6.4% 6.1%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36]	Favours (PDC+BD) Favours (ITD) Odds Ratio
otal (95% CI) otal events leterogeneity: Chi ² = 14. est for overall effect: Z = Other complications in PDC tudy or Subgroup ai HH 2012 ong ZT 2014 I-Geidie 2010 a JP 2004 ameel 2008 iu WS 2017 lartin 1998 arra-Membrives 2017	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0	397 0 (P = 0 0.01) 7 134 97 61 12 48 49 55	71 1.15); I [≥] = TTD Events 1 6 3 2 2 2 5	390 31% 100 90 61 26 10 12 61	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.25 (0.01, 6.12) 0.45 (0.11, 1.84) 0.14 (0.01, 2.69) 1.09 (0.09, 13.35) 0.36 (0.06, 2.33) 0.57 (0.10, 3.36) 0.09 (0.00, 1.71)	Favours (PDC+BD) Favours (ITD) Odds Ratio
otal (95% CI) otal events eterogeneity: Chi ² = 14.: est for overall effect: Z = Other complications in PDC tudy or Subgroup ai HH 2012 ong ZT 2014 I-Geidie 2010 a JP 2004 armeel 2008 iu WS 2017 artin 1998 arra-Membrives 2017 fen SQ 2017	45 59, df = 10 2.52 (P = 2.52 (P = PDC Events 0 3 0 1 4 5 0 3 3 0 1 3 3 0 3 3 3 0 3 3 3 3 3 3 3 3	397 0 (P = 0 0.01) 7 134 97 61 12 48 49 55 36	71 1.15); ² = TTD <u>Events</u> 1 6 3 2 2 2 2 2 5 12	390 31% 100 90 61 26 10 12 61 52	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9% 18.9%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70]	Favours (PDC+BD) Favours (ITD) Odds Ratio
otal (95% CI) otal events eterogeneity: Chi ² = 14.: est for overall effect: Z = Other complications in PDC tudy or Subgroup ai HH 2012 ong ZT 2014 I-Geidie 2010 a JP 2004 armeel 2008 hu WS 2017 artin 1998 arra-Membrives 2017 <i>i</i> HJ 2015	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0 3 2 1	397 0 (P = 0 0.01) 7 134 97 61 12 48 49 55 36 35 36 91	71 1.15); ² = TTD Events 1 6 3 2 2 2 2 5 12 12 1 0	390 31% 100 90 61 26 10 12 61 52 33 51	Weight 3.6% 12.7% 2.4% 6.4% 6.1% 10.9% 18.9% 2.5% 1.3%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68]	Favours (PDC+BD) Favours (ITD) Odds Ratio
otal (95% CI) otal events eterogeneity: Chi ² = 14. est for overall effect: Z = Other complications in PDC tudy or Subgroup ai HH 2012 ong ZT 2014 I-Geidie 2010 a JP 2004 ameel 2008 iu WS 2017 artin 1998 arra-Membrives 2017 fen SQ 2017 i HJ 2015 hang LD 2008	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 1 4 5 0 3 2	397 0 (P = 0 0.01) Total 134 97 61 12 48 49 55 366 52	71 1.15); ² = TTD Events 1 6 3 2 2 2 2 5 12 12 1	390 31% 100 90 61 26 10 12 61 52 33	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9% 18.9% 2.5%	Odds Ratio <u>M-H, Fixed, 95% CI</u> 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70]	Favours (PDC+BD) Favours (ITD) Odds Ratio
otal (95% CI) otal events leterogeneity: Chi ² = 14.: est for overall effect: Z = Other complications in PDC tudy or Subgroup tai HH 2012 long ZT 2014 I-Geidie 2010 Ia JP 2004 ameel 2008 iu WS 2017 Iartin 1998 arra-Membrives 2017 Ven SQ 2017 i HJ 2015 hang LD 2008 hang WJ 2015	45 59, df = 10 2.52 (P = PDC Eversus TTL 0 3 0 1 4 5 0 3 2 1 2	397 0 (P = 0 0.01) 7 134 97 61 12 48 49 55 36 55 36 52 91 40	71 1.15); I ² = TTD <u>Events</u> 1 6 3 2 2 2 5 12 1 1 0 5	390 31% 100 90 61 26 10 26 61 52 33 51 40 46	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9% 18.9% 2.5% 1.3%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02]	Favours (PDC+BD) Favours (TTD) Odds Ratio
otal (95% CI) Total events Total events	45 59, df = 10 2.52 (P = PDC Eversus TTL 0 3 0 1 4 5 0 3 2 1 2	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 36 55 36 52 91 40 47	71 1.15); I ² = TTD <u>Events</u> 1 6 3 2 2 2 5 12 1 1 0 5	390 31% 100 90 61 26 10 26 61 52 33 51 40 46	Weightt 3.6% 12.7% 7.3% 2.4% 6.1% 10.9% 18.9% 2.5% 1.3% 10.0% 17.9%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11]	Favours (PDC+BD) Favours (TTD) Odds Ratio
Total (95% CI) Total events Heterogeneity: Chi ² = 14.1 Test for overall effect: Z = Other complications in PDC Study or Subgroup Cai HH 2012 Dong ZT 2014 I-Geidie 2010 Ha JP 2004 armel 2008 Jur WS 2017 Martin 1998 Parra-Membrives 2017 Ven SQ 2017 THJ 2015 Chang UD 2008 Chang WJ 2015 Total (95% CI) Total events Heterogeneity: Chi ² = 4.4	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0 3 2 1 2 3 3 7, df = 11	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 36 52 91 40 47 722 (P = 0.9	71 1.15); ² = TTD Events 1 6 3 2 2 2 5 12 1 0 5 9 48 95); ² = 0	390 31% 100 90 61 26 12 61 52 33 51 46 582	Weightt 3.6% 12.7% 7.3% 2.4% 6.1% 10.9% 18.9% 2.5% 1.3% 10.0% 17.9%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11]	Favours (PDC+BD) Favours (ITTD)
Total (95% CI) Total events Heterogeneity: Chi ² = 14.1 Test for overall effect: Z = Other complications in PDC Study or Subgroup Cai HH 2012 Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Jameel 2008 Liu WS 2017 Yarra-Membrives 2017 Yen SQ 2017 TH J015 Chang LD 2008 Chang WJ 2015 Total events Heterogeneity: Chi ² = 4.4.4	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0 3 2 1 2 3 7, df = 11 3.69 (P =	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 366 52 91 40 47 722 (P = 0.9 0.0002	71 1.15); ² = TTD Events 1 6 3 2 2 2 5 12 1 0 5 9 48 95); ² = 0	390 31% 100 90 61 26 12 61 52 33 51 46 582	Weightt 3.6% 12.7% 7.3% 2.4% 6.1% 10.9% 18.9% 2.5% 1.3% 10.0% 17.9%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11]	Favours (PDC+BD) Favours (TTD)
Total (95% CI) Total events Heterogeneity: Chi ² = 14.1 Test for overall effect: Z = Other complications in PDC Study or Subgroup Cai HH 2012 Dong ZT 2014 E-Geidie 2010 Ha JP 2004 Jarnel 2008 Ju WS 2017 Martin 1998 Parra-Membrives 2017 Yen SQ 2017 Thang LD 2008 Chang WJ 2015 Total (95% CI) Total events Heterogeneity: Chi ² = 4.4	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0 3 2 1 2 3 3 2 1 2 3 3 2 4 7, df = 11 3.69 (P = C+BD versu	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 36 55 36 55 36 52 91 40 47 722 (P = 0.9 0.0002 s TTD BD	71 1.15); ² = TTD Events 1 6 3 2 2 2 5 12 1 0 5 9 48 95); ² = 0	390 31% 100 90 61 26 12 61 52 33 51 40 582 %	Weightt 3.6% 12.7% 7.3% 2.4% 6.1% 10.9% 18.9% 2.5% 1.3% 10.0% 17.9%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11]	Favours (PDC+BD) Favours [TTD]
Total (95% CI) Total events Heterogeneity: Chi ² = 14.1 Test for overall effect: Z = Other complications in PDC Study or Subgroup Tai HH 2012 Dong ZT 2014 El-Geidie 2010 Ha JP 2004 ameel 2008 Jut WS 2017 Tara-Membrives 2017 Yen SQ 2017 Thay 2015 Chang LD 2008 Chang WJ 2015 Total events Heterogeneity: Chi ² = 4.4' Test for overall effect: Z = Other complications in PDC	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 1 4 5 0 3 2 1 2 3 3 2 4 7, df = 11 3.69 (P = C+BD versu PDC+E	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 36 55 36 55 36 52 91 40 47 722 (P = 0.9 0.0002 s TTD BD	71 1.15); ² = TTD <u>Events</u> 1 6 3 2 2 2 5 12 1 2 5 9 9 9 9 9 9 9 9 9 9 1 1 1 1 1 1 1 1 1 1 1 1 1	390 31% 100 90 126 10 26 10 26 10 26 51 40 46 582 %	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9% 18.9% 1.3% 1.3% 10.0% 17.9%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 1.3.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.22, 0.63]	Favours (PDC+BD) Favours [TTD]
otal (95% CI) otal events leterogeneity: Chi ² = 14.1 est for overall effect: Z = Other complications in PDC tudy or Subgroup tai HH 2012 tong ZT 2014 H-Geidie 2010 ta JP 2004 ameel 2008 iu WS 2017 tartin 1998 varra-Membrives 2017 Ven SQ 2017 TH J 2015 thang LD 2008 thang WJ 2015 otal (95% CI) otal events leterogeneity: Chi ² = 4.4 'est for overall effect: Z = .Other complications in PDC tudy or Subgroup	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0 3 2 1 2 3 3 2 1 2 3 3 2 4 7, df = 11 3.69 (P = C+BD versu	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 36 55 36 55 36 52 91 40 47 722 (P = 0.9 0.0002 s TTD BD	71 1.15); ² = TTD <u>Events</u> 1 6 3 2 2 2 5 12 1 2 5 9 9 9 9 9 9 9 9 9 9 1 1 1 1 1 1 1 1 1 1 1 1 1	390 31% 100 90 126 10 26 10 26 10 26 51 40 46 582 %	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9% 18.9% 1.3% 10.0% 17.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11] 0.37 [0.22, 0.63] Odds Ratio	Favours (PDC+BD) Favours [TTD]
Total (95% CI) Total events Heterogeneity: Chi ² = 14.1 Test for overall effect: Z = Other complications in PDC Study or Subgroup Sai HH 2012 Dong ZT 2014 I-Geidie 2010 Ha JP 2004 ameel 2008 Ju WS 2017 Karra-Membrives 2017 Ven SQ 2017 Thang LD 2008 Chang VU 2015 Total (95% CI) Total events Heterogeneity: Chi ² = 4.4.4 Fest for overall effect: Z = Other complications in PDC Study or Subgroup Striniatsos 2005	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 1 4 5 0 3 2 1 2 3 3 69 (P = C+BD versu PDC+T Events 0 2	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 366 52 91 49 52 91 40 47 722 (P = 0.9 0.0002 s TTD BD Total	71 1.15); ² = TTD <u>Events</u> 1 6 3 2 2 2 5 12 2 1 0 5 9 9 95); ² = 0 2 2 1 0 5 9 9 95); ² = 1 0 5 1 1 0 5 1 1 0 5 1 1 0 5 1 1 1 0 5 1 1 0 5 1 1 1 1 1 1 1 1 1 1 1 1 1	390 31% 100 90 61 26 12 61 52 33 51 46 582 %	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9% 18.9% 12.5% 1.3% 10.0% 17.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.36] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11] 0.37 [0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI	Favours (PDC+BD) Favours [TTD]
Total (95% CI) Total events Heterogeneity: Chi [™] = 14.1 Test for overall effect: Z = Other complications in PDC Study or Subgroup Sai HH 2012 Dong ZT 2014 El-Geidie 2010 Ha JP 2004 ameel 2008 Ju WS 2017 Yearra-Membrives 2017 Ven SQ 2017 THJ 2015 Chang LD 2008 Total events Heterogeneity: Chi [™] = 4.4' Test for overall effect: Z = Other complications in PDC Study of Subgroup Priniatsos 2005 Huang SM 2010	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 1 4 5 0 3 2 1 2 3 3 2 4 7, df = 11 3.69 (P = C+BD versu PDC+H Events 0 2 3	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 36 52 91 40 47 722 (P = 0.9 0.0002 \$ TTD BD Total 21	71 1.15); ² = TTD Events 1 6 3 2 2 2 2 5 12 1 0 5 9 48 85); ² = 0 2 2 5 12 1 0 5 9 48 85); ² = 0 2 2 2 2 5 12 1 0 5 9 48 85 2 2 2 5 12 1 0 5 9 48 85 2 12 1 0 5 9 48 85 2 12 1 0 5 9 48 85 12 1 0 5 9 48 85 12 1 0 5 9 48 85 12 12 1 0 5 9 48 85 12 12 12 12 12 12 12 12 12 12	390 31% Total 100 90 61 26 10 26 12 61 52 33 51 46 582 % Total 32	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9% 18.9% 1.3% 10.0% 17.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11] 0.37 [0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI 0.28 [0.01, 6.21]	Favours (PDC+BD) Favours [TTD]
otal (95% CI) otal events leterogeneity: Chi ² = 14.1 est for overall effect: Z = Other complications in PDC tudy or Subgroup ai HH 2012 bong ZT 2014 l-Geidie 2010 ta JP 2004 ameel 2008 lu WS 2017 tartin 1998 'arra-Membrives 2017 Ven SQ 2017 THJ 2015 chang LD 2008 hang LD 2008 hang VJ 2015 otal events leterogeneity: Chi ² = 4.4' est for overall effect: Z = .Other complications in PDC Study or Subgroup Priniatsos 2005 hang SM 2010 dm and Lee 2004	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 1 4 5 0 3 2 1 2 3 3 69 (P = C+BD versu PDC+T Events 0 2	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 366 52 91 40 47 722 (P = 0.9 0.0002 s TTD BD Total 10 10 10 10 10 10 10 10 10 10	71 1.15); ² = TTD <u>Events</u> 1 6 3 2 2 2 5 12 2 3 9 48 95); ² = 0 2) TTD <u>Events</u> 2 3 3 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 1 0 5 5 1 2 2 2 1 0 5 5 1 2 2 2 1 2 2 2 5 5 1 2 2 2 2 5 5 1 2 2 2 5 5 1 2 2 2 2 5 5 1 2 2 2 2 5 5 2 2 2 2 5 5 5 5 5 5 5 7 7 7 7 7 7 7 7 7 7 7 7 7	390 31% Total 100 90 61 266 12 61 52 33 51 40 46 582 % Total 32 40	Weight 3.6% 12.7% 7.3% 2.4% 6.1% 10.9% 18.9% 2.5% 1.3% 10.0% 17.9% 100.0% Weight 7.7% 3.8%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11] 0.37 [0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI 0.28 [0.01, 6.21] 0.38 [0.44, 21.58]	Favours (PDC+BD) Favours (TTD) Odds Ratio M-H, Fixed, 95% CI
otal (95% CI) otal events leterogeneity: Chi ² = 14.1 est for overall effect: Z = Other complications in PDC cudy or Subgroup ai HH 2012 Dong ZT 2014 l-Geidie 2010 la JP 2004 arrea-Membrives 2017 Ven SQ 2017 1 HJ 2015 chang LD 2008 chang WJ 2015 otal (95% CI) otal events leterogeneity: Chi ² = 4.41 est for overall effect: Z = .Other complications in PDC Study or Subgroup Striniatsos 2005 fuang SM 2010 Sim and Lee 2004 yon 2014	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 1 4 5 0 3 2 1 2 3 3 2 4 7, df = 11 3.69 (P = C+BD versu PDC+H Events 0 2 3	397 0 (P = 0 0.01) 134 97 61 124 48 49 55 52 91 40 52 91 40 722 (P = 0.9 0.0002 s TTD 3D Total 10 50 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 52 91 40 52 52 91 40 52 52 91 40 55 52 91 40 55 52 52 52 52 52 52 52 52 52	71 1.15); ² = TTD <u>Events</u> 1 6 3 2 2 2 2 2 5 12 1 0 5 9 9 9 9 9 9 9 9 9 9 9 9 9	390 31% Total 100 90 61 26 12 61 52 33 51 40 582 % Total 32 40 36 32 40 36	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 10.9% 18.9% 1.3% 10.0% 17.9% 100.0% Weight 7.7% 3.8% 4.3%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11] 0.37 [0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI 0.28 [0.01, 6.21] 3.08 [0.44, 21.58] 2.23 [0.22, 22.40] 0.14 [0.01, 3.41] 0.45 [0.04, 5.25]	Favours (PDC+BD) Favours (TTD) Odds Ratio M-H, Fixed, 95% CI
iotal (95% CI) iotal events Heterogeneity: Chi ² = 14.1 iest for overall effect: Z = Other complications in PDC itudy or Subgroup cai HH 2012 Dong ZT 2014 I-Geidie 2010 ta JP 2004 ameel 2008 iu WS 2017 Ven SQ 2017 Yen SQ 2017 'i HJ 2015 Chang LD 2008 Chang VU 2015 otal (95% CI) otal events Heterogeneity: Chi ² = 4.4 'est for overall effect: Z = .Other complications in PDC Study or Subgroup Priniatsos 2005 fum and Lee 2004 yon 2014 faminations 2012 fam and Lee 2004 yon 2014 familia 2012 familia 2012	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0 3 2 1 2 3 3 2 4 7, df = 11 3.69 (P = C+BD versu PDC+H Events 0 3 3 0 1 2 3 3 0 0 2 3 3 0 0 2 4 7, df = 10 0 3 0 0 1 4 5 0 2 3 3 0 0 0 1 2 3 0 0 0 0 1 2 2 3 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	397 0 (P = 0 0.01) 134 97 61 12 48 49 55 36 52 91 40 47 722 (P = 0.5 0.0002 s TTD BD Total 10 55 52 91 40 47 722 (P = 0.5 0.002 57 10 10 10 10 10 10 10 10 10 10	71 1.15); ² = TTD Events 1 6 3 2 2 2 5 12 1 0 5 9 9 9 9 9 9 9 9 9 12 1 0 5 9 9 9 9 9 9 9 9 9 9 9 9 9	390 31% Total 100 901 266 102 61 522 351 40 46 582 % Total 32 40 34	Weight 3.6% 12.7% 7.3% 6.4% 6.4% 10.9% 18.9% 2.5% 1.3% 10.0% 17.9% 100.0% 17.9% 100.0% 17.9% 100.0% 1.3% 8.3%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 0.30 [0.08, 1.16] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11] 0.37 [0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI 0.28 [0.01, 2.2] 0.28 [0.04, 21.58] 2.23 [0.22, 22.40] 0.14 [0.01, 3.41]	Favours (PDC+BD) Favours (TTD) Odds Ratio M-H, Fixed, 95% CI
Total (95% CI) Total events Heterogeneity: Chi ² = 14.1 Test for overall effect: Z = Other complications in PDC Study or Subgroup Sai HH 2012 Dong ZT 2014 El-Geidie 2010 Ha JP 2004 ameel 2008 Jut WS 2017 Haran Hembrives 2017 Yerna-Membrives 2017 Yen SQ 2017 TH J 2015 Chang LD 2008 Chang WJ 2015 Total events Heterogeneity: Chi ² = 4.4' Test for overall effect: Z = .Other complications in PDC Study or Subgroup Priniatsos 2005 Huang SM 2010 Gim and Lee 2004 Yon 2014	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 1 4 5 0 3 2 1 2 3 2 4 7, df = 11 3.69 (P = C+BD versu PDC+H Events 0 2 3 0 1 1 3.69 (P = 2 1 2 3 0 1 1 3.69 (P = 2 4 2 3 0 1 1 3 1 2 4 7 7 8 1 1 3 1 1 3 1 2 4 7 7 8 1 1 3 3 1 1 3 1 2 4 7 7 8 1 1 1 3 1 2 4 7 7 1 1 3 3 1 2 4 7 7 1 1 3 3 1 1 3 3 1 1 3 3 1 1 3 3 1 1 3 3 1 1 3 3 1 1 3 3 1 1 3 3 1 1 3 3 1 1 3 3 3 1 1 3 3 3 1 1 3 3 1 1 3 3 1 1 3 3 3 1 1 3 3 3 1 1 3 3 3 1 1 3 3 3 1 1 3 3 3 3 1 1 3 3 3 3 1 1 3	397 0 (P = 0 0.01) 134 97 61 134 97 61 134 97 61 134 97 61 134 97 61 134 97 61 12 48 49 55 366 52 91 47 722 (P = 0.9 0.002 8 TTD 30 50 8 12 47 722 8 17 10 10 10 10 10 10 10 10 10 10	71 1.15); [≠] = TTD <u>Events</u> 1 6 3 2 2 2 2 5 12 2 2 5 12 2 3 3 5 9 9 9 9 9 9 9 9 9 9 9 9 9	390 31% Total 100 90 61 26 12 61 52 33 51 46 582 % Total 32 36 36 36 36 36 36 36 36 36 36	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 10.9% 18.9% 2.5% 1.3% 10.0% 17.9% 100.0% Weight 7.7% 3.8% 4.3% 8.3% 7.9%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11] 0.37 [0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI 0.28 [0.01, 6.21] 3.08 [0.44, 21.58] 2.23 [0.22, 22.40] 0.14 [0.01, 3.41] 0.45 [0.04, 5.25]	Favours (PDC+BD) Favours [TTD]
otal (95% CI) otal events leterogeneity: Chi ² = 14.1 leterogeneity: Chi ² = 14.1 leterogeneity: Chi ² = 14.1 leterogeneity: Chi ² = 14.2 other complications in PDC tudy or Subgroup leterogeneity 2014 leterogeneity 2017 leterogeneity: Chi ² = 4.42 leterogeneity: Chi ² = 4.42 leterogene	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 1 4 5 0 0 3 2 1 2 3 7, df = 11 3.69 (P = C+BD versu PDC+I Events 0 2 3 0 1 1 3.69 (P = 2 3 0 1 1 3.69 (P = 2 1 2 3 0 1 1 3.69 (P = 2 4 7, df = 10 1 2 3 1 2 4 7, df = 10 1 3 1 2 3 3 1 2 4 7, df = 10 2 3 3 1 1 2 3 3 1 1 3 5 5 1 1 3 5 1 1 3 5 5 5 5 5 5	397 0 (P = 0 0.01) 134 97 61 124 48 49 55 36 52 91 40 47 722 (P = 0.9 0.0002 s TTD 30 Total 10 50 52 91 40 47 722 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 52 91 40 722 55 52 91 40 722 55 52 91 40 722 55 50 50 50 50 50 50 50 50 50	71 1.15); ² = TTD Events 1 6 3 2 2 2 2 2 2 2 2 2 2 2 2 2	390 31% Total 100 90 61 26 12 61 52 33 51 40 582 % Total 32 40 36 32 40 36 34 22 8	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 10.9% 18.9% 1.3% 100.0% Weight 7.7% 3.8% 4.3% 8.3% 8.3% 11.2%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.22, 0.03] 0.37 [0.22, 0.63] 0.37 [0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI 0.28 [0.01, 6.21] 3.08 [0.44, 21.58] 0.23 [0.22, 22.40] 0.14 [0.01, 3.41] 0.45 [0.44, 3.75] 0.40 [0.04, 3.75] 0.69 [0.27, 1.77] 1.39 [0.30, 6.39]	Favours (PDC+BD) Favours (TTD) Odds Ratio M-H, Fixed, 95% CI
otal (95% CI) otal events leterogeneity: Chi ² = 14.: est for overall effect: Z = Other complications in PDC tudy or Subgroup tai HH 2012 orong ZT 2014 I-Geidie 2010 Ia JP 2004 ameel 2008 iu WS 2017 Iartin 1998 arra-Membrives 2017 Ven SQ 2017 i HJ 2015 hang LD 2008 hang WJ 2015 otal events leterogeneity: Chi ² = 4.4: est for overall effect: Z = .Other complications in PDC tudy or Subgroup triniatsos 2005 luang SM 2010 im and Lee 2004 yon 2014 langla 2012 laritinez-Baena 2013 arra-Membrives 2017 ang CN 2006	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0 3 2 1 2 3 3 7, df = 11 3.69 (P = C+BD versu PDC+I Events 0 2 3 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1	397 0 (P = 0 0.01) 134 97 61 124 48 49 55 366 52 91 40 47 722 (P = 0.9 0.0002 s TTD BD Total 121 134 49 55 52 91 40 47 722 s TTD BD Total 21 121 21 50 50 50 50 50 50 50 50 50 50	71 1.15); ² = TTD <u>Events</u> 1 6 3 2 2 2 5 12 2 1 0 5 12 2 3 9 9 9 9 9 9 9 9 9 9 5 12 1 0 5 12 1 0 5 12 2 2 2 5 12 2 2 2 5 12 2 2 2 2 5 12 2 2 2 5 12 2 2 2 2 5 12 2 2 2 5 12 2 2 2 2 5 12 2 2 2 5 12 2 2 2 2 5 12 2 2 2 5 12 2 2 2 2 5 12 2 2 2 2 2 1 0 5 9 9 5 5 12 2 2 2 1 0 5 5 12 2 2 2 1 0 5 5 12 2 2 2 1 1 2 2 2 2 1 1 2 2 2 2 1 2 2 2 1 2 2 2 2 1 2 2 2 1 2 2 2 2 1 2 2 2 2 2 2 2 2 2 2 2 2 2	390 31% Total 100 90 61 266 12 61 226 12 33 510 46 582 % Total 22 32 32 32 32 32 32 32 32 32	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 6.1% 10.9% 18.9% 2.5% 1.3% 10.0% 17.9% 100.0% Weight 7.7% 3.8% 4.3% 8.3% 7.9% 11.3% 41.2%	Odds Ratio M-H, Fixed, 95% CI 0.25 (0.01, 6.12) 0.45 (0.11, 1.84) 0.14 (0.01, 2.69) 1.09 (0.09, 13.35) 0.36 (0.06, 2.33) 0.57 (0.10, 3.36) 0.09 (0.00, 1.71) 0.30 (0.08, 1.16) 1.28 (0.11, 14.70) 1.71 (0.07, 42.68) 0.37 (0.07, 2.02) 0.28 (0.07, 1.11) 0.37 (0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI 0.28 (0.01, 6.21) 3.08 (0.44, 21.58) 2.23 (0.22, 22.40) 0.14 (0.01, 3.41) 0.45 (0.04, 5.25) 0.40 (0.04, 3.75) 0.69 (0.27, 1.77)	Favours (PDC+BD) Favours (TTD) Odds Ratio M-H, Fixed, 95% CI
total (95% CI) otal events leterogeneity: $Chi^{2} = 14$. leterogeneity: $Chi^{2} = 4$. leterogeneity: $Chi^{2} $	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 1 4 5 0 0 3 2 1 2 3 7, df = 11 3.69 (P = C+BD versu PDC+I Events 0 2 3 0 1 1 3.69 (P = 2 3 0 1 1 3.69 (P = 2 1 2 3 0 1 1 3.69 (P = 2 4 7, df = 10 1 2 3 1 2 4 7, df = 10 1 3 1 2 3 3 1 2 4 7, df = 10 2 3 3 1 1 2 3 3 1 1 3 5 5 1 1 3 5 1 1 3 5 5 5 5 5 5	397 0 (P = 0 0.01) 134 97 61 124 48 49 55 36 52 91 40 47 722 (P = 0.9 0.0002 s TTD 30 Total 10 50 52 91 40 47 722 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 91 40 52 52 91 40 722 55 52 91 40 722 55 52 91 40 722 55 50 50 50 50 50 50 50 50 50	71 1.15); ² = TTD Events 1 6 3 2 2 2 2 2 2 2 2 2 2 2 2 2	390 31% Total 100 90 61 26 12 61 52 33 51 46 582 % Total 32 46 582 % Total 32 46 32 46 582 32 40 32 46 32 51 46 582 582 52 52	Weight 3.6% 12.7% 7.3% 2.4% 6.4% 10.9% 18.9% 1.3% 100.0% Weight 7.7% 3.8% 4.3% 8.3% 8.3% 11.2%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.22, 0.03] 0.37 [0.22, 0.63] 0.37 [0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI 0.28 [0.01, 6.21] 3.08 [0.44, 21.58] 0.23 [0.22, 22.40] 0.14 [0.01, 3.41] 0.45 [0.44, 3.75] 0.40 [0.04, 3.75] 0.69 [0.27, 1.77] 1.39 [0.30, 6.39]	Favours (PDC+BD) Favours (TTD) Odds Ratio M-H, Fixed, 95% CI
otal (95% CI) otal events leterogeneity: $Chi^2 = 14$. est for overall effect: $Z =$ Other complications in PDC tudy or Subgroup tai HH 2012 orong ZT 2014 H-Geidie 2010 ta JP 2004 ameel 2008 iu WS 2017 tartin 1998 arra-Membrives 2017 Ven SQ 2017 i HJ 2015 hang LD 2008 hang VJ 2015 otal events leterogeneity: $Chi^2 = 4.4$ est for overall effect: $Z =$.Other complications in PDC tudy or Subgroup printatsos 2005 tuang SM 2010 tim and Lee 2004 yon 2014 tartinez-Baena 2013 arra-Membrives 2017 ang CN 2006 Vei Q 2004	45 59, df = 10 2.52 (P = PDC Events 0 3 0 1 4 5 0 3 2 1 2 3 3 2 4 7, df = 11 3.69 (P = C+BD versu PDC+E Events 0 2 3 0 1 1 1 10 5 0 0 2 2 2 2 3 0 1 1 1 2 2 2 4 7, df = 10 0 3 3 2 1 2 1 2 3 3 0 1 1 3 6 9 (P = 2 4 7, df = 10 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2 1 2	397 0 (P = 0 0.01) 134 97 61 134 97 61 12 48 49 55 36 52 91 49 52 91 47 722 (P = 0.9 0.0002 s <i>TTD</i> 30 50 82 12 134 49 55 36 52 91 47 722 13 134 49 55 36 52 91 47 722 31 134 49 55 36 52 91 47 722 31 134 49 55 36 52 91 47 722 31 134 49 55 36 52 91 47 722 31 50 50 50 50 50 50 50 50 50 50	71 1.15); [≠] = TTD <u>Events</u> 1 6 3 2 2 2 5 12 2 1 0 5 9 9 95); [≠] = 0 2 3 1 2 2 3 1 1 2 2 3 1 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 5 1 2 2 2 3 9 9 5 1 2 2 3 9 9 5 1 2 2 2 3 1 2 2 3 9 2 2 3 1 2 2 3 1 2 2 3 1 2 2 3 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 2 3 1 1 2 3 1 1 2 3 1 1 2 3 1 1 2 3 1 2 3 1 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 1 1 2 3 2 3 1 1 2 3 2 3 1 1 2 3 1 2 3 1 2 3 1 2 3 1 2 3 2 2 3 2 2 3 2 2 2 2 2 2 2 2 2 2 2 2 2	390 31% Total 100 90 61 26 12 61 52 33 51 46 582 % Total 32 46 582 % Total 229 46 32 46 582 32 46 32 46 582 32 46 32 46 582 32 36 36 36 36 36 582 32 36 36 36 36 36 37 36 37 37 36 37 37 37 37 37 37 37 37 37 37	Weight 3.8% 12.7% 7.3% 2.4% 6.4% 10.9% 18.9% 2.5% 1.3% 10.0% 17.9% 100.0% 100.0% 17.9% 100.0% 1.3% 4.3% 8.3% 7.7% 3.8% 11.2% 4.3%	Odds Ratio M-H, Fixed, 95% CI 0.25 [0.01, 6.12] 0.45 [0.11, 1.84] 0.14 [0.01, 2.69] 1.09 [0.09, 13.35] 0.36 [0.06, 2.33] 0.57 [0.10, 3.36] 0.09 [0.00, 1.71] 1.28 [0.11, 14.70] 1.71 [0.07, 42.68] 0.37 [0.07, 2.02] 0.28 [0.07, 1.11] 0.37 [0.22, 0.63] Odds Ratio M-H, Fixed, 95% CI 0.28 [0.01, 6.21] 3.08 [0.44, 21.58] 2.23 [0.22, 22.40] 0.14 [0.01, 3.41] 0.45 [0.44, 3.75] 0.69 [0.27, 1.77] 1.39 [0.30, 6.39] 0.56 [0.02, 14.25]	Favours (PDC+BD) Favours (TTD) Odds Ratio M-H, Fixed, 95% CI

Figure 1. Forest plots of postoperative overall morbidity and other complications. PDC, primary duct closure; TTD, T tube drainage; BD, biliary drainage; CI:, confidence interval.

a.Bile leak in PDC versus TTD

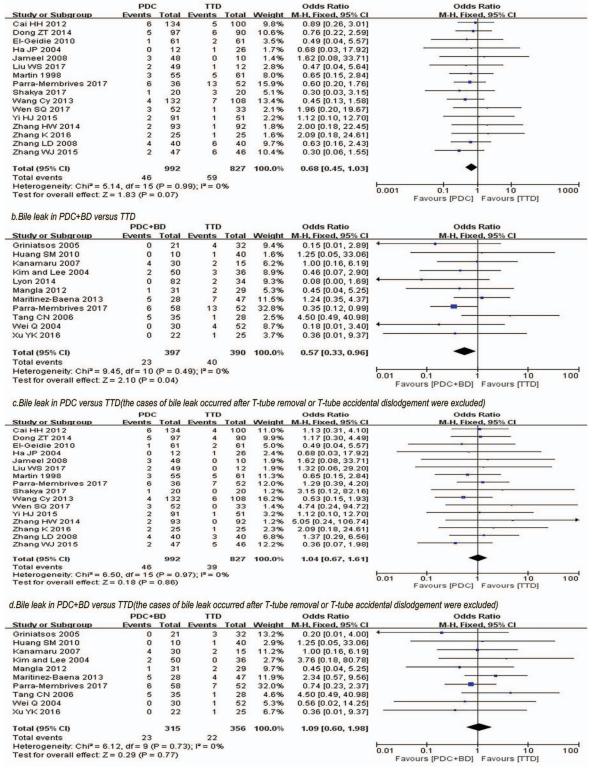


Figure 2. Forest plots of bile leak. PDC, primary duct closure; TTD, T tube drainage; BD, biliary drainage; CBD, common bile duct; CI, confidence interval.

a.Bile peritonitis in PDC versus TTD

	PDO		TTD			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Cai HH 2012	0	134	1	100	8.0%	0.25 [0.01, 6.12]	• • •
Dong ZT 2014	0	97	2	90	12.1%	0.18 [0.01, 3.83]	• • • • • • • • • • • • • • • • • • •
El-Geidie 2010	0	61	2	61	11.6%	0.19 [0.01, 4.12]	• • • • • • • • • • • • • • • • • • •
Martin 1998	0	55	3	61	15.4%	0.15 [0.01, 2.98]	· · · · · · · · · · · · · · · · · · ·
Parra-Membrives 2017	0	36	3	52	13.3%	0.19 [0.01, 3.87]	· · · · · ·
Wang Cy 2013	0	132	1	108	7.7%		
Wen SQ 2017	0	52	1	33	8.5%	0.21 [0.01, 5.22]	• • • • • • • • • • • • • • • • • • •
Zhang LD 2008	0	40	3	40	16.2%		← ■
Zhang WJ 2015	0	47	1	46	7.0%		
Total (95% CI)		654		591	100.0%	0.20 [0.07, 0.55]	-
Total events	0		17				
Heterogeneity: Chi ² = 0.2	25. df = 8 (P = 1.0	0): $I^2 = 0.9$	6			tes et de set
Test for overall effect: Z =	= 3.10 (P =	: 0.002)					0.01 0.1 1 10 100 Favours (PDC) Favours (TTD)
b.Bile peritonitis in PDC+Bl	D versus I	TD					
	PDC+	BD	TTD)		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Griniatsos 2005	0	21	1	32	7.2%		
Huang SM 2010	Ő	10	1	40	3.7%		
	0	50	3		24.8%		
Kim and Lee 2004				36			
Lyon 2014	0	82	2	34	21.6%		
Maritinez-Baena 2013	1	28	3	47	13.3%		
Parra-Membrives 2017	0	58	3	52	22.6%	0.12 [0.01, 2.40]	•
Wei Q 2004	0	30	1	52	6.7%	0.56 [0.02, 14.25]	
Total (95% CI)		279		293	100.0%	0.26 [0.09, 0.77]	-
Total events	1		14				16 25 25
Heterogeneity: Chi ² = 2.9	31, df = 6 (P = 0.8	2); $I^2 = 09$	6			0.01 0.1 1 10 100
Test for overall effect: Z =	= 2.44 (P =	0.01)					Favours [PDC+BD] Favours [TTD]
c.Bile peritonitis in PDC ve	10000	the case	111000	peritoni	tis occurre		l or T-tube accidental dislodgement were excluded)
	PDC		TTD			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total I	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
El-Geidie 2010	0	61	2	61	40.3%	0.13 [0.01, 2.15]	+ -
Martin 1998	0	55	3	61	59.7%	0.14 [0.01, 1.42]	
Total (95% CI)		116		122	100.0%	0.14 [0.02, 0.82]	
Total events	0	1000	5	PARAMENT.	10.01.00.000.000.0000		
Heterogeneity: Chi ² = 0		(P - 0	-	0.9%			
Test for overall effect: Z				0.0			0.01 0.1 1 10 100
Test for overall effect. 2	.= 2.18 (F	= 0.03)				Favours [PDC] Favours [TTD]
d.Bile peritonitis in PDC+E	BD versus	TTD(the	e cases of	bile pe	ritonitis o	ccurred after T-tube rei	moval or T-tube accidental dislodgement were excluded
	PDC+		TTE			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup					Weight	Peto, Fixed, 95% Cl	
Huang SM 2010	O		1	40	i land of a land	the second s	
Maritinez-Baena 2013	0	28	1	40	40.0%		
	0						
Total (95% CI) Total events	0	38	2	87	100.0%	0.23 [0.01, 5.30]	

Figure 3. Forest plots of bile peritonitis. PDC, primary duct closure; TTD, T tube drainage; BD, biliary drainage; CI, confidence interval.

95% CI = 0.37–19.09, P = .33; no heterogeneity was found; $I^2 = 0\%$, P = .62) (**Figure 4B**).

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%

Test for overall effect: Z = 0.91 (P = 0.36)

One patient³² in the TTD group had postoperative pancreatitis due to T-tube migration; none of the patients in the PDC+BD group developed postoperative pancreatitis.

Other Complications

0.01

0.1

The other complications included stent migration or blockage, T-tube dislodgement or twisting, other nonbiliary complications due to T-tube removal, wound infection, pneumonia, intra-abdominal bleeding, and venous thrombus.

Favours [PDC+BD] Favours [TTD]

10

100

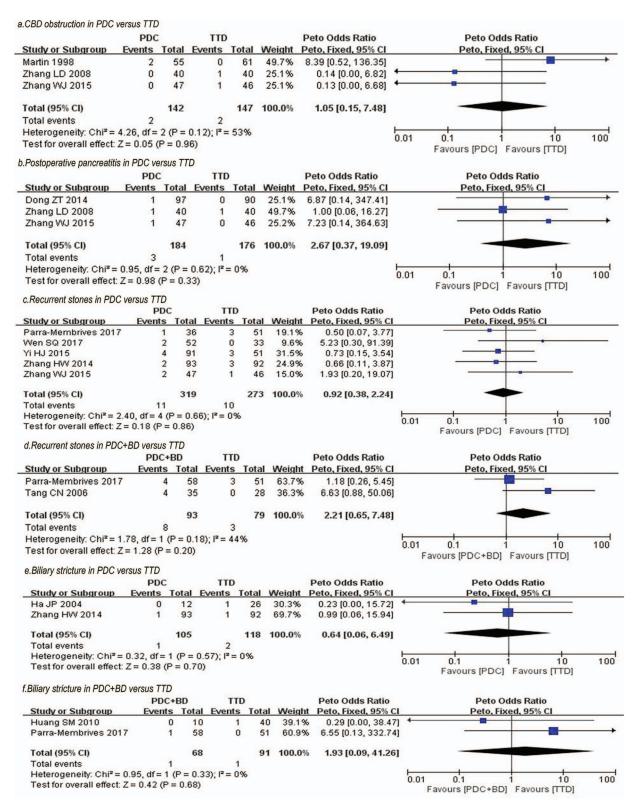


Figure 4. Forest plots of CBD obstruction, postoperative pancreatitis, recurrent stones, and biliary stricture. PDC, primary duct closure; TTD, T tube drainage; BD, biliary drainage; CBD, common bile duct; CI, confidence interval.

Twenty-four patients in the PDC group and 48 patients in the TTD group developed other postoperative complications; the PDC group had a significantly lower incidence of other complications^{9,12,23,26,28,34,37–39,41,43,44} (OR = 0.37, 95% CI = 0.22–0.63, P = .0002; no heterogeneity was found; $I^2 = 0\%$, P = .95) (**Figure 1C**). Fifteen patients^{9,12,21,23,26,28,30,33,34,38,39,43} in the TTD group had T-tube dislodgement, T-tube twisting, or nonbiliary complications after T-tube removal (**Table 2**).

In the subgroup analysis, 22 patients in the PDC+BD group and 29 patients in the TTD group had other postoperative complications; the result tended to favor the PDC+BD group but showed no significant difference^{24,25,27–29,32,35,36,45} (OR = 0.79, 95% CI = 0.44–1.42, P = .44; no heterogeneity was found; I² = 0%, P = .71) (**Figure 1D**). Seven patients in the PDC+BD group had stent migration and dislodgement.^{27,28} Nine patients in the TTD group had T-tube dislodgement or nonbiliary complications after T-tube removal^{27–29,32,45} (**Table 2**).

Recurrent CBD Stones

Recurrence of CBD stones was defined as development of stones not earlier than 6 months after the initial CBD stones were completely removed.^{46,47}

Eleven studies^{23,26,28,30,33,37–40,41,43} that compared PDC with TTD investigated recurrent CBD stones during the follow-up period; in 5 studies,^{26,28,33,37,43} 11/759 (1.4%) patients in the PDC group and 10/662 (1.5%) patients in the TTD group had recurrent CBD stones during the follow-up period. However, no significant difference was discovered (Peto OR = 0.92, 95% CI = 0.38–2.24, P = .86; no heterogeneity was found; I² = 0%, P = .66) (**Figure 4C**).

In the subgroup analysis, 4 studies^{25,27,28,35} investigated recurrent CBD stones, and two studies^{25,28} reported positive findings. Further, 8/147 (5.4%) patients in the PDC+BD group and 3/155 (1.9%) patients in the TTD group had recurrent CBD stones during the follow-up period. However, the result had no significant difference (Peto OR = 2.21, 95% CI = 0.65–7.48, P = .20; the heterogeneity could be accepted; $I^2 = 44\%$, P = .18) (**Figure 4D**).

Biliary Stricture

Eleven studies^{23,26,28,30,33,37–40,41,43} that compared PDC with TTD reported biliary stricture during the follow-up period; in two studies,^{33,41} one patient in the PDC group and two patients in the TTD group had biliary stricture

during the follow-up period. However, the result had no significant difference (Peto OR = 0.64, 95% CI = 0.06-6.49, P = .70; no heterogeneity was found; $I^2 = 0\%$, P = .57) (**Figure 4E**).

In the subgroup analysis, one patient in the PDC+BD group and one patient in the TTD group had biliary stricture during the follow-up period^{28,35}; however, the result had no significant difference (Peto OR = 1.93, 95% CI = 0.09-41.26, P = .68; no heterogeneity was found; $I^2 = 0\%$, P = .33) (**Figure 4F**).

Surgical Time

Thirteen studies^{9,21,23,26,30,33,34,37–41,43} compared the surgical time; the surgical time was significantly shorter in the PDC group than in the TTD group (weighted mean differences, -20.65, 95% CI = -30.17 to -11.13, P < .0001; a heterogeneity was found; I² = 96%, P < .00001) (**Figure 5A**).

In the subgroup analysis, seven studies^{24,25,27,29,31,35,36} reported the surgical time; the surgical time was significantly shorter in the PDC+BD group than in the TTD group (weighted mean differences, -18.61, 95% CI = -32.10 to 5.12, P = .007; a heterogeneity was found; I² = 84%, P < .00001) (**Figure 5B**).

Postoperative Hospital Stay

Twelve studies^{9,23,26,30,33,34,37–40,41,43} reported the duration of postoperative hospital stay; the PDC group had a significantly shorter hospital stay duration (weighted mean differences. -2.89, 95% CI = -3.96 to 1.82, P < .00001; a heterogeneity was found; I² = 96%, P < .00001) (**Figure 5C**).

In the subgroup analysis, the PDC+BD group had a significantly shorter hospital stay duration^{24,25,27,29,31,32,35,36,45} (weighted mean differences, -3.16, 95% CI = -4.65 to 1.68, P < .0001; a heterogeneity was found; $I^2 = 94\%$, P < .0001) (**Figure 5D**).

Publication Bias

No significant publication biases were found on the basis of the funnel plots of the postoperative overall morbidity and bile leak (**Figure 6**).

DISCUSSION

The traditional management after LCBDE for choledocholithiasis is insertion of a T tube; this biliary decompression measure is necessary in cases when high pressure

a.Surgical time in PDC versus TTD

Study or Subarous		DC	Total	Maan	TTD	Total	Moint	Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean	SD		Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Cai HH 2012	92.4	15.2	137	125.7	32.6	102			
Dong ZT 2014	102.6	15.2	101	128.6	20.4	93	8.9%		
I-Geidie 2010	100.6	7.5	61	125.1	10	61	9.1%		
la JP 2004	90	37 12.9	12 49	120	35.2	26	5.6% 8.6%	-30.00 [-54.93, -5.07]	
iu WS 2017	96.2			110.3	12.3	12		-14.10 [-21.94, -6.26]	
Shakya 2017		14.05	20	95.25	9.66	20	8.7%	the second s	
Vang Cy 2013	95.3	17.5	132	138.2	41.6	108	8.6%		Contraction of the second s
Ven SQ 2017		15.14	52	95.92		33	8.9%	18.00 [11.91, 24.09]	
'i HJ 2015	168.9	50.1	91	198	59.6	51	6.7%	-29.10 [-48.43, -9.77]	
Thang HW 2014		10.71	93	108.92		92	9.1%	-4.80 [-8.10, -1.50]	and the second sec
Zhang K 2016	141	85	25	158	71	25	3.2%	-17.00 [-60.41, 26.41]	
hang LD 2008	116	54.6	40	133	58.3	40	5.7%	-17.00 [-41.75, 7.75]	
Thang WJ 2015	106	22.6	47	126.4	29.5	46	8.2%	-20.40 [-31.10, -9.70]	2 Contraction of the second
otal (95% CI)			860			709	100.0%	-20.65 [-30.17, -11.13]	•
leterogeneity: Tau ² =	256.96; 0	hi ² = 28	37.55, 0	if = 12 (F	< 0.00				-100 -50 0 50 100
est for overall effect:	Z = 4.25 (P < 0.00	001)						-100 -50 0 50 100 Favours [PDC] Favours [TTD]
									Pavous (PDO) Pavous (PD)
Survival time in DDC	D unrou								
Surgical time in PDC-									
		C+BD			TTD	and the second		Mean Difference	Mean Difference
study or Subgroup	Mean	SD	Total	Mean			Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Griniatsos 2005	100	7.5	21	115	5	32	20.8%	-15.00 [-18.65, -11.35]	
luang SM 2010	138	37	10	191	75	40	9.4%	-53.00 [-85.65, -20.35]	
(anamaru 2007	234	61.3	30	319	72.3	15	6.8%	-85.00 [-127.66, -42.34]	<u>←</u>
(im and Lee 2004	188.3	52.9	50	166.7	46.2	36	13.9%	21.60 [0.56, 42.64]	
langla 2012	139.19		31	161.1	19.21	29	19.1%	-21.91 [-31.41, -12.41]	
Fang CN 2006	111.1	33.9	35	141.4	45.1	28	14.3%	-30.30 [-50.43, -10.17]	
Vei Q 2004	178	33.5	30	173	45	52	15.7%		
Wel @ 2004	170	34	30	175	40	52	10.7 %	5.00 [-12.25, 22.25]	
Total (95% CI)			207			232	100.0%	-18.61 [-32.10, -5.12]	
					0.0000			- 18.01 [-32.10, -5.12]	
Heterogeneity: Tau ² =				= 6 (P <	0.0000	1); [*=	84%		-100 -50 0 50 100
Test for overall effect:	2=2.70(P = 0.00	00						Favours [PDC+BD] Favours [TTD]
		-							
c.Hospital stay in PDO	C versus I	ID							
		PDC							
Study or Subgroup			-	1.444	TTD			Mean Difference	Mean Difference
Cai HH 2012		n SD			SD.		Weight	IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
	3.1	n SD 1 2.4	137	5.7	SD 4.3	102	8.6%	V. Random, 95% Cl -2.60 [-3.53, -1.67]	
Dong ZT 2014	3.1	n SD 1 2.4 2 2.1	137	5.7 4.9	SD 4.3 3.2	102 93	8.6% 8.7%	 IV, Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] 	
Dong ZT 2014 El-Geidie 2010	3.1 3.2 2.3	n <u>SD</u> 1 2.4 2 2.1 2 1	137 101 61	5.7 4.9 5.6	SD 4.3 3.2 1.8	102 93 61	8.6% 8.7% 9.0%	V, Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004	3.1 3.2 2.1	n <u>SD</u> 1 2.4 2 2.1 2 1 5 2.6	137 101 61 12	7 5.7 4.9 5.5 2 8.6	SD 4.3 3.2 1.8 2.4	102 93 61 26	8.6% 8.7% 9.0% 7.4%	V, Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017	3.1 3.1 2.1 3.1	n SD 1 2.4 2 2.1 2 1 5 2.6 8 0.9	137 101 61 12 49	7 5.7 4.9 5.6 2 8.6 3 4.9	SD 4.3 3.2 1.8 2.4 1.1	102 93 61 26 12	8.6% 8.7% 9.0% 7.4% 8.8%	IV. Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013	3.1 3.1 2.1 3.1 3.1 3.1	n SD 1 2.4 2 2.1 2 1 5 2.6 8 0.9 5 2.1	137 101 61 12 49 132	7 5.7 4.9 5.6 2 8.6 9 4.9 2 6.1	SD 4.3 3.2 1.8 2.4 1.1 4.5	102 93 61 26 12 108	8.6% 8.7% 9.0% 7.4% 8.8% 8.6%	IV. Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017	3.1 3.2 3.8 3.8 3.8	n SD 1 2.4 2 2.1 2 1 5 2.6 8 0.9 5 2.1 4 1.12	137 101 61 12 49 132	7 5.7 4.9 5.6 2 8.6 3 4.9 2 6.1 2 5.11	SD 4.3 3.2 5 1.8 5 2.4 1.1 4.5 1.8	102 93 61 26 12 108 33	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 8.8%	IV. Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015	3.1 3.2 3.8 3.8 8.55	n SD 1 2.4 2 2.1 2 1 5 2.6 8 0.9 5 2.1 4 1.12 9 6	137 101 61 12 49 132 52 91	7 5.7 4.9 1 5.5 2 8.5 3 4.9 2 6.1 2 5.11 1 14.96	SD 4.3 3.2 5 1.8 5 2.4 1.1 4.5 1.8 5.4	102 93 61 26 12 108 33 51	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 8.8% 7.1%	IV. Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -8.37 [-8.30, -4.44]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014	3.1 3.2 3.1 3.1 3.1 8.5 6.9	SD 1 2.4 2 2.1 2 1 5 2.6 8 0.9 5 2.1 4 1.12 9 6 5 0.73	137 101 61 12 49 132 52 91 93	7 5.7 4.9 2 8.5 2 8.5 3 4.9 2 6.1 2 5.11 4 14.96 3 12.05	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 1.08	102 93 61 26 12 108 33 51 92	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 8.8% 7.1% 9.1%	IV, Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016	3. 3. 2. 3. 3. 3. 8.5 6.9 5.	SD 1 2.4 2 2.1 2 1 5 2.6 8 0.9 5 2.1 4 1.12 9 6 5 0.73 3 1.4	137 101 61 12 49 132 52 91 93 26	7 5.7 4.9 2 8.5 2 6.1 2 5.11 1 14.98 3 12.05 5 6.7	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 1.08 4.3	102 93 61 26 12 108 33 51 92 25	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 8.8% 7.1% 9.1% 7.3%	IV. Random, 95% CI -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37]	
Dong ZT 2014 EI-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016 Zhang LD 2008	3.1 3.2 3.1 3.1 8.55 6.9 5.1 5.1	SD 1 2.4 2 2.1 5 2.6 8 0.9 5 2.1 4 1.12 9 6 5 0.73 3 1.4 2 2.2	137 101 61 12 49 132 52 91 93 26 40	7 5.7 4.9 2 8.5 2 6.1 2 5.11 14.98 3 12.05 5 6.7 0 8.3	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 1.08 4.3 3.6	102 93 61 26 12 108 33 51 92 25 40	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 8.8% 7.1% 9.1% 7.3% 8.1%	IV. Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.10 [-3.77, 0.37] -3.10 [-4.41, -1.79]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016	3. 3. 2. 3. 3. 3. 8.5 6.9 5.	SD 1 2.4 2 2.1 2 1 5 2.6 8 0.9 5 2.1 4 1.12 9 6 5 0.73 3 1.4 2 2.2	137 101 61 12 132 132 52 91 93 25 40	7 5.7 4.9 2 8.5 2 6.1 2 5.11 14.98 3 12.05 5 6.7 0 8.3	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 1.08 4.3 3.6	102 93 61 26 12 108 33 51 92 25	8.6% 9.0% 7.4% 8.8% 8.6% 8.8% 7.1% 9.1% 7.3% 8.1%	IV, Random, 95% Cl -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.10 [-4.41, -1.79]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016 Zhang LD 2008 Zhang WJ 2015	3.1 3.2 3.1 3.1 8.55 6.9 5.1 5.1	SD 1 2.4 2 2.1 2 1 5 2.6 8 0.9 5 2.1 4 1.12 9 6 5 0.73 3 1.4 2 2.2	137 101 61 12 49 132 52 91 93 25 25 40 40	7 5.7 4.9 1 5.5 2 8.5 3 4.9 2 6.1 2 5.11 1 14.96 3 12.05 3 12.05 7 8.4	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 1.08 4.3 3.6	102 93 61 26 12 108 33 51 92 25 40 46	8.6% 9.0% 7.4% 8.8% 8.6% 7.1% 9.1% 7.3% 8.1% 8.6%	IV. Random, 95% CI -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.10 [-4.41, -1.79] -3.30 [-4.23, -2.37]	
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016 Zhang LD 2008 Zhang WJ 2015 Total (95% CI)	3.1 3.2 3.6 8.5 6.9 5.1 5.1	sp 1 2.4 2 2.1 2 1 5 2.6 8 0.9 5 2.1 4 1.12 9 6 5 0.73 3 1.4 2 2.21 1 1.6	137 101 61 12 49 132 52 91 93 25 40 40 47 840	7 5.7 1 4.9 1 5.5 2 8.5 3 4.9 2 6.1 2 5.11 1 14.96 3 12.05 6.7 0 8.3 7 8.4 0	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 5.4 5.4 5.4 3.6 3.6 2.8	102 93 61 26 12 108 33 51 92 25 40 46 689	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 7.1% 9.1% 7.3% 8.1% 8.6% 100.0 %	IV. Random, 95% CI 2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.30 [-4.23, -2.37] -3.30 [-4.23, -2.37]	IV, Random, 95% Cl
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016 Zhang LD 2008 Zhang WJ 2015 Total (95% CI) Heterogeneity: Tau	3.1 3.2 3.8 3.8 5.9 5.1 5.1 5.1 5.1 5.1	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	137 101 61 12 49 132 52 91 93 26 40 47 840 273.53	7 5.7 1 4.9 1 5.5 2 8.5 9 4.9 2 6.1 2 6.1 1 14.96 3 12.05 5 6.7 0 8.3 7 8.4 0 , df = 11	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 5.4 5.4 5.4 3.6 3.6 2.8	102 93 61 26 12 108 33 51 92 25 40 46 689	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 7.1% 9.1% 7.3% 8.1% 8.6% 100.0 %	IV. Random, 95% CI 2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.30 [-4.23, -2.37] -3.30 [-4.23, -2.37]	N, Random, 95% Cl
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang LD 2008 Zhang UJ 2015 Total (95% CI)	3.1 3.2 3.8 3.8 5.9 5.1 5.1 5.1 5.1 5.1	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	137 101 61 12 49 132 52 91 93 26 40 47 840 273.53	7 5.7 1 4.9 1 5.5 2 8.5 9 4.9 2 6.1 2 6.1 1 14.96 3 12.05 5 6.7 0 8.3 7 8.4 0 , df = 11	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 5.4 5.4 5.4 3.6 3.6 2.8	102 93 61 26 12 108 33 51 92 25 40 46 689	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 7.1% 9.1% 7.3% 8.1% 8.6% 100.0 %	IV. Random, 95% CI 2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.30 [-4.23, -2.37] -3.30 [-4.23, -2.37]	IV, Random, 95% Cl
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016 Zhang LD 2008 Zhang WJ 2015 Total (95% CI) Heterogeneity: Tau Test for overall effe	3. 3. 2. 4 3. 3. 3. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5.	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	137 101 61 12 49 132 93 25 40 47 840 273.53 0.0000	7 5.7 1 4.9 1 5.5 2 8.5 9 4.9 2 6.1 2 6.1 1 14.96 3 12.05 5 6.7 0 8.3 7 8.4 0 , df = 11	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 5.4 5.4 5.4 3.6 3.6 2.8	102 93 61 26 12 108 33 51 92 25 40 46 689	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 7.1% 9.1% 7.3% 8.1% 8.6% 100.0 %	IV. Random, 95% CI 2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.30 [-4.23, -2.37] -3.30 [-4.23, -2.37]	N, Random, 95% Cl
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016 Zhang LD 2008 Zhang WJ 2015 Total (95% CI) Heterogeneity: Tau Test for overall effe	3. 3. 2. 4 3. 3. 3. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5.	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	137 101 61 12 49 132 93 25 40 47 840 273.53 0.0000	7 5.7 1 4.9 1 5.5 2 8.5 9 4.9 2 6.1 2 6.1 1 14.96 3 12.05 5 6.7 0 8.3 7 8.4 0 , df = 11	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 5.4 5.4 5.4 3.6 3.6 2.8	102 93 61 26 12 108 33 51 92 25 40 46 689	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 7.1% 9.1% 7.3% 8.1% 8.6% 100.0 %	IV. Random, 95% CI 2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.30 [-4.23, -2.37] -3.30 [-4.23, -2.37]	N, Random, 95% Cl
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016 Zhang LD 2008 Zhang WJ 2015 Total (95% CI) Heterogeneity: Tau Test for overall effe	3. 3. 3. 3. 3. 3. 4. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	137 101 61 12 49 132 52 91 93 93 93 93 26 40 47 840 273.53 0.0000	7 5.7 1 4.9 1 5.5 2 8.5 9 4.9 2 6.1 2 6.1 1 14.96 3 12.05 5 6.7 0 8.3 7 8.4 0 , df = 11	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 5.4 5.4 5.4 5.4 3.6 3.6 2.8	102 93 61 26 12 108 33 51 92 25 40 46 689	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 7.1% 9.1% 7.3% 8.1% 8.6% 100.0 %	IV. Random, 95% CI 2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.30 [-4.23, -2.37] -3.30 [-4.23, -2.37]	IV. Random, 95% Cl
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang LD 2008 Zhang WJ 2015 Total (95% CI) Heterogeneity: Tau Test for overall effet d.Hospital stay in PD0	3. 3. 3. 3. 3. 3. 4. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5	$\begin{array}{rrrr} n & SD \\ 1 & 2.4 \\ 2 & 2.1 \\ 2 & 1 \\ 5 & 2.6 \\ 8 & 0.9 \\ 5 & 2.1 \\ 4 & 1.12 \\ 9 & 6 \\ 5 & 0.73 \\ 3 & 1.4 \\ 2 & 2.2 \\ 1 & 1.6 \\ \hline \\ Chi^2 = 2 \\ 29 (P < \\ Sus TTD \\ PDC+BE \\ \end{array}$	137 101 61 12 49 132 52 93 93 93 93 93 93 93 93 93 93 93 93 93	7 5.7 1 4.9 1 5.5 2 8.5 9 4.9 2 6.1 2 6.1 1 14.96 3 12.05 5 6.7 0 8.3 7 8.4 0 , df = 11	SD 4.3 3.2 5.1.8 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4	102 93 61 26 12 108 33 51 92 25 40 46 689	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 7.1% 9.1% 7.3% 8.1% 8.6% 100.0 %	IV. Random, 95% CI -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.30 [-4.23, -2.37] -3.30 [-4.23, -2.37]	V, Random, 95% Cl
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang LD 2008 Zhang WJ 2015 Total (95% Cl) Heterogeneity: Tat Test for overall effet d.Hospital stay in PDI Study or Subgroup	3. 3. 3. 3. 3. 3. 3. 4. 3. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	137 101 61 49 132 52 91 93 25 40 40 47 840 273.53 0.0000 0 0 7 Tota	7 5.7 4 4.9 5.5 2 8.5 9 4.9 2 6.1 2 5.11 1 14.96 8 12.05 5 6.7 0 8.3 7 8.4 0 , df = 11 01)	SD 4.3 3.2 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4 5.4	102 93 61 26 122 108 33 51 92 25 40 46 46 689 00001)	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 8.6% 9.1% 7.3% 8.6% 8.1% 8.6% 100.0%	IV. Random, 95% CI -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.30 [-4.23, -2.37] -3.30 [-4.23, -2.37] -2.89 [-3.96, -1.82] Mean Difference IV, Random, 95% CI	IV, Random, 95% Cl
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang LD 2008 Zhang WJ 2015 Total (95% CI) Heterogeneity: Tau Test for overall effe d.Hospital stay in PDI Study or Subgroup	3.3 3.2 2.2 4 3.8 3.5 5.3 5.1 5.1 5.1 5.1 5.1 5.1 5.1 5.1 5.1 5.1	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	137 101 11 12 49 132 52 91 93 26 40 40 273.53 0.0000 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	7 5.7 4 4.9 1 5.5 2 8.6 3 4.9 2 6.1 2 5.11 1 14.96 3 12.05 5 6.7 0 8.3 7 8.4 0 , df = 11 01) 1 Mean 1 5.5	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 1.08 4.33 3.6 2.8 (P < 0.	102 93 61 266 12 108 33 51 92 25 40 46 689 000001) 000001) 7000001 32	8.6% 8.7% 9.0% 8.8% 8.8% 7.1% 9.1% 7.3% 8.1% 8.6% 100.0%); *= 96% Weightt 14.4%	t IV, Random, 95% CI -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.10 [-4.41, -1.79] -3.30 [-4.23, -2.37] -2.89 [-3.96, -1.82] Mean Difference IV, Random, 95% CI -2.50 [-3.21, -1.79]	IV, Random, 95% Cl
Dong ZT 2014 El-Geidie 2010 Ha JP 2004 Liu WS 2017 Wang Cy 2013 Wen SQ 2017 Yi HJ 2015 Zhang HW 2014 Zhang K 2016 Zhang LD 2008 Zhang WJ 2015 Total (95% CI) Heterogeneity: Tau Test for overall effe	3. 3. 3. 3. 3. 3. 3. 4. 3. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	137 101 11 12 49 132 52 91 93 25 40 40 47 840 273.53 0.0000 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	7 5.7 4 4.9 1 5.5 2 8.5 2 8.1 2 5.1 1 14.96 8 12.05 6 7 8 4 9 . df = 11 01) 1 Mean 1 5.5 0 10 0 10	SD 4.3 3.2 1.8 2.4 1.1 4.5 1.8 5.4 1.8 4.3 3.6 2.8 (P < 0.	102 93 61 26 12 108 33 51 92 25 40 46 689 00001)	8.6% 8.7% 9.0% 7.4% 8.8% 8.6% 8.6% 9.1% 7.3% 8.6% 8.1% 8.6% 100.0%	IV. Random, 95% CI -2.60 [-3.53, -1.67] -1.70 [-2.47, -0.93] -3.30 [-3.82, -2.78] -3.50 [-5.24, -1.76] -1.10 [-1.77, -0.43] -2.60 [-3.52, -1.68] -1.11 [-1.80, -0.42] -6.37 [-8.30, -4.44] -5.10 [-5.37, -4.83] -1.40 [-3.17, 0.37] -3.30 [-4.23, -2.37] -3.30 [-4.23, -2.37] -2.89 [-3.96, -1.82] Mean Difference IV, Random, 95% CI	IV, Random, 95% Cl Cl Cl Cl Cl Cl Cl Cl Cl Cl

Huang SM 2010	7	3	10	10	3	40	11.5%	-3.00 [-5.08, -0.92]			-		
Kanamaru 2007	18	5	30	34	7.8	15	6.6%	-16.00 [-20.33, -11.67]			-		
Kim and Lee 2004	4.8	1.5	50	7.8	3.3	36	13.7%	-3.00 [-4.16, -1.84]			-		
Lyon 2014	1	0.2	82	3.4	1	34	14.8%	-2.40 [-2.74, -2.06]			-		
Mangla 2012	3.9	2	31	6.41	4.99	29	11.9%	-2.51 [-4.46, -0.56]			-		
Maritinez-Baena 2013	5	10.26	28	12	10.6	47	5.8%	-7.00 [-11.86, -2.14]			-		
Tang CN 2006	8.8	9.3	35	10	7.4	28	6.9%	-1.20 [-5.32, 2.92]			+		
Wei Q 2004	5	1.5	30	4	1.5	52	14.5%	1.00 [0.33, 1.67]			1		
Total (95% CI)			317			313	100.0%	-3.16 [-4.65, -1.68]			•		
Heterogeneity: Tau ² = 3.1	87; Chi ²	= 131.6	7, df = 1	8 (P < 0	0.00001); 2 = !	94%		100	10	<u> </u>	10	100
Test for overall effect: Z =	= 4.17 (F	P < 0.000	01)	0.057					-100 Fa	-50 vours (PD	C+BD] Favo	50 urs [TTD]	100

Figure 5. Forest plots of surgical time and hospital stay. PDC, primary duct closure; TTD, T tube drainage; BD, biliary drainage; CI, confidence interval.

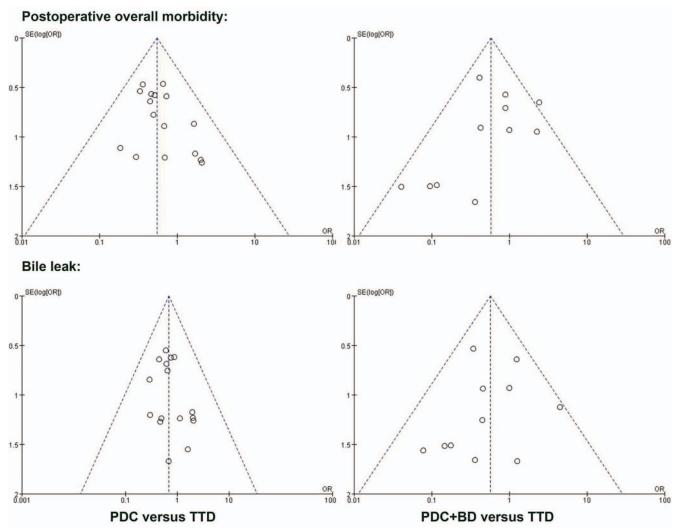


Figure 6. Funnel plots of the distribution of the ORs for postoperative overall morbidity and bile leak of 16 studies comparing PDC with TTD and 11 studies comparing PDC+BD with TTD. PDC, primary duct closure; TTD, T tube drainage; BD, biliary drainage; OR, odds ratio.

exists in biliary tract, with the role of preventing postoperative biliary stricture and treating residual stones conveniently. However, TTD is associated with a number of postoperative complications and causes inconvenience to patients in terms of management of the T tube for a long period after discharge.

Our analysis showed a significantly decreased postoperative overall morbidity in the PDC/PDC+BD group compared with that in the TTD group. More than 30% of the postoperative complications that occurred in the TTD group were associated with T-tube removal, accidental dislodgement, or T-tube twisting. Wills et al¹³ demonstrated that significant morbidity was associated with T- tube insertion after choledochotomy; more than half of the complications were due to planned T-tube removal or dislodgement. Yin et al¹⁵ reported a higher incidence of overall and biliary-specific complications when the T tube was removed between 8 and 16 days than when the T tube was removed after more than 21 days. Therefore, T-tube removal or accidental dislodgement can be recognized as an important cause of the significant increase in postoperative morbidity in TTD compared with that in PDC or PDC+BD.

The incidence of bile leak was lower in the PDC group than in the TTD group (OR = 0.68, P = .07) and in the PDC+BD group than in the TTD group (OR = 0.57, P =

.04). However, some patients in the TTD group had bile leak due to planned T-tube removal or accidental dislodgement. This is probably because of the premature removal of the T tube. Laparoscopic surgery reduces abdominal inflammatory response and adhesion formation compared with open surgery. The material of the T tube has been changed from the previous red rubber to the current silicon-coated latex; the latter is less irritating to abdominal inflammation. Both conditions lead to slow formation of the trans-tube sinus tract composed of granulation and fibrous tissues. In this case, bile leak may occur and develop into bile peritonitis after T-tube removal, since bile flows out of the immature trans-tube sinus tract.14,48 He et al16 compared the ORs of bile leak between short- (less than 3 weeks) and long-term (more than 3 weeks) T-tube indwelling; however, no meaningful results were found (less than 3 weeks: OR = 0.79, P = .74in PDC versus TTD; OR = 1.20, P = .73 in PDC+BD versus TTD; more than 3 weeks: OR = 1.27, P = .54 in PDC versus TTD; OR = 0.82, P = .64 in PDC+BD versus TTD); hence, the suitable time of T-tube removal needs further exploration. Wills et al¹³ presented that T-tube indwelling has a minimal effect of preventing the occurrence of bile leak, with cases of biliary peritonitis occurring after the T tube had been indwelling for 1 month. Similarly, when we excluded the cases of bile leak due to inappropriate T-tube removal, the pooled ORs of bile leak between the PDC and TTD groups and between the PDC+BD and TTD groups were 1.04 and 1.09, respectively. The results indicated that although decompression TTD was performed, the incidence of bile leak did not decrease. In other words, TTD seemed to have equal effects as PDC alone or PDC+BD in managing bile leak when T tube is continuously indwelling without the circumstance of inappropriate T tube removal or dislodgement. However, the use of PDC is limited by swelling of the sphincter of Oddi and severe acute pyogenic cholangitis because both conditions can cause increased pressure in the biliary tree; further, CBD drainage for decompression of the biliary system is required.33 Therefore, PDC may be necessary to be combined with BD methods for the purpose of CBD decompression in such cases.^{42,45}

The incidence of bile peritonitis was significantly higher in the TTD group than in the PDC group; further, 12/17 patients in the TTD group had bile peritonitis due to T-tube removal or dislodgement. In the subgroup analysis, a significantly higher incidence of bile peritonitis in the TTD group than in the PDC+BD group was found, and 12/14 patients had bile peritonitis due to T-tube removal or dislodgement. This is probably due to the immature T-tube sinus tract or disruption of the sinus tract during the T-tube removal process.⁴⁸ Further, the bile directly flows into the peritoneal cavity without being timely controlled; consequently, bile peritonitis or local biloma emerges.

The incidence of other complications increased significantly in the TTD group compared with that in the PDC group probably because the complications associated with T-tube use accounted for a considerable proportion in the TTD group; the views on postoperative complications identified may vary among different physicians, and some mild and temporary postoperative problems without the need for interventions are considered as complications. No significant difference was found in other complications between PDC+BD and TTD.

The incidence of recurrent stones showed no significant difference between PDC and TTD and between PDC+BD and TTD; a relatively low incidence of recurrent stones was found. Further, 11/759 (1.4%) patients in the PDC group and 10/662 (1.5%) patients in the TTD group had recurrent CBD stones. In the subgroup analysis, 8/147 (5.4%) patients in the PDC+BD group and 3/155 (1.9%) patients in the TTD group had recurrent CBD stones. The risk factors for recurrent stones mainly included bile stasis, sustained dilation of the bile duct, aberrant papilla location, and duodenal-biliary reflux^{46,47}; based on these and our findings, various types of treatment modalities after LCBDE may not be associated with recurrent CBD stones, and more well-designed clinical trials are needed to confirm this.

Biliary stricture seems rare after choledochotomy in LCBDE; the risk factor of biliary stricture after LCBDE is mainly related to a short CBD diameter. The appropriate CBD diameter for a safe and successful choledochotomy remains controversial for the purpose of preventing biliary stricture after choledochotomy; in imaging studies, a CBD diameter larger than 8 mm was recommended for LCBDE.37 Gigot et al49 suggested a CBD diameter larger than 9 mm if PDC is implemented following choledochotomy. Our findings revealed no difference in the incidence of biliary stricture between PDC/PDC+BD and TTD, and very few patients had biliary stricture during the follow-up period. Decker et al⁵⁰ investigated 100 patients who underwent laparoscopic choledochotomy and found that none of them had biliary stricture after PDC. Therefore, PDC/PDC+BD and TTD may have a minimal contribution on biliary stricture if PDC is performed under a suitable CBD diameter.

The TTD group had a longer surgical time and hospital stay probably because of the complex procedures in Ttube insertion and subsequent CBD incision closure during surgery; further, TTD patients need a longer time for postoperative recovery and ensuring the patency of the T tube. However, under the diverse medical policies in different hospitals for hospital stay, eg, pursuing shorter lengths of hospital stay, the impact of man-made interference might generate bias in the results.

We conducted this meta-analysis based on a larger sample size of 2552 patients; thus, the analysis results were more persuasive to a certain degree. We carefully considered the definitions of complications; residual stones are not a complication but should be considered as a cure failure because they are not associated with PDC or other various BD methods after LCBDE. Considering that a number of postoperative complications were caused by T-tube dislodgement or planned removal, we attempted to evaluate the risk of bile leak or bile peritonitis when the T tube was indwelling and found that TTD had no valuable effect on preventing bile leak and bile peritonitis. We also analyzed the difference in the incidence of postoperative recurrent CBD stones and biliary stricture between the PDC/ PDC+BD and TTD groups, which had not been reported in previous meta-analyses. The Peto OR was employed for comparing low incidence events, which may be the most effective method and was able to minimize bias. The OR distributions in the funnel plots for postoperative overall morbidity and bile leak were basically symmetrical, reflecting the relatively small bias in this meta-analysis.

In summary, PDC alone or PDC+BD yielded a significantly lower postoperative morbidity than did TTD. Decompression TTD did not seem to be effective in preventing the occurrence of bile leak or bile peritonitis; PDC+BD was a reasonable alternative if the condition was not suitable for PDC alone, eg, when biliary decompression was required. Furthermore, PDC and PDC+BD yielded a shorter surgical time and hospital stay and might be safe in terms of biliary stricture under a suitable CBD diameter. However, further large and well-designed randomized controlled trials that would evaluate the effectiveness and safety of various drainage methods after LCBDE are needed to confirm these findings.

References:

1. Tazuma S. Gallstone disease: epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). *Best Pract Res Clin Gastroenterol.* 2006;20(6):1075–1083.

2. Williams E, Beckingham I, El SG, et al. Updated guideline on the management of common bile duct stones (CBDS). *Gut.* 2017;66(5):765–782.

3. Vannijvel M, Lesurtel M, Bouckaert W, et al. A survey of European-African surgeons' management of common bile duct stones. *HPB (Oxford)*. 2016;18(12):959–964.

4. Wandling MW, Hungness ES, Pavey ES, et al. Nationwide assessment of trends in choledocholithiasis management in the United States from 1998 to 2013. *JAMA Surg.* 2016;151(12):1125–1130.

5. Gilsdorf D, Henrichsen J, Liljestrand K, et al. Laparoscopic common bile duct exploration for choledocholithiasis: analysis of practice patterns of Intermountain HealthCare. *J Am Coll Surg.* 2018;226(6):1160–1165.

6. Rogers SJ, Cello JP, Horn JK, et al. Prospective randomized trial of LC+LCBDE vs ERCP/S+LC for common bile duct stone disease. *Arch Surg.* 2010;145(1):28–33.

7. Singh AN, Kilambi R. Single-stage laparoscopic common bile duct exploration and cholecystectomy versus two-stage endoscopic stone extraction followed by laparoscopic cholecystectomy for patients with gallbladder stones with common bile duct stones: systematic review and meta-analysis of randomized trials with trial sequential analysis. *Surg Endosc.* 2018;32(9):3763– 3776.

8. Feng Q, Huang Y, Wang K, et al. Laparoscopic transcystic common bile duct exploration: advantages over laparoscopic choledochotomy. *PLoS One.* 2016;11(9):e0162885.

9. El-Geidie AA. Is the use of t-tube necessary after laparoscopic choledochotomy? *J Gastrointest Surg.* 2010;14(5):844– 848.

10. Chen CC, Wu SD, Tian Y, Zeng XT, Siwo EA, Xian GZ. The fading role of T-tube in laparoscopic choledochotomy: primary choledochorrhaphy and over pigtail j and endonasobiliary drainage tubes. *J Laparoendosc Adv Surg Tech A*. 2010;20(10):807–811.

11. Cuschieri A, Croce E, Faggioni A, et al. EAES ductal stone study. Preliminary findings of multi-center prospective randomized trial comparing two-stage vs single-stage management. *Surg Endosc.* 1996;10(12):1130–1135.

12. Martin IJ, Bailey IS, Rhodes M, O'Rourke N, Nathanson L, Fielding G. Towards T-tube free laparoscopic bile duct exploration: a methodologic evolution during 300 consecutive procedures. *Ann Surg.* 1998;228(1):29–34.

13. Wills VL, Gibson K, Karihaloot C, Jorgensen JO. Complications of biliary T-tubes after choledochotomy. *ANZ J Surg.* 2002; 72(3):177–180.

14. Parra-Membrives P, Martínez-Baena D, Márquez-Muñoz M, Pino-Díaz V. Does laparoscopic approach impair T-tube-related sinus-tract formation? *Surg Laparosc Endosc Percutan Tech*. 2013;23(1):55–60.

15. Yin Z, Xu K, Sun J, et al. Is the end of the T-tube drainage era in laparoscopic choledochotomy for common bile duct stones is coming? A systematic review and meta-analysis. *Ann Surg.* 2013; 257(1):54–66.

16. He MY, Zhou XD, Chen H, et al. Various approaches of laparoscopic common bile duct exploration plus primary duct closure for choledocholithiasis: a systematic review and metaanalysis. *Hepatobiliary Pancreat Dis Int.* 2018;17(3):183–191.

17. Podda M, Polignano FM, Luhmann A, Wilson MS, Kulli C, Tait IS. Systematic review with meta-analysis of studies comparing primary duct closure and T-tube drainage after laparoscopic common bile duct exploration for choledocholithiasis. *Surg Endosc.* 2016;30(3):845–861.

18. Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240(2): 205–213.

19. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [Updated March 2011]. The Cochrane Collaboration, 2011. Available from: http://www. cochrane-handbook.org.

20. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/ clinical_epidemiology/oxford.asp.

21. Shakya JPS, Agrawal N, Kumar A, et al. Primary closure versus T-tube drainage after laparoscopic choledocholithotomy: a prospective randomized study. *Int Surg J.* 2017;4(5):1762–1764.

22. Zhang W, Li G, Chen YL. Should T-Tube drainage be performed for choledocholithiasis after laparoscopic common bile duct exploration? A systematic review and meta-analysis of randomized controlled trials. *Surg Laparosc Endosc Percutan Tech.* 2017;27(6):415–423.

23. Leida Z, Ping B, Shuguang W, Yu H. A randomized comparison of primary closure and T-tube drainage of the common bile duct after laparoscopic choledochotomy. *Surg Endosc.* 2008; 22(7):1595–1600.

24. Mangla V, Chander J, Vindal A, Lal P, Ramteke VK. A randomized trial comparing the use of endobiliary stent and T-tube for biliary decompression after laparoscopic common bile duct exploration. *Surg Laparosc Endosc Percutan Tech.* 2012;22(4): 345–348.

25. Tang CN, Tai CK, Ha JP, Tsui KK, Wong DC, Li MK. Antegrade biliary stenting versus T-tube drainage after laparoscopic choledochotomy—a comparative cohort study. *Hepatogastroenterology*. 2006;53(69):330–334.

26. Wen S, Hu Q, Wan M, et al. Appropriate patient selection is essential for the success of primary closure after laparoscopic

common bile duct exploration. *Dig Dis Sci.* 2017;62(5):1321–1326.

27. Wei Q, Hu HJ, Cai XY, Li LB, Wang GY. Biliary drainage after laparoscopic choledochotomy. *World J Gastroenterol.* 2004; 10(21):3175–3178.

28. Parra-Membrives P, Martínez-Baena D, Lorente-Herce J, Jiménez-Riera G. comparative study of three bile duct closure methods following laparoscopic common bile duct exploration for choledocholithiasis. *J Laparoendosc Adv Surg Tech A*. 2018; 28(2):145–151.

29. Griniatsos J, Karvounis E, Arbuckle J, Isla AM. Cost-effective method for laparoscopic choledochotomy. *ANZ J Surg.* 2005; 75(1–2):35–38.

30. Wang C, Wang Q, Sun D, Chen X, Sun Y. Immunogenic alteration in laparoscopic common bile duct exploration. *J Surg Res.* 2014;187(1):302–309.

31. Kanamaru T, Sakata K, Nakamura Y, Yamamoto M, Ueno N, Takeyama Y. Laparoscopic choledochotomy in management of choledocholithiasis. *Surg Laparosc Endosc Percutan Tecb.* 2007; 17(4):262–266.

32. Martínez-Baena D, Parra-Membríves P, Díaz-Gómez D, Lorente-Herce JM. Laparoscopic common bile duct exploration and antegrade biliary stenting: leaving behind the Kehr tube. *Rev Esp Enferm Dig.* 2013;105(3):125–129.

33. Zhang HW, Chen YJ, Wu CH, Li WD. Laparoscopic common bile duct exploration with primary closure for management of choledocholithiasis: a retrospective analysis and comparison with conventional T-tube drainage. *Am Surg.* 2014;80(2):178.

34. Liu WS, Zou Y, Yang B, Jiang Y, Sun DL. Laparoscopic exploration can salvage recurrent common bile duct stone after cholecystectomy. *Am Surg.* 2017;83(12):1343–1346.

35. Huang SM, Yao CC, Cheng YW, et al. Laparoscopic primary closure of common bile duct combined with percutaneous cholangiographic drainage for treating choledocholithiasis. *Am Surg.* 2010;76(5):517–521.

36. Kim EK, Lee SK. Laparoscopic treatment of choledocholithiasis using modified biliary stents. *Surg Endosc.* 2004;18(2):303– 306.

37. Yi HJ, Hong G, Min SK, Lee HK. Long-term outcome of primary closure after laparoscopic common bile duct exploration combined with choledochoscopy. *Surg Laparosc Endosc Percutan Tech.* 2015;25(3):250–253.

38. Dong ZT, Wu GZ, Luo KL, Li JM. Primary closure after laparoscopic common bile duct exploration versus T-tube. *J Surg Res.* 2014;189(2):249–254.

39. Cai H, Sun D, Sun Y, Bai J, Zhao H, Miao Y. Primary closure following laparoscopic common bile duct exploration combined

with intraoperative cholangiography and choledochoscopy. *World J Surg.* 2012;36(1):164–170.

40. Zhang K, Zhan F, Zhang Y, et al. Primary Closure Following Laparoscopic Common Bile Duct Reexploration for the Patients Who Underwent Prior Biliary Operation. *Indian J Surg.* 2016; 78(5):364–370.

41. Ha JP, Tang CN, Siu WT, Chau CH, Li MK. Primary closure versus T-tube drainage after laparoscopic choledochotomy for common bile duct stones. *Hepatogastroenterology*. 2004;51(60): 1605–1608.

42. Xu Y, Dong C, Ma K, et al. Spontaneously removed biliary stent drainage versus T-tube drainage after laparoscopic common bile duct exploration. *Medicine*. 2016;95(39):e5011.

43. Zhang WJ, Xu GF, Huang Q, et al. Treatment of gallbladder stone with common bile duct stones in the laparoscopic era. *BMC Surg.* 2015;15:7.

44. Jameel M, Darmas B, Baker AL. Trend towards primary closure following laparoscopic exploration of the common bile duct. *Ann R Coll Surg Engl.* 2008;90(1):29–35.

45. Lyon M, Menon S, Jain A, Kumar H. Use of biliary stent in laparoscopic common bile duct exploration. *Surg Endosc.* 2015; 29(5):1094–1098.

46. Zhang R, Luo H, Pan Y, et al. Rate of duodenal-biliary reflux increases in patients with recurrent common bile duct stones: evidence from barium meal examination. *Gastrointest Endosc.* 2015;82(4):660–665.

47. Kim DI, Kim MH, Lee SK, et al. Risk factors for recurrence of primary bile duct stones after endoscopic biliary sphincterotomy. *Gastrointest Endosc.* 2001;54(1):42–48.

48. Maghsoudi H, Garadaghi A, Jafary GA. Biliary peritonitis requiring reoperation after removal of T-tubes from the common bile duct. *Am J Surg.* 2005;190(3):430–433.

49. Gigot JF, Navez B, Etienne J, et al. A stratified intraoperative surgical strategy is mandatory during laparoscopic common bile duct exploration for common bile duct stones. Lessons and limits from an initial experience of 92 patients. *Surg Endosc.* 1997; 11(7):722–728.

50. Decker G, Borie F, Millat B, et al. One hundred laparoscopic choledochotomies with primary closure of the common bile duct. *Surg Endosc.* 2003;17(1):12–18.

17