

Citation: Feng Q, Huang Y, Wang K, Yuan R, Xiong X, Wu L (2016) Laparoscopic Transcystic Common Bile Duct Exploration: Advantages over Laparoscopic Choledochotomy. PLoS ONE 11(9): e0162885. doi:10.1371/journal.pone.0162885

Editor: Heather Francis, Digestive Disease Research Center, Scott & White Healthcare, UNITED STATES

Received: April 9, 2016

Accepted: August 30, 2016

Published: September 26, 2016

Copyright: © 2016 Feng et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This work was supported by Youth Science Fund of Jiangxi Provincial Science and Technology Department (No. 20161BAB215252). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

RESEARCH ARTICLE

Laparoscopic Transcystic Common Bile Duct Exploration: Advantages over Laparoscopic Choledochotomy

Qian Feng¹[®], Yong Huang¹[®], Kai Wang¹, Rongfa Yuan¹, Xiaoli Xiong², Linquan Wu¹*

1 Department of General Surgery, The Second Affiliated Hospital of Nanchang University, Nanchang, 330006, China, 2 Department of Radiology, The Second Affiliated Hospital of Nanchang University, Nanchang, 330006, China

• These authors contributed equally to this work.

* Wulqnc@163.com

Abstract

Purpose

The ideal treatment for choledocholithiasis should be simple, readily available, reliable, minimally invasive and cost-effective for patients. We performed this study to compare the benefits and drawbacks of different laparoscopic approaches (transcystic and choledochot-omy) for removal of common bile duct stones.

Methods

A systematic search was implemented for relevant literature using Cochrane, PubMed, Ovid Medline, EMBASE and Wanfang databases. Both the fixed-effects and randomeffects models were used to calculate the odds ratio (OR) or the mean difference (MD) with 95% confidence interval (CI) for this study.

Results

The meta-analysis included 18 trials involving 2,782 patients. There were no statistically significant differences between laparoscopic choledochotomy for common bile duct exploration (LCCBDE) (n = 1,222) and laparoscopic transcystic common bile duct exploration (LTCBDE) (n = 1,560) regarding stone clearance (OR 0.73, 95% CI 0.50–1.07; P = 0.11), conversion to other procedures (OR 0.62, 95% CI 0.21–1.79; P = 0.38), total morbidity (OR 1.65, 95% CI 0.92–2.96; P = 0.09), operative time (MD 12.34, 95% CI –0.10–24.78; P = 0.05), and blood loss (MD 1.95, 95% CI –9.56–13.46; P = 0.74). However, the LTCBDE group showed significantly better results for biliary morbidity (OR 4.25, 95% CI 2.30–7.85; P<0.001), hospital stay (MD 2.52, 95% CI 1.29–3.75; P<0.001), and hospital expenses (MD 0.30, 95% CI 0.23–0.37; P<0.001) than the LCCBDE group.

Conclusions

LTCBDE is safer than LCCBDE, and is the ideal treatment for common bile duct stones.

Introduction

Approximately 10% of gallstone patients have concomitant common bile duct (CBD) stones [1, 2], which are related to serious complications such as cholangitis and pancreatitis. Therefore, it is particularly important to improve and standardize the process of diagnosis and treatment of CBD stones. The conventional approach of open CBD exploration is considered an effective treatment option [3–5]. However, surgical trauma, bile leakage, biliary tract blood loss, and other complications are not conducive to postoperative rehabilitation [6]. With rapid developments in technology, laparoscopic CBD exploration (LCBDE) was proven to be safe, cost-effective, and reliable, regardless of whether it was performed as elective or emergency treatment [7, 8]. Clinical prospective randomized trials have shown that laparoscopic procedures are superior to open operations with regard to reduced postoperative hospital stay, morbidity and postsurgical pain [9, 10].

Laparoscopic surgery for CBD stones could be categorized into transcystic and choledochotomy approaches [11]. In laparoscopic choledochotomy for CBD exploration (LCCBDE), the integrity of the CBD is lost due to the incision over the duct. In contrast, the cystic duct is used for laparoscopic transcystic CBD exploration (LTCBDE), thus minimizing the size of the incision over the CBD [12]. Moreover, application of a separate laparoscopic suture over the stump of the cystic duct dramatically decreases the postoperative incidence of bile leakage [6]. Our research and that of several groups has reported that LTCBDE is certainly the least invasive, safest, and most efficient option, with low morbidity rates [13–15]. LTCBDE avoids choledochotomy and eliminates the subsequent requirement of a T-tube; thus avoiding T-tube prolapse or displacement, CBD stricture, electrolyte imbalance, acid-base balance disorders, and complications caused by bile drainage and invasive treatments [16]. Additionally, the treatment facilitates rapid recovery. In LCCBDE, the traditional approach is to incise the common bile duct from the front. The operative procedure is simpler than LTCBDE, and it is safe and mature.

LTCBDE has not been universally accepted because the operation is relatively complex [17], and multi-center studies have not been conducted. Furthermore, no clear guidelines for the indications of the transcystic approach versus choledochotomy are available. The aim of this study was to pool analysis by investigating published data on LCBDE by the transcystic approach and choledochotomy. We assumed that LTCBDE is the ideal treatment for CBD stones.

Methods

Literature search

A systematic search was carried out using Cochrane, PubMed, Ovid Medline, EMBASE and Wanfang databases using the following keywords: bile duct exploration, laparoscopic CBD exploration, laparoscopic cholecystectomy, CBD stones, LCBDE, choledochotomy, laparoscopic transcystic CBD exploration, or LTCBDE. The latest search was updated on May 20th, 2016. The eligible studies were independently selected by two reviewers. Disagreement on article inclusion between the two reviewers was resolved by discussion with a third reviewer.

Inclusion and exclusion criteria

All controlled experimental studies about LTCBDE + laparoscopic cholecystectomy (LC) compared with LCCBDE+ LC were selected. The following were the inclusion criteria for the selected studies: (1) Patients with no contraindications for the laparoscopic approach, with no requirement of additional procedures; (2) Patients with confirmed or suspected CBD stones with gallstones; (3) Studies that included data on stone clearance, conversion to other procedures, total and biliary morbidity, blood loss (ml), length of hospital stay (days), operative time (min) and hospital expenses (wan renminbi).

The total morbidity (bile leakage, biliary stricture, bleeding, clinical pancreatitis, pneumonia, acute myocardial infarction, cholangitis, sepsis, cerebrovascular events, early reoperation, and pulmonary embolus), bile duct clearance and biliary morbidity (bile leakage and biliary stricture), conversion to other procedures (any endoscopic or surgical procedure other than the one allocated for failed bile duct clearance or any procedure for the management of a complication), operative time, length of hospital stay, hospital expenses, and blood loss were included.

The exclusion criteria were non-experimental trials, articles not reporting outcomes, editorials, review articles, and nonhuman studies. The names of the authors and the journals containing the literature did not influence our decision on the articles.

Statistical analysis

The analyses were performed using Review Manager version 5.1 (RevMan, Cochrane Collaboration, Oxford, England). The results of this study were expressed as the odds ratios (ORs) for dichotomous data and mean difference (MD) for continuous data, with 95% confidence intervals (CIs) for both. The inverse variance method was used for continuous variables, while the Mantel-Haenzsel method was used for dichotomous variables. Statistical heterogeneity was evaluated by χ^2 test. *P* < 0.05 was considered significant. If heterogeneity was significant, we used the random-effects model. Otherwise, we used the fixed-effects model. If data reported a median and range rather than a mean and standard deviation (SD), then the mean and SD were estimated as described previously [18].

Results

Study selection and characteristics

Fig 1 illustrates the final selection of relevant studies and our search process. We analyzed 18 trials [19-36] that met the criteria, involving 2,782 patients (Table 1).

CBD Stone clearance

Stone clearance was reported in 12 trials. Stone clearance from the CBD was achieved in 87.3% of patients (693 of 794) in the LCCBDE group and in 88.9% (1,158 of 1,303) in the LTCBDE group. There was no significant difference between the two groups (OR 0.73, 95% CI 0.50–1.07; P = 0.11) (Fig 2A).

Conversion

We identified ten trials with relevant data. Conversion occurred in 7.5% (62 of 831) and 10.9% (105 of 959) of patients in the LCCBDE and LTCBDE groups, respectively. There was also no statistically significant difference between the two groups (OR 0.62, 95% CI 0.21–1.79; P = 0.38) (Fig 2B).

Total morbidity

Eleven trials reported total morbidity, with rates of 15.0% (117 of 781) and 10.3% (115 of 1,116) in the LCCBDE and LTCBDE groups, respectively. There was also no significant difference between the two groups (OR 1.65, 95% CI 0.92–2.96; P = 0.09) (Fig 2C).

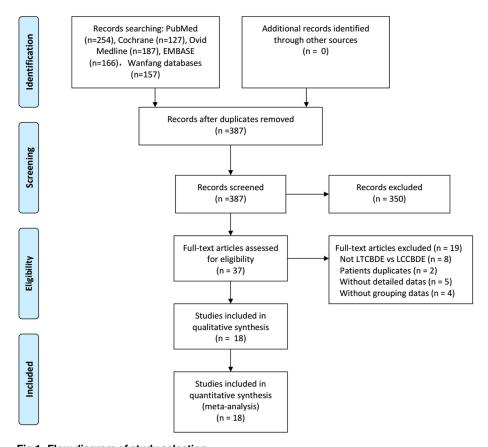


Fig 1. Flow diagram of study selection.

doi:10.1371/journal.pone.0162885.g001

Biliary morbidity

Biliary morbidity was reported in nine trials, and occurred in 6.1% (52 of 855) of patients in the LCCBDE group versus 1.3% (13 of 1,000) in the LTCBDE group. The biliary morbidity for LTCBDE was significantly lower than in the LCCBDE group (OR 4.25, 95% CI 2.30–7.85; P<0.001). (Fig 2D).

Operative time

Twelve trials included data about for operative time. There was still no significant difference between the two groups (MD 12.34, 95% CI –0.10 to 24.78; P = 0.05) (Fig 3A).

Length of hospital stay

The length of hospital stay was evaluated in 14 studies. Consequently, according to our predefined plan, the median and range were converted to mean and SD as described previously [18]. The length of hospital stay of the LTCBDE group was 2.52 days shorter than that of the LCCBDE group (MD 2.52 days, 95% CI 1.29–3.75; P<0.001) (Fig 3B).

Hospitalization expenses

The hospitalization charges were recorded in only three trials. The hospital expenses in the LTCBDE group were significantly lower than in the LCCBDE group (MD 0.30 WanRMB, 95% CI 0.23–0.37; P<0.001) (Fig 3C).

Author	Year	LCCBDE/ LTCBDE	Conversion to other procedure	Stone clearance	Total morbidity	Biliary morbidity	Operative time (min)	Hospital stay (day)	Hospital expenses (WanRMB)	Blood loss (ml)
Martin [12]	1998	55/158		54/145	3/14	2/0	136.25±59.53/ 126.25±78.31 ^a	3.25±2.15/4.5 ±3.75 ª		
Rhodes [13]	1998	12/28	5/5	7/23	0/6	1	1		•	
Cuschieri [14]	1999	53/56	8/11	45/45	1	1	-	1		
Tokumura [15]	2002	126/91	1/13	123/89	12/19	7/1	159±42/131±35	15.6±8.7/8.1 ±2.4		
Waage [16]	2003	57/118	5/8	55/112	1	ı	260±148.87/251 ±87.3 ^a	6.4±5.6/7.6 ±6.1 ^a		
Topal [17]	2007	30/83	2/2	28/77	5/4	1	115±54.35/105 ±63.05 ^a	12±10.2/7 ±7.51 ^a		
Chen[18]	2007	24/40	0/0	24/40	0/0	0/0	1	9.8±1.9/7.8 ±1.3	1.076±0.124/0.869 ±0.109	34±10/26±7
Paganini [19]	2007	138/191		126/185	29/25	3/2	1			
Jameel [20]	2008	50/9	I	1	0/6	1	94.21±21.67/ 112.86±19.69 ^a	7.33±5.78/ 5.72±3.54 ^a		
ElGeidie[21]	2011	49/57	2/0	47/56	8/4	5/3		3.8±2.41/1.6 ±0.62 ª		
Grubnik [22]	2012	62/76	1/1	58/72	1	1	96.25±33.39/71 ±23.67 ^a	7.6±2.5/3.4 ±1.7		
Chen [23]	2013	100/110		1	10/1	1	120±42.2/100 ±30.4	7.9±1/3.6±0.9		
Tao[24]	2013	59/59	0/13	1/13	10/2	9/2	81.8±18.6/85.5 ±20.9	1		
Poh [25]	2014	3/80	I	3/44	ı	1		6.5±0.65/6 ±1.74 ^a		1
Wu[26]	2014	33/29		33/29	1	4/0	107.19±14.58/ 115.68±16.64	5.1±0.6/4.43 ±0.38	1.1197±0.0794/ 0.7944±0.0833	15.5±4.6/ 19.25±4.3
Zhang [27]	2015	93/237	5/11	89/228	24/32	7/3	116.1±28.1/76 ±20.2	6.7±2.8/3.9 ±1.8	1.09687±0.11564/ 0.74353±0.09948	1
Aawsaj[28]	2015	233/85	0/12		1	14/0	144±48.67/107.5 ±52.96 ^a	10.5±7.4/2.75 ±2.0 7 ^a		
Huang[29]	2015	45/53	I	ı	7/8	1/2	112.41±19.63/ 115.36±21.51	8.32±1.15/ 8.15±0.35	1	ı

^a The mean and SD were estimated by median and a range.

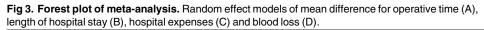
doi: 10.1371/journal.pone.0162885.t001

Ctudy or Cub marrie	LCCI		LTC		Wolsh	Odds Ratio	Odds Ratio M-H, Fixed, 95% Cl
Study or Subgroup		Total	Events		Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1998 Martin	54	55	145	158	2.3%	4.84 [0.62, 37.90]	
1998 Rhodes	7	12	23	28	9.6%	0.30 [0.07, 1.37]	
1999 Cuschieri	45	53	45	56	11.0%	1.38 [0.51, 3.74]	
2002 Tokumura	123	126	89	91	4.1%	0.92 [0.15, 5.63]	
2003 Waage	55	57	112	118	4.3%	1.47 [0.29, 7.54]	
2007 Paganini	126	138	185	191	22.5%	0.34 [0.12, 0.93]	
2007 Topal	28	30	77	83	4.5%	1.09 [0.21, 5.72]	
2011 ElGeidie	47	49	56	57	3.5%	0.42 [0.04, 4.77]	
2012 Grubnik	58	62	72	76	6.9%	0.81 [0.19, 3.36]	
2013 Tao	1	59	13	59	21.3%	0.06 [0.01, 0.48]	•
2014 Poh	3	3	44	80	0.9%	5.74 [0.29, 114.79]	
2015 Zhang	89	93	228	237	9.2%	0.88 [0.26, 2.92]	
Total (95% CI)		794		1303	100.0%	0.73 [0.50, 1.07]	•
Total events	693		1158				
Heterogeneity: Chi ² = Test for overall effect:				² = 35%	6		0.01 0.1 1 10 1 Favours [experimental] Favours [control]
В						Odda Datia	
Study or Subarou-	LCCB		LTCB		Waight	Odds Ratio	Odds Ratio
Study or Subgroup	Events					M-H, Random, 95% C	I M-H, Random, 95% CI
1998 Rhodes	5	12	5	28	11.8%	3.29 [0.73, 14.74]	
1999 Cuschieri	8	53	11	56	13.5%	0.73 [0.27, 1.98]	
2002 Tokumura	1	126	13	91	9.8%	0.05 [0.01, 0.37]	
2003 Waage	5	57	8	118	13.0%	1.32 [0.41, 4.24]	
2007 Topal	2	30	2	83	9.9%	2.89 [0.39, 21.52]	
2011 ElGeidie	2	49	0	57	6.8%	6.05 [0.28, 129.16]	
2012 Grubnik	1	62	1	76	7.5%	1.23 [0.08, 20.06]	
2013 Tao	0	59	13	59	7.3%	0.03 [0.00, 0.50]	
2015 Aawsaj	0	233	12	85	7.3%	0.01 [0.00, 0.22]	•
2015 Zhang	5	93	11	237	13.2%	1.17 [0.39, 3.46]	
				050	100.0%	0.62 [0.21, 1.79]	
Total (95% CI)		831		959	100.070	0.0	
Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2		= 33.66					0.01 0.1 1 10 1 Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: 2	1.92; Chi ² : Z = 0.88 (P LCCB	= 33.66 = 0.38 DE	, df = 9 (F) LTCB	DE = 0.00	001); I² = 7	3% Odds Ratio	Favours [experimental] Favours [control] Odds Ratio
Total events Heterogeneity: Tau ² = Test for overall effect: 2 C Study or Subgroup	1.92; Chi ² : Z = 0.88 (P LCCB Events	= 33.66 = 0.38 DE Total	, df = 9 (F) LTCB Events	DE Total	001); I² = 7 Weight	'3% Odds Ratio <u>M-H. Random, 95% C</u>	Favours [experimental] Favours [control] Odds Ratio M-H, Random, 95% Cl
Total events Heterogeneity: Tau ² = Test for overall effect: 2 C Study or Subgroup 1998 Martin	1.92; Chi ² : Z = 0.88 (P LCCB Events 3	= 33.66 = 0.38 DE Total 55	, df = 9 (F) LTCB <u>Events</u> 14	DE Total 158	001); I ² = 7 <u>Weight</u> 9.4%	3% Odds Ratio <u>M-H. Random, 95% C</u> 0.59 [0.16, 2.15]	Favours [experimental] Favours [control] Odds Ratio Cl. M-H. Random. 95% Cl.
Total events Heterogeneity: Tau ² = Test for overall effect: 2 C Study or Subgroup 1998 Martin 1998 Rhodes	1.92; Chi ² : Z = 0.88 (P LCCB Events 3 0	= 33.66 = 0.38 DE Total 55 12	, df = 9 (F) LTCB Events 14 6	DE Total 158 28	001); I ² = 7 <u>Weight</u> 9.4% 3.2%	Odds Ratio <u>M-H, Random, 95% C</u> 0.59 [0.16, 2.15] 0.14 [0.01, 2.67]	Favours [experimental] Favours [control] Odds Ratio Cl M-H, Random, 95% Cl
Total events Heterogeneity: Tau ² = Test for overall effect: : <u>Study or Subgroup</u> 1998 Martin 1998 Rhodes 2002 Tokumura	1.92; Chi ² : Z = 0.88 (P LCCB Events 3 0 12	= 33.66 = 0.38 DE Total 55 12 126	, df = 9 (F) LTCB Events 14 6 19	DE Total 158 28 91	001); l ² = 7 <u>Weight</u> 9.4% 3.2% 13.1%	Odds Ratio <u>M-H. Random, 95% C</u> 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87]	Favours [experimental] Favours [control] Odds Ratio Odds Ratio Cl M-H. Random, 95% Cl
Total events Heterogeneity: Tau ² = Test for overall effect: 2 Study or Subgroup 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Paganini	1.92; Chi ² : Z = 0.88 (P LCCB Events 3 0 12 29	= 33.66 = 0.38 DE Total 55 12 126 138	, df = 9 (F) LTCB Events 14 6 19 25	DE Total 158 28 91 191	Weight 9.4% 3.2% 13.1% 14.6%	Odds Ratio <u>M-H. Random. 95% C</u> 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: 2 C Study or Subgroup 1998 Martin 1998 Rhodes 2007 Pokumura 2007 Popal	1.92; Chi ² : Z = 0.88 (P LCCB Events 3 0 12 29 5	= 33.66 = 0.38 DE Total 55 12 126 138 30	, df = 9 (F) LTCB Events 14 6 19 25 4	DE Total 158 28 91 191 83	Weight 9.4% 3.2% 13.1% 14.6% 8.7%	Odds Ratio M-H. Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: 2 Study or Subgroup 1998 Martin 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Topal 2008 Jameel	1.92; Chi ² : Z = 0.88 (P <u>LCCB</u> <u>Events</u> 3 0 12 29 5 9	= 33.66 = 0.38 DE Total 55 12 126 138 30 50	, df = 9 (F) LTCB Events 14 6 19 25 4 0	DE Total 158 28 91 191 83 9	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2%	Odds Ratio <u>M-H. Random, 95% C</u> 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Study or Subgroup 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Fagainin 2007 Topal 2007 Topal 2008 Jameel 2011 ElGeidie	1.92; Chi ² = Z = 0.88 (P <u>LCCB</u> <u>Events</u> 3 0 12 29 5 5 9 8	= 33.66 = 0.38 DE <u>Total</u> 55 12 126 138 30 50 49	, df = 9 (F) <u>LTCB</u> <u>Events</u> 14 6 9 25 4 0 4	DE Total 158 28 91 191 83 9 57	Weight 9.4% 3.2% 13.1% 8.7% 3.2% 9.5%	Odds Ratio <u>M-H. Random, 95% C</u> 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: 2 C Study or Subgroup 1998 Martin 1998 Rhodes 2007 Paganini 2007 Paganini 2007 Topal 2008 Jameel 2011 ElGeidie 2013 Chen	1.92; Chi ² : Z = 0.88 (P LCCB Events 3 0 12 29 5 9 8 10	= 33.66 = 0.38 DE Total 55 12 126 138 30 50 49 100	, df = 9 (F) Events 14 6 19 25 4 0 4 1	DE Total 158 28 91 191 83 9 57 110	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 9.5% 5.4%	Odds Ratio <u>M-H. Random, 95% C</u> 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: J Study or Subgroup 1998 Martin 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Topal 2008 Jameel 2013 Tao	1.92; Chi ² = Z = 0.88 (P LCCB Events 3 0 0 12 29 5 9 8 10 10	= 33.66 = 0.38 DE Total 55 12 126 138 30 50 49 100 59	, df = 9 (F) Events 14 6 19 25 4 0 4 1 2 5	DE Total 158 28 91 191 83 9 57 110 59	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 9.5% 5.4% 7.7%	Odds Ratio <u>M-H. Random, 95% C</u> 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Study or Subgroup 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Pagainin 2007 Topal 2008 Jameel 2011 ElGeidie 2013 Chen 2015 Huang	1.92; Chi ² : Z = 0.88 (P <u>LCCB</u> <u>Events</u> 3 0 12 29 5 9 8 8 10 10 7	= 33.66 = 0.38 Total 55 12 126 138 30 50 49 100 59 45	, df = 9 (F) LTCB Events 14 6 19 25 4 0 4 1 2 5 8	DE Total 158 28 91 191 83 9 57 110 59 53	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 9.5% 5.4% 7.7% 10.6%	Odds Ratio M-H. Random. 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: J Study or Subgroup 1998 Martin 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Topal 2008 Jameel 2013 Tao	1.92; Chi ² = Z = 0.88 (P LCCB Events 3 0 0 12 29 5 9 8 10 10	= 33.66 = 0.38 DE Total 55 12 126 138 30 50 49 100 59	, df = 9 (F) Events 14 6 19 25 4 0 4 1 2 5	DE Total 158 28 91 191 83 9 57 110 59	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 9.5% 5.4% 7.7%	Odds Ratio <u>M-H. Random, 95% C</u> 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Study or Subgroup 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Pagainin 2007 Topal 2008 Jameel 2011 ElGeidie 2013 Chen 2013 Tao 2015 Huang 2015 Zhang Total (95% CI)	1.92; Chi ² : Z = 0.88 (P <u>LCCBB</u> <u>Events</u> 0 12 29 5 9 8 10 10 10 7 24	= 33.66 = 0.38 Total 55 12 126 138 30 50 49 100 59 45	, df = 9 (F) LTCB Events 14 6 19 25 4 0 4 1 2 5 4 0 4 1 2 5 32	DE Total 158 28 91 191 83 9 57 110 53 237	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 9.5% 5.4% 7.7% 10.6%	Odds Ratio M-H. Random. 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> C Study or Subgroup 1998 Martin 1998 Rhodes 2007 Tokumura 2007 Topal 2007 Topal 2007 Topal 2011 ElGeidie 2013 Chen 2013 Tao 2015 Zhang Total (95% CI) Total events	1.92; Chi ² : Z = 0.88 (P <u>LCCB</u> <u>Events</u> 3 0 12 29 5 9 9 8 10 10 7 24 117	= 33.66 = 0.38 DE Total 55 12 126 138 30 50 49 100 59 45 93 781	, df = 9 (F) LTCB <u>Events</u> 14 6 19 25 4 0 4 1 2 8 32 115	DE Total 158 28 91 191 83 9 57 110 59 53 237 1116	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 5.4% 7.7% 10.6% 14.5%	Odds Ratio M-H. Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Study or Subgroup 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Pagainin 2007 Topal 2008 Jameel 2011 ElGeidie 2013 Chen 2013 Tao 2015 Huang 2015 Zhang Total (95% CI)	1.92; Chi ² : Z = 0.88 (P <u>LCCB</u> <u>Events</u> 3 0 12 29 5 9 8 10 10 7 24 117 0.52; Chi ²	= 33.66 = 0.38 DE Total 126 138 30 50 49 100 59 45 93 781 = 27.8(, df = 9 (F) LTCB <u>Events</u> 14 6 19 25 4 0 4 1 2 8 32 115 0, df = 10	DE Total 158 28 91 191 83 9 57 110 59 53 237 1116	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 5.4% 7.7% 10.6% 14.5%	Odds Ratio M-H. Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: : C <u>Study or Subgroup</u> 1998 Martin 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Topal 2008 Jameel 2013 Chen 2013 Tao 2013 Tao 2013 Fluang 2015 Zhang Total (95% CI) Total events Heterogeneity: Tau ² =	1.92; Chi ² : Z = 0.88 (P <u>Events</u> 3 0 12 29 5 9 8 10 10 7 24 117 0.52; Chi ² : Z = 1.67 (F	= 33.66 = 0.38 DE Total 126 55 12 126 30 50 49 100 59 93 781 = 27.8(0 > = 0.05	, df = 9 (F) LTCB <u>Events</u> 14 6 19 25 4 0 4 1 25 4 0 4 1 25 32 115 0, df = 10 3)	DE Total 158 28 91 191 83 9 57 110 53 237 1116 (P = 0.	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 5.4% 7.7% 10.6% 10.6% 14.5% 100.0%	Odds Ratio M-H. Random. 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54%	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: : C <u>Study or Subgroup</u> 1998 Martin 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Topal 2008 Jameel 2013 Chen 2013 Tao 2013 Tao 2013 Fluang 2015 Zhang Total (95% CI) Total events Heterogeneity: Tau ² =	1.92; Chi ² + Z = 0.88 (P <u>LCCB</u> <u>Events</u> 3 0 12 29 5 9 8 10 10 7 24 117 0.52; Chi ² Z = 1.67 (F	= 33.66 = 0.38 DE Total 55 12 126 50 49 93 781 = 27.8(8 P = 0.09 CBDE	, df = 9 (F) LTCB Events 14 6 19 25 4 0 4 1 2 8 32 115 0, df = 10 3)	DE Total 158 28 91 191 83 9 57 110 59 53 237 1116 (P = 0.	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 5.4% 7.7% 10.6% 10.6% 14.5% 100.0%	Odds Ratio <u>M-H. Random, 95% C</u> 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Study or Subgroup 1998 Martin 1998 Martin 1998 Rhodes 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2007 Janag 2015 LiGeidie 2013 Tao 2015 Zhang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup	1.92; Chi ² + Z = 0.88 (P <u>LCCB</u> <u>Events</u> 3 0 12 29 9 8 10 10 7 24 117 0.52; Chi ² + Z = 1.67 (F <u>LCC</u>	= 33.66 = 0.38 DE Total 55 12 126 138 30 50 49 100 59 45 93 781 = 27.8(P = 0.05	, df = 9 (F) LTCEB Events 14 6 19 25 5 4 0 4 1 2 8 32 115 5 0, df = 10)) LTT LT LTCEB	DE Total 158 28 91 191 83 9 57 110 59 53 237 1116 (P = 0. CBDEE 5 Tota	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 9.5% 10.6% 14.5% 100.0% 002); l ² = 6	Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.355 [0.38, 45.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 64% Odds Ratio M-H, Fixed, 95% C	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Study or Subgroup 1998 Martin 1998 Martin 1998 Martin 2007 Pagainin 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2015 Alang 2015 Alang 2015 Alang 2015 Jhang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D <u>Study or Subgroup</u> 1998 Martin	1.92; Chi ² : Z = 0.88 (P <u>LCCB</u> Events 3 0 12 29 5 9 8 10 10 10 7 24 117 0.52; Chi ² Z = 1.67 (F <u>LCC</u> Events Z = 1.67 (F	= 33.66 = 0.38 DE Total 55 12 126 138 30 59 100 59 93 781 = 27.8(8 59 - 0.09 CBDE CBDE	, df = 9 (F) LTCEB Events 14 6 19 25 4 0 4 4 1 1 5 5 () , df = 10 9)	DE Total 158 28 9 57 110 59 53 237 11116 (P = 0. CBDE 5 Total 5 9 53 237	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 14.6% 14.6% 14.5% 10.6% 10.6% 10.6% 10.6% 10.6% 10.0% 002); l ² = (1.4% 10.0% 002); l ² = (1.4% 1.	Odds Ratio M-H. Random. 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H. Fixed, 95% C 14.81 [0.70, 313.45]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: : Study or Subgroup 1998 Martin 1998 Rhodes 2007 Tokumura 2007 Paganni 2007 Topal 2007 Topal 2007 Topal 2018 Elecide 2013 Chen 2013 Chen 2015 Zhang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2002 Tokumura	1.92; Chi ² + Z = 0.88 (P <u>LCCB</u> Events 3 0 12 29 5 9 8 8 10 0 12 29 5 9 8 8 10 0 10 7 24 117 0.52; Chi ² 2 4 0.52; Chi ² 2 4 2 4 7 7 7 7 7 7	= 33.66 = 0.38 DE Total 126 138 30 55 50 49 100 59 45 93 781 = 27.8(EBDE CBDE CBDE 55 55 126 55 126 55 120 55 120 120 55 120 120 55 120 120 120 120 120 120 120 120 120 120	, df = 9 (F)) LTCB Events. 14 6 19 25 4 0 4 1 2 5 32 115 5 32 115 5 0, df = 10))) LTC Events. 5 5 4 0 0 12 5 12 5 12 5 12 5 12 5 12 5 12 5	DE Total 158 28 9 9 7 110 59 53 237 1116 (P = 0. (P = 0. (P = 0.) 59 59 50 237 1116 (P = 0.) 155 159 159 159 159 159 159 159 159 159	Weight 9.4% 3.2% 13.1% 14.6% 5.4% 7.7% 10.6% 100.0% 1	Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 84% Odds Ratio M-H, Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: : C Study or Subgroup 1998 Martin 1998 Rhodes 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2008 Jameel 2011 ElGeidie 2013 Chen 2013 Tao 2015 Zhang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2002 Tokumura 2007 Paganini	1.92; Chi ² + Z = 0.88 (P <u>LCCB</u> Events 3 0 12 29 5 9 8 10 10 7 24 117 0.52; Chi ² Z = 1.67 (F <u>LCC</u> Events 2 7 3	= 33.66 = 0.38 DE Total 126 138 30 55 52 126 138 30 50 59 93 781 = 27.8(20.55 93 781 = 27.8(20.55 126 20.55 126 20.55 126 126 138 126 126 126 126 126 126 126 126 126 126	, df = 9 (F) LTCEB Events 14 6 19 19 225 4 0 4 4 0 4 4 11 2 8 32 115 5 0, df = 10)) LTT LTELEVENTS 5 0, df = 10 12 12 12 12 12 12 12 12 12 12 12 12 12	DE Total 158 28 91 191 83 97 7100 59 53 237 11116 (P = 0. (P = 0. CBDE S Tota 1 9 2 19	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 9.5% 10.6% 7.7% 10.6% 10.0% 002); l ² = (1. Weight 8. 2.1% 1. 9.4% 1. 1. 9.4% 1. 1. 9.4% 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	Odds Ratio M-H. Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% Cl 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Study or Subgroup 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Topal 2008 Jameel 2017 Elecidie 2013 Tao 2015 Huang 2015 Jhang Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2007 Tokumura 2007 Tokumura 2007 Tokumura 2007 Tokumura 2007 Paganini 2011 ElGeidie	1.92; Chi ² : Z = 0.88 (P Events 3 0 12 29 5 9 8 10 10 7 24 117 0.52; Chi ² Z = 1.67 (F Events 2 7 3 5 2 4 2 2 7 3 5 2 2 2 2 2 3 2 2 3 5 2 2 3 2 2 3 5 5 2 2 3 5 5 5 5 5 5 5 5 5 5 5 5 5	= 33.66 = 0.38 DE Total 12 126 138 30 50 49 100 59 45 93 781 = 27.8(> = 0.05 CBDE 50 50 45 93 781 = 27.8(50 50 50 50 50 50 50 50 50 50 50 50 50	, df = 9 (F) LTCEB Events 14 6 19 25 4 0 4 1 1 2 8 32 32 115 5 10, df = 10 9)	DE Total 1588 91 191 191 191 191 191 191 191 59 53 237 1116 (P = 0. (P = 0. (P = 0.) 59 53 237 1116 (P = 0.) 59 53 237 1116 (P = 0.) 59 53 237 116 (P = 0.) 59 53 237 237 237 237 237 237 237 237 237 23	Weight 9.4% 3.2% 13.1% 14.6% 8.7% 3.2% 14.6% 14.6% 14.5% 10.6% 10.0% 100.0% 100.0% 100.0% 100.0% 100.0% 100.12 = 4 1 Weight 8 2.1% 1 9.4% 1 9.4% 1 4.1% 7 7 21.13%	Odds Ratio M-H. Random. 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H. Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>;</i> C Study or Subgroup 1998 Martin 1998 Rhodes 2007 Tokumura 2007 Paganini 2007 Topal 2007 Jameel 2013 Chen 2013 Chen 2013 Chen 2015 Zhang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2002 Tokumura 2007 Paganini 2011 ElGeidie 2013 Tao	1.92; Chi ² + Z = 0.88 (P <u>LCCB</u> Events 3 0 12 29 5 9 8 8 10 0 12 29 5 9 8 8 10 0 10 7 24 117 0.52; Chi ² 2 4 2 4 117 0.52; Chi ² 2 4 3 5 5 5 7 8 8 7 8 8 7 8 7 8 8 8 7 8 8 8 7 8 7	= 33.66 = 0.38 DE Total 55 12 126 138 30 0 49 45 93 781 = 27.8(4 93 781 = 27.8(5 59 781 = 27.8(5 59 781 = 27.8(5) 59 59 59 59 781 55 55 55 55 55 55 55 55 55 55 55 55 55	, df = 9 (F)) LTCB Events. 14 6 19 25 4 0 0 4 4 0 0 4 4 0 0 12 25 4 3 22 5 5 5 0 5 5 5 5 5 5 5 5 5 5 5 5 5 5	P = 0.00 Total 158 28 91 191 83 9 57 110 59 53 237 1116 (P = 0. (P =	Weight 9.4% 9.4% 3.2% 13.1% 14.6% 14.6% 5.4% 7.7% 10.6% 100.0% 002); I² = 0 1 Weight 8 2.1% 1 9.4% 3.2% 3.2% 9.5% 5.4% 7.7% 100.0% 002); I² = 0 1 1 9.4% 1 9.4% 1 9.4% 1 14.1% 7 21.3% 9 14.5%	Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 84% Odds Ratio M-H, Fixed, 95% Cl 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: : C Study or Subgroup 1998 Martin 1998 Rhodes 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2003 Jameel 2011 ElGeidie 2013 Chen 2013 Tao 2015 Chang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2007 Paganini 2011 ElGeidie 2013 Tao 2007 Paganini 2011 ElGeidie 2013 Tao 2014 Wu	1.92; Chi ² + Z = 0.88 (P LCCB Events 3 0 12 29 9 8 10 10 7 24 117 0.52; Chi ² Z = 1.67 (F LCC Events 2 4 5 9 4 4 4 5 9 9 4 10 10 10 10 10 10 10 10 10 10	= 33.66 = 0.38 DE Total 55 12 126 50 45 93 781 = 27.8(8 = 0.09 781 = 27.8(8 = 0.09 781 55 52 52 52 52 52 52 53 53 53 53 54 55 55 55 55 55 55 55 55 55 55 55 55	, df = 9 (f)) LTCEB Events 14 6 19 19 225 5 4 0 4 4 0 4 4 11 2 8 8 32 115 5 0, df = 10)) LTT L Events 5 5 6 7 8 8 32 115 5 1 9 9 11 9 12 5 5 5 14 14 9 19 19 19 19 19 19 19 19 19 19 19 19 1	DE Total 158 28 91 191 191 191 191 191 191 53 237 1110 (P = 0. (P = 0. (P = 0. (P = 0.) 237 1116 (P = 0.) 237 1116 (P = 0.) 237 237 237 237 237 237 237 237 237 237	Weight 9.4% 3.2% 13.1% 14.6% 7.7% 10.6% 10.6% 100.0% 002); I ² = (1. Weight 8.2.1% 1.9.4% 1.9.4% 1.9.4% 9.3.9%	Odds Ratio M-H. Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% Cl 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 24.87] 9.00 [0.46, 174.72]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Study or Subgroup 1998 Martin 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Paganini 2007 Topal 2008 Jameel 2013 Tao 2015 Huang 2015 Ji Chen 2015 Anang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D <u>Study or Subgroup</u> 1998 Martin 2007 Paganini 2011 ElGeidie 2013 Tao 2017 Bumura 2007 Paganini 2011 ElGeidie 2013 Tao 2014 Wu	1.92; Chi ² + Z = 0.88 (P <u>LCCB</u> <u>Events</u> 3 0 12 29 5 9 8 10 10 12 29 5 9 8 10 10 7 24 117 0.52; Chi ² Z = 1.67 (f <u>LCC</u> 2 7 3 3 5 9 4 4 4	= 33.66 = 0.38 DE Total 126 55 12 126 50 50 93 781 = 27.8(293 781 = 27.8(293 781 781 781 781 781 781 781 781 781 781	, df = 9 (F) LTCEB Events 14 6 19 25 4 0 4 4 1 1 2 8 32 32 115 5 (0, df = 10)) LTC LTCE Events 5 (0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	DE Total 158 28 91 158 33 9 57 110 59 53 237 1116 (P = 0. (P = 0. (P = 0. (P = 0.) 155 9 9 155 9 155 9 2 192 193 3 5 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5 2 5	Weight 9.4% 3.2% 13.1% 14.6% 9.5% 5.4% 7.4% 10.6% 10.6% 10.6% 10.6% 10.0% 002); l ² = (1.4% 1.4% 1.4.1% 9.4% 1.4.5% 9.4% 1.4.5% 9.5% 9	Odds Ratio M-H. Random. 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H. Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> C Study or Subgroup 1998 Martin 1998 Rhodes 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2013 Chen 2013 Chen 2013 Chen 2013 Chen 2015 Zhang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2002 Tokumura 2007 Toganini 2011 ElGeidie 2013 Tao 2014 Wu 2015 Aawsaj 2015 Huang	1.92; Chi ² + Z = 0.88 (P LCCB Events 3 0 12 29 5 9 8 8 10 10 12 29 5 9 8 8 10 10 10 24 117 0.52; Chi ² 2 2 1.67 (F LCC Events 3 0 12 29 9 8 8 10 12 29 9 8 8 10 10 10 10 10 10 10 10 10 10	= 33.66 = 0.38 DE Total 126 55 12 126 30 50 93 781 = 27.8(\$ 93 781 = 27.8(\$ 93 781 = 27.8(\$ 93 781 = 27.8(\$ 5 93 781 = 27.8(\$ 5 5 5 93 781 = 27.8(\$ 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	, df = 9 (F)) LTCB Events. 144 6 19 25 4 4 0 0 4 4 0 0 12 25 4 4 0 0 19 25 5 4 0 0 19 25 5 25 9 3 2 5 5 5 2 5 9 2 5 5 2 5 9 10 10 10 10 10 10 10 10 10 10 10 10 10	DE Total 158 28 91 191 191 191 59 57 110 59 53 237 (P = 0. (P = 0. (P = 0.) (P = 0.)	Weight 9.4% 9.4% 3.2% 13.1% 14.6% 14.6% 5.4% 7.7% 10.6% 100.0% 002); I² = 0 Weight 14.1% 7.7% 10.6% 100.0% 10.2; I² = 0 1.14.5% 10.6% 1.2.7% 10.6% 1.3.7% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 1.4.5% 3.14.5% 1.4.5%	Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 84% Odds Ratio M-H, Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46] 0.58 [0.05, 6.61]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> Study or Subgroup 1998 Martin 1998 Rhodes 2002 Tokumura 2007 Topal 2008 Jameel 2017 Elecidie 2013 Tao 2015 Huang 2015 Jhang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2007 Tokumura 2007 Paganini 2011 ElGeidie 2013 Tao 2017 Julie Geidie 2013 Tao 2014 Wu 2015 Aawsaj 2015 Huang 2015 Zhang	1.92; Chi ² + Z = 0.88 (P <u>LCCB</u> <u>Events</u> 3 0 12 29 5 9 8 10 10 12 29 5 9 8 10 10 7 24 117 0.52; Chi ² Z = 1.67 (f <u>LCC</u> 2 7 3 3 5 9 4 4 4	= 33.66 = 0.38 DE Total 126 55 12 126 50 50 93 781 = 27.8(93 781 = 27.8(55 126 138 93 781 = 27.8(55 126 126 55 126 126 138 93 781 = 2.7,8(55 55 12 126 138 30 59 781 = 2.7,8(55 55 12 126 138 30 59 59 781 = 2.7,8(55 55 12 126 138 30 59 781 = 2.7,8(55 55 12 126 138 30 59 781 = 2.7,8(55 55 55 12 126 138 30 59 781 781 781 781 781 781 781 781 781 781	, df = 9 (F) LTCEB Events 14 6 19 25 4 0 4 4 1 1 2 8 32 32 115 5 (0, df = 10)) LT L T L Events 5 6 (0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	DE Total 158 28 91 183 3 9 57 110 59 53 237 1116 (P = 0. (P = 0. (P = 0.) 155 9 9 1116 (P = 0.) 237 237 1116 (P = 0.) 237 237 237 25 25 25 25 25 25 25 25 23 237	Weight 9.4% 3.2% 13.1% 14.6% 9.5% 5.4% 7.4% 10.6% 10.6% 10.0% 002); l² = 4 1 1 4.5% 100.0% 002); l² = 4 1 4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 </td <td>Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46] 0.58 [0.05, 6.61] 6.35 [1.61, 25.11]</td> <td>Favours [experimental] Favours [control]</td>	Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46] 0.58 [0.05, 6.61] 6.35 [1.61, 25.11]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> C Study or Subgroup 1998 Martin 1998 Rhodes 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2007 Jameel 2013 Chen 2013 Chen 2013 Chen 2015 Zhang Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2002 Tokumura 2007 Toganini 2001 Effectie 2013 Tao 2014 Wu 2015 Zhang 2015 Huang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Zhang Total (95% Cl)	1.92; Chi ² + Z = 0.88 (P <u>LCCB</u> Events 3 0 12 29 5 9 8 8 10 0 12 29 5 9 8 8 10 0 10 7 24 117 0.52; Chi ² 2 4 117 0.52; Chi ² 2 4 117 0.52; Chi ² 2 4 117 0.52; Chi ² 2 4 7 7 7 7 8 8 8 10 9 8 8 10 9 9 8 8 10 10 10 10 10 10 10 10 10 10 10 10 10	= 33.66 = 0.38 DE Total 126 55 12 126 30 50 93 781 = 27.8(cBDE = 0.05 CBDE 55 126 93 781 = 27.8(cBDE 55 126 93 781 = 27.8(cBDE 55 12 12 126 93 781 = 27.8(cBDE 55 12 12 126 93 781 = 27.8(cBDE 55 12 12 126 93 781 = 27.8(cBDE 55 12 12 126 93 781 = 27.8(cBDE 55 12 12 126 93 781 = 27.8(cBDE 55 12 12 126 93 781 781 = 27.8(cBDE 55 12 12 126 126 126 126 126 126 126 126 1	, df = 9 (F)) LTCB Events. 144 6 19 25 4 4 0 0 4 4 0 12 25 4 4 0 0 19 25 5 4 0 0 19 25 5 4 0 0 19 25 5 4 0 0 19 25 5 4 0 0 0 19 25 5 5 4 0 0 19 25 5 5 4 0 0 19 25 5 5 19 19 25 5 5 19 19 25 5 5 19 19 25 5 5 19 19 25 5 5 19 19 25 5 5 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 5 10 19 19 25 5 10 19 19 25 5 10 19 19 25 5 10 19 19 25 5 10 19 19 25 5 10 19 19 25 5 10 19 19 25 5 10 19 19 25 5 10 19 19 25 5 10 19 10 10 10 10 10 10 10 10 10 10 10 10 10	DE Total 158 28 91 191 191 191 191 59 57 7110 59 53 237 (P = 0. (P = 0. (P = 0.) (P	Weight 9.4% 3.2% 13.1% 14.6% 9.5% 5.4% 7.4% 10.6% 10.6% 10.0% 002); l² = 4 1 1 4.5% 100.0% 002); l² = 4 1 4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 </td <td>Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% Cl 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46] 0.58 [0.05, 6.61] 6.35 [1.61, 25.11]</td> <td>Favours [experimental] Favours [control]</td>	Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% Cl 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46] 0.58 [0.05, 6.61] 6.35 [1.61, 25.11]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: : DStudy or Subgroup 1998 Martin 1998 Rhodes 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2008 Jameel 2013 Chen 2013 Chen 2013 Chen 2015 Zhang Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2007 Paganini 2011 ElGeidie 2007 Paganini 2011 ElGeidie 2007 Paganini 2011 ElGeidie 2013 Tao 2014 Wu 2015 Aawsaj 2015 Zhang Total (95% CI) Total events	1.92; Chi ² + Z = 0.88 (P LCCB Events 3 0 12 29 9 8 10 10 7 24 117 0.52; Chi ² Z = 1.67 (F LCC Events 2 7 7 3 5 9 9 4 14 17 7 5 2 5 5 5 5 5 5 5 5 5 5 5 5 5	= 33.66 = 0.38 DE Total 55 12 126 30 50 45 93 781 = 27.8(8 50 93 781 = 27.8(8 50 50 93 781 = 27.8(8 50 50 93 781 = 27.8(8 50 50 50 50 50 50 50 50 50 50 50 50 50	, df = 9 (f)) LTCEB Events 14 6 19 19 225 4 0 0 4 4 0 0 4 4 1 2 8 8 32 115 5 0, df = 10))) LTT LEvents 5 5 6 1 9 9 9 19 9 9 25 5 5 4 0 0 9 9 19 9 19 9 19 9 19 25 5 5 4 0 0 19 9 19 25 5 5 4 0 0 19 9 19 25 5 5 4 0 0 19 9 19 25 5 5 4 0 0 19 2 5 5 5 4 0 0 19 9 19 2 5 5 5 4 0 0 19 9 19 2 5 5 5 4 0 0 19 9 19 2 5 5 5 10 19 19 2 5 5 5 10 19 19 2 5 5 5 10 19 19 2 5 5 5 10 19 19 2 5 5 5 10 19 19 2 5 5 5 10 19 19 2 5 5 5 10 19 19 2 5 5 5 10 10 19 10 10 10 10 10 10 10 10 10 10 10 10 10	DE Total 158 28 91 191 191 191 191 59 53 237 11116 (P = 0. (P = 0. (P = 0.) (P = 0.)	Weight 9.4% 3.2% 13.1% 14.6% 9.5% 5.4% 7.4% 10.6% 10.6% 10.0% 002); l² = 4 1 1 4.5% 100.0% 002); l² = 4 1 4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 </td <td>Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46] 0.58 [0.05, 6.61] 6.35 [1.61, 25.11]</td> <td>Favours [experimental] Favours [control]</td>	Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46] 0.58 [0.05, 6.61] 6.35 [1.61, 25.11]	Favours [experimental] Favours [control]
Total events Heterogeneity: Tau ² = Test for overall effect: <i>J</i> C Study or Subgroup 1998 Martin 1998 Rhodes 2007 Topal 2007 Topal 2007 Topal 2007 Topal 2007 Jameel 2013 Chen 2013 Chen 2013 Chen 2015 Zhang Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup 1998 Martin 2002 Tokumura 2007 Toganini 2001 Effectie 2013 Tao 2014 Wu 2015 Zhang 2015 Huang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Jiang 2015 Zhang Total (95% Cl)	1.92; Chi ² : Z = 0.88 (P Events 3 0 12 29 5 9 8 10 7 24 117 0.52; Chi ² : Z = 1.67 (f Events 2 7 3 5 9 8 10 7 24 117 0.52; Chi ² : 2 1.67 (f 2 2 5 5 9 8 10 7 24 117 0.52; Chi ² : 2 5 5 9 8 10 7 2 4 117 0.52; Chi ² : 2 5 5 5 9 8 10 7 2 4 117 0.52; Chi ² : 2 5 5 5 5 6 7 7 5 5 5 6 7 7 5 5 5 5 5 6 7 5 5 5 5 5 5 5 5 5 7 5 5 5 5 5 5 5 5 5 5 5 5 5	= 33.66 = 0.38 DE Total 126 55 12 126 50 50 93 781 = 27.8(93 781 = 27.8(55 126 93 781 = 27.8(55 126 93 781 = 27.8(55 126 93 781 = 27.8(55 55 128 93 781 = 27.8(55 55 128 138 30 59 93 781 = 27.8(55 55 128 138 30 59 93 781 = 27.8(55 55 128 138 30 59 93 781 = 27.8(55 55 128 138 30 59 93 781 = 27.8(55 55 128 138 30 59 93 781 = 27.8(55 55 128 138 30 59 93 781 = 27.8(55 55 128 138 30 59 93 781 = 27.8(55 55 128 138 30 59 93 781 = 27.8(55 55 128 128 128 128 128 128 128 128 128 128	, df = 9 (F) LTCEB Events 14 6 19 225 4 0 4 19 225 4 0 4 11 2 8 322 115 5 0, df = 10) LTT LT LT LT LT LT LT LT LT L	DE Total 158 28 91 191 191 191 191 59 53 237 11116 (P = 0. (P = 0. (P = 0.) (P = 0.)	Weight 9.4% 3.2% 13.1% 14.6% 9.5% 5.4% 7.4% 10.6% 10.6% 10.0% 002); l² = 4 1 1 4.5% 100.0% 002); l² = 4 1 4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 1.4.5% 9 </td <td>Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46] 0.58 [0.05, 6.61] 6.35 [1.61, 25.11]</td> <td>Favours [experimental] Favours [control]</td>	Odds Ratio M-H, Random, 95% C 0.59 [0.16, 2.15] 0.14 [0.01, 2.67] 0.40 [0.18, 0.87] 1.77 [0.98, 3.18] 3.95 [0.98, 15.85] 4.35 [0.23, 81.44] 2.59 [0.73, 9.18] 12.11 [1.52, 96.41] 5.82 [1.22, 27.83] 1.04 [0.34, 3.12] 2.23 [1.23, 4.04] 1.65 [0.92, 2.96] 54% Odds Ratio M-H, Fixed, 95% C 14.81 [0.70, 313.45] 5.29 [0.64, 43.80] 2.10 [0.35, 12.74] 2.05 [0.46, 9.04] 5.13 [1.06, 24.87] 9.00 [0.46, 174.72] 11.30 [0.67, 191.46] 0.58 [0.05, 6.61] 6.35 [1.61, 25.11]	Favours [experimental] Favours [control]

Fig 2. Forest plot of meta-analysis. Fixed-effect models of odds ratio for stone clearance (A), randomeffects model of odds ratio for conversion to other procedures (B), random-effects model of odds ratio for total morbidity, (C) and fixed-effects model of odds ratio for biliary morbidity (D).

doi:10.1371/journal.pone.0162885.g002

		CBDE		LTC	BDE			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1998 Martin	136.25	59.53	55	126.25	78.31	158	7.6%	10.00 [-9.92, 29.92]	
2002 Tokumura	159	42	126	131	35	91	8.9%	28.00 [17.73, 38.27]	
2003 Waage	260	148.87	57	251	87.3	118	4.6%	9.00 [-32.73, 50.73]	
2007 Topal	115	54.35	30	105	63.05	83	7.1%	10.00 [-13.71, 33.71]	
2008 Jameel	94.21	21.67	50	112.86	19.69	9	8.5%	-18.65 [-32.85, -4.45]	
2012 Grubnik	96.25	33.39	62	71	23.67	76	9.0%	25.25 [15.38, 35.12]	
2013 Chen	120	42.2	100	100	30.4	110	8.9%	20.00 [9.97, 30.03]	
2013 Tao	81.8	18.6	59	85.5	20.9	59	9.2%	-3.70 [-10.84, 3.44]	
014 Wu	107.19	14.58	33	115.68	16.64	29	9.2%	-8.49 [-16.33, -0.65]	
015 Aawsai	144	48.67	233	107.5	52.96	85	8.6%	36.50 [23.62, 49.38]	
2015 Huang	112.41	19.63	45	115.36	21.51	53	9.1%	-2.95 [-11.10, 5.20]	
015 Zhang	116.1	28.1	93	76	20.2	237	9.3%	40.10 [33.84, 46.36]	-
otal (95% CI)			943			1108	100.0%	12.34 [-0.10, 24.78]	◆
Heterogeneity: Tau ² =	423.84; C	hi² = 18	4.38, df	= 11 (P	< 0.000	001); l ² :	= 94%		
est for overall effect:	Z = 1.94 (P = 0.05	5)						-100 -50 0 50 10 Favours [experimental] Favours [control]
									r arous texpensional - arous teenaol
В		CBDE		LTC				Mean Difference	Mean Difference
Study or Subgroup		SD	Total	Mean		Total	Weight	IV. Random. 95% CI	
1998 Martin	3.25	2.15	55		3.75	158	7.6%	-1.25 [-2.07, -0.43]	•
2002 Tokumura	3.25	2.15	55 126	4.5 8.1	2.4	91	6.9%	7.50 [5.90, 9.10]	· ·
2003 Waage	6.4	5.6	57	7.6	6.1	118	6.7%	-1.20 [-3.02, 0.62]	1
2007 Chen	9.8	1.9	24	7.8	1.3	40	7.6%	2.00 [1.14, 2.86]	
2007 Topal	12		30		7.51	83	4.3%	5.00 [1.01, 8.99]	
2008 Jameel	7.33	5.78	50	5.72	3.54	9	5.6%	1.61 [-1.20, 4.42]	T
2011 ElGeidie	3.8	2.41	49	1.6	0.62	57	7.6%	2.20 [1.51, 2.89]	•
2012 Grubnik	7.6	2.5	62	3.4	1.7	76	7.6%	4.20 [3.47, 4.93]	•
2013 Chen	7.9	1	100	3.6	0.9	110	7.8%	4.30 [4.04, 4.56]	•
2014 Poh	6.5	0.65	3	6	1.74	80	7.6%	0.50 [-0.33, 1.33]	•
2014 Wu	5.1	0.6	33	4.43	0.38	29	7.8%	0.67 [0.42, 0.92]	+
2015 Aawsai	10.5	7.4	233	2.75	2.07	85	7.4%	7.75 [6.70, 8.80]	
2015 Huang	8.32	1.15	45	8.15	0.35	53	7.8%	0.17 [-0.18, 0.52]	•
2015 Zhang	6.7	2.8	93	3.9	1.8	237	7.7%	2.80 [2.19, 3.41]	•
						1226	100.0%	2.52 [1.29, 3.75]	•
-			960			1220		2.02 [1.20, 0.10]	
Total (95% CI)		Li2 - 04	960	6 - 40 /5		0041			L
Total (95% CI) Heterogeneity: Tau ²			1.37, d	f = 13 (F	< 0.00	0001); I	² = 98%		-100 -50 0 50 10
Total (95% CI) Heterogeneity: Tau ²			1.37, d	f = 13 (F	9 < 0.00	0001); l	2 = 98%		-100 -50 0 50 11 Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ²			1.37, d	f = 13 (F	9 < 0.00	0001); l	2 = 98%		
Total (95% CI) Heterogeneity: Tau ²	t: Z = 4.00		1.37, d		e < 0.00	0001); i	² = 98%	Mean Difference	
Total (95% CI) Heterogeneity: Tau ² Test for overall effec	t: Z = 4.00	0 (P < 0	1.37, d .0001)			,	² = 98%		Favours [experimental] Favours [control] Mean Difference
Total (95% CI) Heterogeneity: Tau ² Test for overall effec	t: Z = 4.00	0 (P < 0	1.37, d .0001)	LTC	BDE	D Tota	<u>Weight</u>	IV, Random, 95% C	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Total (95% CI) Heterogeneity: Tau ² Test for overall effec Cudy or Subgroup 007 Chen	t: Z = 4.00 LC Mean	0 (P < 0 BDE <u>SD</u> 0.124	1.37, d .0001) <u>Total</u>	LTC Mean	BDE 	<u>) Tota</u> 9 40	Weight	IV. Random, 95% C 0.21 [0.15, 0.27]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI
Total (95% CI) Heterogeneity: Tau ² Test for overall effec Cudy or Subgroup 007 Chen 014 Wu	t: Z = 4.00 LC <u>Mean</u> 1.076	(P < 0 (BDE <u>SD</u> 0.124 0.0794	1.37, d .0001) <u>Total</u> 24 33	LTC Mean 0.869	BDE 0.109 0.0833	<u>) Tota</u> 9 40 3 29	Weight	IV, Random, 95% C 0.21 [0.15, 0.27] 0.33 [0.28, 0.37]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl
Total (95% CI) Heterogeneity: Tau ² Test for overall effec C Study or Subgroup 2017 Chen 2014 Wu 2015 Zhang	LC Mean 1.076 1.1197	(P < 0 (BDE <u>SD</u> 0.124 0.0794	1.37, d .0001) <u>Total</u> 24 33	LTC <u>Mean</u> 0.869 0.7944	BDE 0.109 0.0833	<u>) Tota</u> 9 40 3 29	Veight 30.1% 33.9% 36.0%	IV. Random. 95% C 0.21 [0.15, 0.27] 0.33 [0.28, 0.37] 0.35 [0.33, 0.38]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% CI
Total (95% CI) Heterogeneity: Tau ² Test for overall effec C 1007 Chen 1014 Wu 1015 Zhang Total (95% CI)	LC Mean 1.076 1.1197 1.0969	BDE 0.124 0.1156	1.37, d .0001) <u>Total</u> 24 33 93 150	LTC Mean 0.869 0.7944 0.7435	BDE 0.109 0.0833 0.0999	D Tota 9 40 3 29 5 237 306	U Weight 30.1% 33.9% 36.0%	IV. Random. 95% C 0.21 [0.15, 0.27] 0.33 [0.28, 0.37] 0.35 [0.33, 0.38]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² Test for overall effec Cutudy or Subgroup 007 Chen 014 Wu 015 Zhang Total (95% CI) Ieterogeneity: Tau ² =	LC Mean 1.076 1.1197 1.0969	BDE 0.124 0.1156 = 19.11	1.37, d .0001) <u>Total</u> 24 33 93 150 I, df = 2	LTC Mean 0.869 0.7944 0.7435	BDE 0.109 0.0833 0.0999	D Tota 9 40 3 29 5 237 306	Veight 30.1% 33.9% 36.0%	IV. Random. 95% C 0.21 [0.15, 0.27] 0.33 [0.28, 0.37] 0.35 [0.33, 0.38]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² Test for overall effec Utudy or Subgroup 007 Chen 014 Wu 015 Zhang otal (95% CI) leterogeneity: Tau ² =	LC Mean 1.076 1.1197 1.0969	BDE 0.124 0.1156 = 19.11	1.37, d .0001) <u>Total</u> 24 33 93 150 I, df = 2	LTC Mean 0.869 0.7944 0.7435	BDE 0.109 0.0833 0.0999	D Tota 9 40 3 29 5 237 306	Veight 30.1% 33.9% 36.0%	IV. Random. 95% C 0.21 [0.15, 0.27] 0.33 [0.28, 0.37] 0.35 [0.33, 0.38]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² Test for overall effec Cutudy or Subgroup 007 Chen 014 Wu 015 Zhang Total (95% CI) Ieterogeneity: Tau ² =	LC Mean 1.076 1.1197 1.0969	BDE 0.124 0.1156 = 19.11	1.37, d .0001) <u>Total</u> 24 33 93 150 I, df = 2	LTC Mean 0.869 0.7944 0.7435	BDE 0.109 0.0833 0.0999	D Tota 9 40 3 29 5 237 306	Veight 30.1% 33.9% 36.0%	IV. Random. 95% C 0.21 [0.15, 0.27] 0.33 [0.28, 0.37] 0.35 [0.33, 0.38]	Favours [experimental] Favours [control] Mean Difference IV. Random. 95% Cl -100 -50 0 50 10
Total (95% CI) Heterogeneity: Tau ² Test for overall effec Cutudy or Subgroup 007 Chen 014 Wu 015 Zhang Total (95% CI) Ieterogeneity: Tau ² =	t: Z = 4.00 <u>LC</u> <u>Mean</u> 1.076 1.1197 1.0969 0.00; Chi ² Z = 8.10 (BDE SDD 0.124 0.1794 0.1156 = 19.11 P < 0.00	1.37, d .0001) <u>Total</u> 24 33 93 150 I, df = 2	LTC Mean 0.869 0.7944 0.7435 (P < 0.0	BDE 0.109 0.0833 0.0999	D Tota 9 40 3 29 5 237 306	Veight 30.1% 33.9% 36.0%	IV. Random. 95% C 0.21 [0.15, 0.27] 0.33 [0.28, 0.37] 0.35 [0.33, 0.38]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² Test for overall effec C 007 Chen 014 Wu 015 Zhang Total (95% CI) leterogeneity: Tau ² = est for overall effect:	t: Z = 4.00 <u>LC</u> <u>Mean</u> 1.076 1.1197 1.0969 0.00; Chi ² Z = 8.10 (BDE 0.124 0.1156 = 19.11	1.37, d .0001) 24 33 93 150 1, df = 2 0001)	LTC Mean 0.869 0.7944 0.7435 (P < 0.0	BDE 0.109 0.0833 0.0999	D Tota 9 40 3 29 5 237 306 = 90%	Weight 30.1% 33.9% 36.0%	V. Random. <u>95%</u> C 0.21 [0.15, 0.27] 0.33 [0.28, 0.37] 0.35 [0.33, 0.38] 0.30 [0.23, 0.37] Mean Difference	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² Test for overall effec C C 2007 Chen 2014 Wu 2015 Zhang Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: . C Study or Subgroup	LC <u>LC</u> <u>Mean</u> 1.076 1.1197 1.0969 0.00; Chi ² Z = 8.10 (CBDE CBDE 0.124 0.1794 0.1156 c= 19.11 P < 0.00 CBDE	1.37, d .0001) 24 33 93 150 1, df = 2 0001)	LTC Mean 0.869 0.7944 0.7435 (P < 0.0	BDE 0.083 0.0999 001); l ² BDE SBDE	D Tota 9 40 3 29 5 237 306 = 90%	Weight 30.1% 33.9% 36.0% 100.0%	V. Random, 95% C 0.21 [0.15, 0.27] 0.33 [0.28, 0.37] 0.35 [0.33, 0.38] 0.30 [0.23, 0.37] Mean Difference	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² Test for overall effec C 2007 Chen 2014 Wu 2015 Zhang Total (95% CI) Heterogeneity: Tau ² = Fest for overall effect: D Study or Subgroup 2007 Chen 2014 Wu	t: Z = 4.00 LCC <u>Mean</u> 1.076 1.1197 1.0969 0.00; Chi ² Z = 8.10 (<u>L</u> <u>Mean</u>	CBDE CBDE 0.124 0.124 0.1156 CBDE CBDE SD	1.37, d .0001) <u>Total</u> 24 33 93 150 1, df = 2 0001) <u>Total</u>	LTC Mean 0.869 0.7944 0.7435 (P < 0.0 (P < 0.0	BDE 0.083 0.0999 001); l ² BDE SBDE	D Tota 9 40 3 29 5 237 306 5 = 90% D Tota 7 40	Weight 30.1% 33.9% 36.0% 100.0%	IV. Random. 95% C 0.21 [0.15, 0.27] 0.35 [0.28, 0.37] 0.35 [0.33, 0.38] 0.30 [0.23, 0.37] Mean Difference IV. Random. 95% C 8.00 [3.45, 12.55]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² Test for overall effec C Budy or Subgroup 007 Chen 0014 Wu 015 Zhang Total (95% CI) Heterogeneity: Tau ² = est for overall effect: . C Budy or Subgroup 2007 Chen 2017 Chen 2017 Chen 2014 Wu	LCC Mean 1.076 1.1197 1.0969 0.00; Chi ² Z = 8.10 (f Mean 34	CBDE CBDE 0.124 0.124 0.1156 = 19.11 P < 0.00 CBDE SD 10	1.37, d .0001) Total 24 33 93 150 1, df = 2 0001) Total 24 33	LTC Mean 0.869 0.7944 0.7435 (P < 0.0 (P < 0.0 LTC Mean 26	BDE <u>SI</u> 0.109 0.083: 0.0999 0001); I ² SBDE <u>S</u>	D Tota 9 40 3 25 5 237 3066 = 90% D Tota 7 44 3 25	L Weight 30.1% 33.9% 36.0% 100.0% L Weight 48.5% 51.5%	IV. Random. 95% C 0.21 [0.15, 0.27] 0.35 [0.38, 0.37] 0.35 [0.33, 0.38] 0.30 [0.23, 0.37] Wean Difference IV. Random. 95% C 8.00 [3.45, 12.55] -3.75 [-5.97, -1.53]	Favours [experimental] Favours [control] Mean Difference V. Random. 95% Cl -100 -50 0 50 10 -100 -50 0 50 10 Favours [experimental] Favours [control] 10 Mean Difference V. Random. 95% Cl 10 Image: Close of the structure of t
Total (95% CI) Heterogeneity: Tau ² Test for overall effec C Study or Subgroup 2017 Chen 2017 Chen 2016 Zhang Total (95% CI) deterogeneity: Tau ² = rest for overall effect: . D Study or Subgroup 2007 Chen	LC Mean 1.076 1.1197 1.0969 0.00; Chi ² Z = 8.10 (Mean 34 15.5	CBDE <u>SD</u> 0.124 0.0794 0.1156 = 19.11 P < 0.00 CBDE <u>SD</u> 10 4.6	1.37, d .0001) 24 33 93 150 1, df = 2 20001) <u>Total</u> 24 33 57	LTC Mean 0.869 0.7944 0.7435 (P < 0.0 (P < 0.0 <u>LTC</u> <u>Mean</u> 26 19.25	BDE <u>SI</u> 0.100 0.0833 0.0999 0001); I ² SBDE <u>S</u> 4.	D Tota 9 4(3 22 5 237 306 = 90% D Tota 7 4(3 22 65	Weight 30.1% 33.9% 36.0% 100.0% 48.5% 51.5% 100.0%	IV. Random. 95% C 0.21 [0.15, 0.27] 0.35 [0.38, 0.37] 0.35 [0.33, 0.38] 0.30 [0.23, 0.37] Wean Difference IV. Random. 95% C 8.00 [3.45, 12.55] -3.75 [-5.97, -1.53]	Favours [experimental] Favours [control] Mean Difference V. Random. 95% Cl -100 -50 0 50 10 -100 -50 0 50 10 Favours [experimental] Favours [control] 10 Mean Difference V. Random. 95% Cl 10 Image: Close of the structure of t



doi:10.1371/journal.pone.0162885.g003

Blood loss

Only two trials included information about blood loss. There was still no significant difference between the two groups (MD 1.95 ml, 95% CI -9.56 to 13.46; P = 0.74) (Fig 3D).

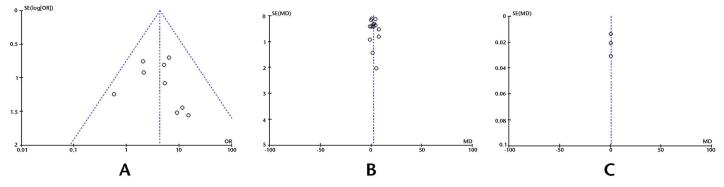
Publication bias

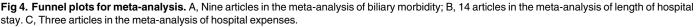
In this meta-analysis, the funnel plot shapes for postoperative complications and postoperative biliary complications showed basic symmetry (Fig 4). No significant publication bias was observed. The results were similar and the combined results were highly reliable.

Discussion

Currently, there are three options for treatment of CBD stones: (1) simultaneous classic CBD exploration and cholecystectomy using the laparotomy approach, (2) combined endoscopic







doi:10.1371/journal.pone.0162885.g004

and LC treatment in a two-step procedure, or (3) simultaneous cholecystectomy and CBD exploration using the laparoscopic approach. Surgeons should be familiar with the limitations and benefits of all these treatment strategies. We performed this study to compare the benefits and drawbacks of different laparoscopic approaches (transcystic and choledochotomy) for removal of CBD stones. We found that LTCBDE is safer than LCCBDE, and is the ideal treatment for CBD stones.

Endoscopic choledocholithiasis surgery is a mature technology; however, it is associated with high complication (19%), failure (10–15%), and mortality (3%) rates [37]. It can not only lead to postoperative complications such as pancreatitis, perforation, blood loss, sepsis, and death, but also to disruption of the sphincter of Oddi, thus causing injury to the physiological barrier function of the sphincter that prevents cholangitis due to duodenobiliary reflux [38, 39]. Natsui et al. [40] reported that the incidence of biliary bacterial contamination 30 months after endoscopic sphincterotomy (EST) was about 78%. Another study reported that the post-operative acute cholangitis rate was 2.4–10.3% in EST [41]. The randomized trials [42] and meta-analysis [43] comparing LCBDE during LC versus postoperative endoscopic retrograde cholangiopancreatography showed no significant difference in the success and complication rates between the two approaches; however, there is a need for fewer procedures and improved cost-effectiveness, as well as shorter hospital stay.

Conventional management of CBD stones included open laparotomy and bile duct exploration, which were first performed by Courvoisier and Thomton separately in 1889 [44]. Classic open CBD exploration is a proven safe and effective option for choledocholithiasis. With advances in laparoscopic technology, LCBDE can now be performed with efficiency and safety [45, 46]. A prospective randomized trial showed the mean operative time in the LCBDE group was similar to that in the laparotomy group, while the morbidity rate and length of postoperative hospitalization were lower in the LCBDE than in the open surgery group [22, 47]. Additionally, LCBDE can be performed without increasing the risk of bile duct complications [48]. Consistent with the modern concept of enhanced recovery after surgery, an LCBDE that exceeds the recommended time interval with no progress should be converted into other treatment options.

LCBDE is substantially better compared to endoscopic and open surgery with regard to hospital stay, postoperative pain, and cosmesis. LCBDE was first reported in 1991, and has been performed in combination with new technologies. It is considered safe and efficient [7, 8]. However, LCBDE has especially high technical requirements and may involve extensive manipulation of instruments such as balloon dilators, guide wires, catheters, and baskets, as well as laparoscopic suturing of the CBD. An argument against LCBDE is the potential risk of bile duct injury and strictures. With improved understanding of biliary anatomy and to reduce complications, some surgeons have attempted removal of CBD stones through the cystic duct instead of performing a direct incision over the CBD. The transcystic duct approach using the lumen of the cystic duct avoids the need to open the CBD; therefore, it may be preferred over a choledochotomy incision. As confirmed by our results, this would greatly reduce the occurrence of complications, especially biliary stricture and bile leakage. We observed that the LTCBDE group showed significantly lower biliary morbidity than the LCCBDE group. A Ttube acts as a foreign body around which bile pigments and salts can precipitate [16]. Therefore, in LTCBDE, the recurrence of stone formation was lower because it eliminated the subsequent need for a T-tube. Additionally, the complications caused by T-tube drainage, including water and electrolyte balance disorders caused by the loss of a large amount of bile, acid-base balance disorders, digestive dysfunction, retrograde infection, prolapse displacement, and living inconvenience were prevented. In fact, suturing of the cystic duct stump could be replaced with a knot or an absorbable clip. The trauma associated with LTCBDE is almost the same as that associated with LC; however, the advantage of LTCBDE is the minimal likelihood of an increase in complications. Although LTCBDE has many advantages, it also has limitations. Most importantly, complete removal of the stone is not always possible. A success rate of about 85% has been reported among all patients for LTCBDE [49]. The success of the transcystic approach depends on whether the choledochoscope is able to enter the CBD. The operation is relatively complex; hence, surgical expertise and adequate equipment (for lavage, biliary endoscopy, cystic duct dilation, trolling with wire baskets or balloon catheters, gravel lavage, and suturing) are indispensable. Moreover, the success of LTCBDE also depends on the anatomy of the cystic duct (duct diameter, and the bifurcation angle of the cystic and hepatic ducts) and CBD stones (location, size, and number of stones). Nevertheless, our results showed there was no significantl difference in operative time between the two groups.

The cystic duct connects the gallbladder and the bile duct. Its length is generally 3 cm and diameter is 0.2–0.3 cm. It consists of two parts, which including 5–12 consecutive half-moon mucosal folds called the Heister spiral valves and a smooth portion close to the CBD. Its elasticity and the smoothness of its interior are similar to the CBD. The muscles of the spiral folds are arranged like an annular valve, which can drive the bile flow by contraction and relaxation. Furthermore, the cystic duct itself functions like a sphincter and can coordinate gallbladder filling. The diameter of the confluence between the cystic and hepatic ducts is wider than the diameter of the CBD. The diameter of the cystic duct can expand to 1 cm or more when the CBD is obstructed, and the expansion is more obvious at the confluence. The anatomical features of the cystic duct and CBD create favorable conditions for LTCBDE.

The advantage of LTCBDE is that the integrity of the CBD is protected. Less injury to the CBD results in fewer postoperative complications. This explains the reduced length of hospital stay and lower hospital expenses for LTCBDE. For a large stone, a microincision at the enlarged confluence between the cystic duct and CBD can be performed; the diameter of the CBD has no significant effect-on the extent of suturing. Our results also showed that biliary morbidity, hospital expenses, and hospital stay in LTCBDE were significantly decreased, compared with LCCBDE. However, there was no significant difference in operative time between the two groups, which could be attributed to advances in suturing techniques. Previously, interrupted suturing was performed; however, suturing speed has greatly improved and the operative time has reduced by using barbed line or continuous sutures.

Preoperative magnetic resonance cholangiopancreatography can not only reveal the size and number of stones but also any variations in the biliary tract. LTCBDE can fail if the angle between the cystic and hepatic duct is small. Pulling the mucosa from the confluence of the cystic duct and CBD using an electrocautery hook and cutting it with scissors can reduce the failure rate caused by the small angle. However, if the incision along the cystic duct towards the CBD is too long, the advantage of using the LTCBDE approach is lost.

The results of our study should be interpreted with caution due to limitations. First, LTCBDE and LCCBDE utilize different levels of technology. Second, although we tried to identify all relevant data, potential publication bias was unavoidable and some data could have been missed (high-quality studies could have been excluded because of missing data or because the standards for LTCBDE were different for different teams). Finally, since this study was restricted to reports published in Chinese and English, publication bias could not be completely ruled out.

Although many experts have suggested criteria for LTCBDE, we believe that there are no fixed standards. The standards should be different for different teams, because they are affected by differences in the level of technology and the anatomical conditions. Based on our surgical experience, we have also developed corresponding standards.

LTCBDE provides a new understanding of biliary anatomy and the concept of choledocholithiasis treatment. Furthermore, it is a successful extension of laparoscopic biliary surgery technology. Although a longer learning time and more laparoscopic skills are required, it should be performed because of its good clinical efficacy.

Supporting Information

S1 PRISMA Checklist. (DOC)

Author Contributions

Conceptualization: LW.

Data curation: YH QF KW XX.

Formal analysis: YH QF KW.

Funding acquisition: YH.

Investigation: YH QF KW XX.

Methodology: LW.

Project administration: YH LW.

Resources: YH QF KW XX.

Software: YH QF KW.

Supervision: YH QF KW.

Validation: YH QF KW.

Visualization: YH QF KW.

Writing - original draft: YH QF XX LW.

Writing - review & editing: YH QF XX LW RY.

References

 Petelin JB. (2003) Laparoscopic common bile duct exploration. Surg Endosc 17: 1705–15. PMID: 12958681

- Tazuma S. (2006) Epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). Best Pract Res Clin Gastroenterol 20: 1075–83.
- Targarona EM, Ayuso RM, Bordas JM, Ros E, Pros I, Martinez J, et al. (1996) Randomised trial of endoscopic sphincterotomy with gallbladder left in situ versus open surgery for common bile duct calculi in high-risk patients. Lancet 347: 926–9. PMID: 8598755
- Neoptolemos JP, Carr-Locke DL, Fossard DP. (1987) Prospective randomised study of preoperative endoscopic sphincterotomy versus surgery alone for common bile duct stones. BMJ 294: 470–4. PMID: 3103731
- Hammarstrom LE, Holmin T, Stridbeck H, Ihse I. (1995) Longterm follow-up of a prospective randomized study of endoscopic versus surgical treatment of bile duct calculi in patients with gallbladder in situ. Br J Surg 82: 1516–7. PMID: 8535807
- Reinders JS, Gouma DJ, Ubbink DT, van Ramshorst B, Boerma D. (2014) Transcystic or transductal stone extraction during single-stage treatment of choledochocystolithiasis: a systematic review. World J Surg 38: 2403–11. doi: 10.1007/s00268-014-2537-8 PMID: 24705779
- Bansal VK, Misra MC, Garg P, Prabhu M. (2010) A prospective randomized trial comparing two-stage versus single-stage management of patients with gallstone disease and common bile duct stones. Surg Endosc 24: 1986–9. doi: 10.1007/s00464-010-0891-7 PMID: 20135172
- Chan DS, Jain PA, Khalifa A, Hughes R, Baker AL. (2014) Laparoscopic common bile duct exploration. Br J Surg 101: 1448–52. doi: 10.1002/bjs.9604 PMID: 25123479
- Grubnik VV, Tkachenko AI, Ilyashenko VV, Vorotyntseva KO. (2012) Laparoscopic common bile duct exploration versus open surgery: comparative prospective randomized trial. Surg Endosc 26: 2165– 71. doi: 10.1007/s00464-012-2194-7 PMID: 22350244
- Lien HH, Huang CC, Huang CS, Shi MY, Chen DF, Wang NY, et al. (2005) Laparoscopic Common Bile Duct Exploration with T-Tube Choledochotomy for the Management of Choledocholithiasis. J Laparoendosc Adv Surg Tech A 15: 298–302. PMID: 15954833
- 11. Kristiansen VB, Rosenberg J. (2002) Laparoscopic treatment of uncomplicated common bile duct stones: what is the evidence? Scand J Gastroenterol 37: 993–8. PMID: 12374243
- Hanif F, Ahmed Z, Samie MA, Nassar AH. (2010) Laparoscopic transcystic bile duct exploration: the treatment of first choice for common bile duct stones. Surg Endosc 24: 1552–6 doi: 10.1007/s00464-009-0809-4 PMID: 20044767
- Fang L, Zou S, Wang K, Lou S, Huang C, Zhou F. (2011) Combined laparoscopic and duodenoscopic transcystic duct for common bile duct stone extraction. Chin J General Surg 20: 642–3.
- Zhu JG, Han W, Guo W, Su W, Bai ZG, Zhang ZT. (2015) Learning curve and outcome of laparoscopic transcystic common bile duct exploration for choledocholithiasis. Br J Surg 102: 1691–7. doi: 10.1002/ bjs.9922 PMID: 26395452
- Strömberg C, Nilsson M, Leijonmarck CE. (2008) Stone clearance and risk factors for failure in laparoscopic transcystic exploration of the common bile duct. Surg Endosc 22: 1194–9. doi: <u>10.1007/</u> s00464-007-9448-9 PMID: 18363068
- 16. Rienhoff WF. (1960) Primary closure of common bile duct. Ann Surg 151: 255–60. PMID: 17859621
- Lyass S, Phillips EH. (2006) Laparoscopic transcystic duct common bile duct exploration. Surg Endosc 20(Suppl 2): S441–5. PMID: 16544067
- Hozo SP, Djulbegovic B, Hozo I. (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5: 13. PMID: 15840177
- Martin IJ, Bailey IS, Rhodes M, O'Rourke N, Nathanson L, Fielding G. (1998) Towards T-tube free laparoscopic bile duct exploration: a methodologic evolution during 300 consecutive procedures. Ann Surg 228: 29–34. PMID: 9671063
- Rhodes M, Sussman L, Cohen L, Lewis MP. (1998) Randomised trial of laparoscopic exploration of common bile duct versus postoperative endoscopic retrograde cholangiography for common bile duct stones. Lancet 351: 159–61. PMID: 9449869
- 21. Cuschieri A, Lezoche E, Morino M, Croce E, Lacy A, Toouli J, et al. (1999) E.A.E.S. multicenter prospective randomized trial comparing two-stage vs single-stage management of patients with gallstone disease and ductal calculi. Surg Endosc 13: 952–7. PMID: 10526025
- Tokumura H, Umezawa A, Cao H, Sakamoto N, Imaoka Y, Ouchi A, et al. (2002) Laparoscopic management of common bile duct stones: transcystic approach and choledochotomy. J Hepatobiliary Pancreat Surg 9: 206–12. PMID: 12140608
- Waage A, Strömberg C, Leijonmarck CE, Arvidsson D. (2003) Long-term results from laparoscopic common bile duct exploration. Surg Endosc 17: 1181–5. PMID: <u>12739114</u>

- Topal B, Aerts R, Penninckx F. (2007) Laparoscopic common bile duct stone clearance with flexible choledochoscopy. Surg Endosc 21: 2317–21. PMID: 17943379
- Chen Xiaoyan, Ding Youming, Wang Weixin, Zhang Aimin, Wang Ping, Wang Bin, et al. (2007) The comparative study on two types of laparoscopic common bile duct exploration. J Clin Surg 15: 520–1.
- 26. Paganini AM, Guerrieri M, Sarnari J, De Sanctis A, D'Ambrosio G, Lezoche G, et al. (2007) Thirteen years' experience with laparoscopic transcystic common bile duct exploration for stones. Effectiveness and long-term results. Surg Endosc 21: 34–40. PMID: 17111284
- Jameel M, Darmas B, Baker AL. (2008) Trend towards primary closure following laparoscopic exploration of the common bile duct. Ann R Coll Surg Engl 90: 29–35. doi: 10.1308/003588408X242295 PMID: 18201497
- ElGeidie AA, ElShobary MM, Naeem YM. (2011) Laparoscopic exploration versus intraoperative endoscopic sphincterotomy for common bile duct stones: a prospective randomized trial. Dig Surg 28: 424– 31. doi: 10.1159/000331470 PMID: 22236538
- Grubnik VV, Tkachenko AI, Ilyashenko VV, Vorotyntseva KO. (2012) Laparoscopic common bile duct exploration versus open surgery: comparative prospective randomized trial. Surg Endosc 26: 2165– 71. doi: 10.1007/s00464-012-2194-7 PMID: 22350244
- 30. Chen XM, Zhang Y, Cai HH, Sun DL, Liu SY, Duan YF, et al. (2013) Transcystic approach with microincision of the cystic duct and its confluence part in laparoscopic common bile duct exploration. J Laparoendosc Adv Surg Tech A 23: 977–81. doi: 10.1089/lap.2013.0309 PMID: 24138388
- Tao Yongze, Chen Dexin, Li Haibin, Zhu Andong, Xing Jin. (2013) Comparison of transcyst with transduct incision in laparoscopic choledochotomy with primary ductal closure. Chin J Min Inv Surg 13: 869–72.
- Poh B, Cashin P, Bowers K, Ackermann T, Tay YK, Dhir A, et al. (2014) Management of choledocholithiasis in an emergency cohort undergoing laparoscopic cholecystectomy: a single-centre experience. HPB (Oxford) 16: 629–34.
- Wu S, Zhan S, Qiu H. (2014) The clinical study of treatment common bile duct stones by laparoscopic cystic duct approach. Anhui Medical Journal 35: 685–6.
- Zhang WJ, Xu GF, Huang Q, Luo KL, Dong ZT, Li JM, et al. (2015) Treatment of gallbladder stone with common bile duct stones in the laparoscopic era. BMC Surg 15: 7. doi: <u>10.1186/1471-2482-15-7</u> PMID: 25623774
- Aawsaj Y, Light D, Horgan L. (2016) Laparoscopic common bile duct exploration: 15-year experience in a district general hospital. Surg Endosc 30: 2563–6. doi: 10.1007/s00464-015-4523-0 PMID: 26307600
- Huang S. (2015) Efficacy Comparison of laparoscopic common bile duct through the cystic duct lithotomy and choledocholithotomy surgery. ModernPractical Medicine 27: 213–4.
- Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. (1996) Complications of endoscopic biliary sphincterotomy. N Engl J Med 335: 909–18. PMID: 8782497
- Wang P, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, et al. (2009) Risk factors for ERCP-related complications: a prospective multicenter study. Am J Gastroenterol 104: 31–40. doi: 10.1038/ajg.2008.5 PMID: 19098846
- Freeman ML. (1998) Complications of endoscopic sphincterotomy. Endoscopy 30: A216–20. PMID: 9932784
- 40. Natsui M, Honma T, Genda T, Nakadaira H. (2011) Effects of endoscopic papillary balloon dilation and endoscopic sphincterotomy on bacterial contamination of the biliary tract. Eur J Gastroenterol Hepatol 23: 818–24. doi: 10.1097/MEG.0b013e328348c0bf PMID: 21730870
- Doi S, Yasuda I, Mukai T, Iwashita T, Uemura S, Yamauchi T, et al. (2013) Comparison of long-term outcomes after endoscopic sphincterotomy versus endoscopic papillary balloon dilation: a propensity score-based cohort analysis. J Gastroenterol 48: 1090–6. doi: 10.1007/s00535-012-0707-8 PMID: 23142970
- Rhodes M, Sussman L, Cohen L, Lewis MP. (1998) Randomised trial of laparoscopic exploration of common bile duct versus postoperative endoscopic retrograde cholangiography for common bile duct stones. Lancet 351: 159–61. PMID: 9449869
- 43. Bansal VK, Misra MC, Rajan K, Kilambi R, Kumar S, Krishna A, et al. (2014) Single-stage laparoscopic common bile duct exploration and cholecystectomy versus two-stage endoscopic stone extraction followed by laparoscopic cholecystectomy for patients with concomitant gallbladder stones and common bile duct stones: a randomized controlled trial. Surg Endosc 28: 875–85. doi: 10.1007/s00464-013-3237-4 PMID: 24162138
- 44. Beal JM. (1984) Historical perspective of gallstone disease. Surg Gynecol Obstet 158: 181–9. PMID: 6364426

- Thompson MH, Tranter SE. (2002) All-comers policy for laparoscopic exploration of the common bile duct. Br J Surg 89: 1608–12. PMID: <u>12445074</u>
- **46.** Tinoco R, Tinoco A, El-Kadre L, Peres L, Sueth D. (2008) Laparoscopic common bile duct exploration. Ann Surg 247: 674–9. doi: 10.1097/SLA.0b013e3181612c85 PMID: 18362631
- Lien HH, Huang CC, Huang CS, Shi MY, Chen DF, Wang NY, et al. (2005) Laparoscopic Common Bile Duct Exploration with T-Tube Choledochotomy for the Management of Choledocholithiasis. J Laparoendosc Adv Surg Tech A 15: 298–302. PMID: 15954833
- Waage A, Strömberg C, Leijonmarck CE, Arvidsson D. (2003) Long-term results from laparoscopic common bile duct exploration. Surg Endosc 17: 1181–5. PMID: <u>12739114</u>
- Lyass S, Phillips EH. (2006) Laparoscopic transcystic duct common bile duct exploration. Surg Endosc 20: S441–5. PMID: 16544067