ejpmr, 2023, 10(6), 87-101

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article
ISSN 2394-3211
EJPMR

LAPAROSCOPIC COMMON BILE DUCT EXPLORATION VERSUS PRE- OR INTRAOPERATIVE ENDOSCOPIC TREATMENT FOR CHOLEDOCHOLITHIASIS A SYSTEMATIC REVIEW AND META-ANALYSIS

Victor Hugo B. Custódio[1], Amanda G. Oliveira[1], Fábio A. Gonçalves - Jr[1], João Pedro A. Carani[1], Isabella B. Aguiar[1], Antonio José M. Cataneo[2] and César T. Spadella[2*]

[1]Salesian Catholic University Center Auxilium (UNISALESIANO), Medical School, Aracatuba, Sao Paulo, Brazil.
[2]Department of Surgery and Orthopedics, Faculty of Medicine of Botucatu, Sao Paulo State University - UNESP, Botucatu, Sao Paulo, Brazil.

***Corresponding Author: César T. Spadella**
Department of Surgery and Orthopedics, Faculty of Medicine of Botucatu, Sao Paulo State University - UNESP, Botucatu, Sao Paulo, Brazil.

Article Received on 07/04/2023 **Article Revised on 28/04/2023** **Article Accepted on 18/05/2023**

ABSTRACT
Aim: This systematic review aimed to compare laparoscopic common bile duct exploration (LCBDE) with pre- or intraoperative endoscopic retrograde cholangiopancreatography with sphincterotomy (ERCP/S), both associated with laparoscopic cholecystectomy (LC), for the treatment of choledocholithiasis. **Methods:** Only RCTs were included in this review, which were searched in major literature databases from 1970 to 2021. **Results:** Meta-analysis of 14 primary studies with 2214 patients showed that successful CBD stone clearance was higher in LC+LCBDE than in pre-ERCP/S+LC (91.3% vs. 90.1%) but lower than in intra-ERCP/S+LC (88.5% vs. 91.6%). However, there were no significant differences among the groups. Except for conversion to open surgery, the laparoscopic arm had lower rates of retained stones, failure of procedure, cross over to other procedure, total morbidity, and mortality compared to pre-ERCP/S+LC. On the other hand, the rates of all those secondary outcomes were lower in intra-ERCP/S+LC than in LC+LCBDE, but there were no significant differences among the groups. Pancreatitis episodes were significantly more frequent in both endoscopic groups, while bile leakage was higher in LC+LCBDE. Overall, operative time was significantly higher in LC+LCBDE than in pre-ERCP/S+LC but lower than in the intra-ERCP/S+LC group. The length of hospital stay was significantly shorter in the laparoscopic arm than in the pre-ERCP/S+LC group but longer in the intra-ERCP/S+LC group. **Conclusion:** This systematic review shows that either LC+LCBDE or pre- and intra-ERCP/S+LC are safe and highly effective in removing CBD stones. However, the results suggest that single-step interventions are better for appropriate patients and health services.

KEYWORDS: Laparoscopic Common Bile Duct Exploration. Endoscopic Retrograde Cholangiopancreatography/Sphyncterotomy. Laparoscopic Cholecystectomy. Cholelithiasis. Choledocholithiasis. Systematic Review and Meta-Analysis.

INTRODUCTION
Cholelithiasis is one of the most common digestive tract diseases, affecting approximately 10–15% of the world's adult population.[1,2] Typically, about 80% of patients with cholelithiasis are asymptomatic.[3] However, about 5–15% of patients with symptomatic cholelithiasis have concomitant choledocholithiasis.[4] Of these, 1–2% may experience serious complications of the disease, such as acute cholecystitis, obstructive jaundice, suppurative cholangitis, and severe pancreatitis.[5]

Laparoscopic cholecystectomy (LC) is a well-established treatment for cholelithiasis. However, choledocholithiasis continues to pose a significant challenge for surgical gastroenterology, because the success of the treatment directly links to complete clearance of gallstones from inside the common bile duct (CBD) and the low morbidity rate of the procedures.[6]

Currently, preoperative endoscopic retrograde cholangiopancreatography plus sphincterotomy (pre-ERCP/S) remains the preferred procedure for most surgeons worldwide to remove gallstones from inside the CBD. However, the procedure carries several complications, such as acute pancreatitis, duodenal papilla bleeding, and sphincter of Oddi dysfunction, duodenal perforation, and recurrent bile duct stones.[7]

Furthermore, pre-ERCP/S involves two surgical steps, which may increase the length of hospital stay and the costs and professional fees for health services.[8] As a result, other surgical techniques have been used in conjunction with LC to treat choledocholithiasis in a single procedure, such as LC associated with laparoscopic CBD exploration (LC+LCBDE) or with intraoperative endoscopic retrograde cholangiopancreatography plus sphincterotomy (intra-ERCP/S+LC).[9]

However, since clinical trials assessing the performance of these procedures are always based on intention-to-treat analysis, many published studies do not include in their clinical endpoints only patients who received the treatment to which they were randomized. This makes it difficult to assess the efficacy of the procedures because it is unclear whether the success of the patient's treatment was due to one procedure or another. Once using additional procedures to achieve the desired success is relatively common, such as crossing over to another surgical approach.

In addition, many systematic reviews have relatively small sample sizes and include few studies, some of them with significant heterogeneity in results and the presence of bias in selection, performance and incomplete outcome data. For these reasons, we believe that new systematic reviews and meta-analysis of primary studies addressing these issues may provide the best evidence for choosing the most appropriate treatment for choledocholithiasis.

MATERIALS AND METHODS

This review was carried out according to the PRISMA-P consensus checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols),[10] and its protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42022330946.

The study was developed according to the PICO acronym, where the population studied (P) consisted of patients with cholelithiasis associated with choledocholithiasis; the intervention assessed (I) was the LC+LCBDE; the comparator procedures or controls (C) were the pre- or intra-ERCP/S+LC; and the primary and secondary outcomes found in each analyzed study (O).

Review question

The question to be answered in this systematic review is whether LC+LCBDE is more effective and safer than pre- or intra-ERCP/S+LC for treating patients with cholelithiasis associated with choledocholithiasis, particularly regarding the complete removal of stones from the CBD and the reduction of morbidity rates.

Searches

In this review, we searched the following databases, from 1970 to 2021, without language restrictions: MEDLINE via Pubmed, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, Scopus, Web of Sciences (WoS), and Experimental Clinical Trials database. For the LILACS database, the main descriptors for the search strategy were through the link: https://drive.google.com/file/d/1oYBrQIuP10P8ZShvvpOk63Ov7BNlzB8m/view?usp=sharing

For MEDLINE/Pubmed, EMBASE, Cochrane (CENTRAL), Scopus and Web of Science (WoS) databases, the main descriptors in Medical Subject Headings (MeSHs) for the search strategy were through the link: https://drive.google.com/file/d/1P9CCJ698imBvODtR_qeum6J3K7PBY1MU/view?usp=sharing

Study types included in the meta-analysis

In this review were included only randomized and controlled clinical trials (RCTs). Were excluded from the meta-analysis case reports, case series, case-control studies, retrospective studies, prospective cohorts, conference abstracts, letters from editors, systematic reviews, studies that exclusively analyzed quality of life, hospital costs and professional fees, duplicate articles, irrelevant articles (not focused on the topic of this review), and articles whose full texts cannot be retrieved.

Inclusion and exclusion criteria of study participants

This review analyzed primary studies that included patients who met the following inclusion and exclusion criteria: **Inclusion** - Adult patients of both sexes and ages with a proven or suspected diagnosis of cholelithiasis plus choledocholithiasis suggested by clinical, laboratory, ultrasound, and/or cholangiopancreatography performed by endoscopy, magnetic resonance imaging or intraoperatively. **Exclusion** - Teenagers under 16 years old, high-risk patients (elderly people over 90, morbid obesity, and/or decompensated comorbidities), those who underwent cholecystectomy previously, enteric bypass of the bile ducts, surgeries of the stomach and/or duodenum, and mainly postoperative endoscopic retrograde cholangiopancreatography plus sphincterotomy to treat residual bile duct stones or recurrence of CBD stones.

Study interventions

LC+LCBDE is a laparoscopic surgical procedure performed in a single-step. Initially, the cystic duct is isolated and tied distally to prevent the migration of gallstones to the CBD. For small, non-occlusive gallstones, the cystic duct is usually used to remove them from the CBD. However, for large and/or occlusive stones, a choledochotomy is more appropriate. Various techniques are used to remove gallstones, including lavage, balloon extraction, mechanical lithotripsy, or Dormia basket extraction. In some cases, a choledoscope may be used. After the gallstones are removed from the CBD, the duct is closed, or a T-tube is placed for biliary drainage. Finally, the cholecystectomy is completed.

Pre- and intra-ERCP/S+LC are performed with endoscopic intervention in the bile duct using a side-viewing duodenoscope. First, an intraoperative cholangiography is performed through the duodenal papilla ostium to confirm stones within the CBD. Then, a sphincterotomy is carried out, and gallstones are removed using either balloon, basket extraction, or mechanical lithotripsy for larger stones. Eventually, after CBD stone clearance, a nasobiliary drain tube is inserted into the CBD endoscopically. Pre-ERCP/S is a procedure performed in two surgical steps. At first, CBD clearance is carried out, and later, the patients undergo cholecystectomy. On the other hand, intra-ERCP/S is performed at the same time of LC, and gallstones are removed either by passing the guidewire through the cystic duct (rendezvous technique) or by transampullary via. In this review, all surgical interventions performed by the study authors were primarily intended to treat the patient.

Study outcomes

The primary outcome was the efficacy of procedures for successfully removing the gallbladder and clearing CBD stones. In this review, the success rates of ductal stone clearance were considered only in patients with a confirmed diagnosis of choledocholithiasis. Success was defined as the absence of gallstones within the CBD on cholangiography only after the primary planned intervention. Success rates attributed to cross over to other procedure (including conversion to open surgery) and those resulting from patients with stone-free ducts were also excluded from this review.

The secondary endpoints were the retained stone rates, failure of procedure, cross over to other procedure, conversion to open surgery, operative time (in minutes), length of hospital stay (in days), total morbidity (related to postoperative complications), and mortality. Retained stones were defined as those that remained inside the CBD after the primary planned intervention, regardless of the cause, such as technical failure, surgical inaccessibility, lack of surgeon expertise, or surgical complications that made it impossible to reach or extract the stones.

Studies selection

All resulting initial studies from each database were exported to the Endnote Library to quantify and remove duplicates. The studies were then grouped and evaluated by their titles and abstracts by the review authors independently and blindly to remove studies that did not meet the inclusion criteria. In the second step, the full texts of the potentially relevant studies were retrieved and reviewed. Doubts and possible disagreements among reviewers in including eligible studies for analysis, either in the initial selection or posterior step, were discussed. If a consensus was not reached, the opinion of two researchers with expertise in the area was decisive.

Data extraction

Microsoft Excel spreadsheets were used to extract data from the eligible studies, including the author's name, year of publication, study country, type of study, number of participants in each study, clinical, laboratory, and demographic profiles of the patients, the interventions performed, follow-up time, and all outcomes of interest in this review (primary and secondary). All data were extracted as measured and reported by investigators, excluding those relating to success rates in stone removal in patients who did not have stones in the CBD or resulting from crossing over to another procedure. Five researchers independently extracted all data from the interventions studied. Any disagreements were resolved through discussion among the reviewers, with the decisive opinion of the review supervisor.

Strategy for data synthesis

Data synthesis was performed according to the meta-analysis method by Mantel-Haenszel (1959).[11] The random-effects model was used to analyze outcomes, and the risk ratio with their respective 95% confidence intervals was used to measure treatments' effects. The Cochrane Review Manager 5 (RevMan - version 5.4.1) program was used to aggregate and analyze data from the clinical trials included in this review. The results found in the synthesis of outcomes were summarized in a forest plot, where each horizontal line represented an included study. A square represented the estimated effect, and the size of the square corresponded to the weight of the study in question. The combined effect estimate was represented by a diamond located at the bottom of the graph, and a numerical summary of the meta-analysis was presented at the lower left corner that included the total number of study participants and events, as well as the heterogeneity of the results (I^2), global effect test (Z), and its statistical significance (P).

For statistical analysis of demographic, clinical, and laboratory quantitative data, GraphPad InStat software, Inc., CA, USA (version 3.10) was used when the statistical analysis was not available. Two-tailed unpaired analysis was applied to compare statistical significance between groups using Kolmogorov and Smirnov (KS) test for normally distributed variables and Mann-Whitney U-statistic for non-parametric variables. Statistical significance was assumed when $P<0.05$. Descriptive analysis of the results was used when quantitative data were not available.

Risk of bias assessment

To assess the risk of bias in the clinical trials included in this review, we used the Cochrane Collaboration's "risk of bias" tool, which is an integral part of the Review Manager program. Two independent researchers with expertise in the subject assessed the risk of bias. Any disagreements were resolved through consensus or with the opinion of a third party. We assessed the risk of bias in clinical trials according to the instructions provided in the Cochrane Handbook for Systematic Reviews of Interventions[12] and empirical evidence.[13] The domains analyzed included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting, and other biases (including for-profit bias).

RESULTS

Identification, screening, and eligibility of included studies

A total of 1703 references were identified through electronic database searching, including LILACS (n = 24), EMBASE (n = 296), Web of Science (n = 610), Cochrane Central Register of Controlled Trials (n = 97), MEDLINE/PubMed (n = 375), SCOPUS (n = 297), and other sources (n = 4). After removing duplicates and irrelevant studies, 29 publications were deemed eligible for the study. Of these, 14 met the full criteria for meta-analysis, with one study addressing three types of interventions of interest in this review and included in two comparisons. The study flow diagram is presented in Fig. 1, and Table 1 provides an overview of the characteristics of the studies included in the meta-analysis.

Description of included studies

The distribution of patients among treatment groups was relatively uniform, with 1084 patients in the laparoscopic group and 1130 in the endoscopic group. Eleven studies[14-17, 19, 20, 22-24, 26, 27] compared LC+LCBDE versus pre-ERCP/S+LC and included 779 and 779 patients, respectively. Four studies[18,20,21,25] compared LC+LCBDE versus intra-ERCP/S+LC that included 305 and 351 patients, respectively. One of these studies[20] evaluated laparoscopic treatment and pre- and intraoperative endoscopic treatments. In most patients from the pre-ERCP/S arm, LC was performed during the same admission, but in one trial,[14] surgery only took place 4–6 weeks after ERCP and in another[24] 2 weeks later. Sample size calculation was not performed in three trials,[14, 21, 27] and follow-up was not mentioned in four others.[14, 16, 21, 26] There were several protocol violations and dropouts. Some patients did not come to perform LC after the removal of CBD stones in the pre-ERCP/S arm.

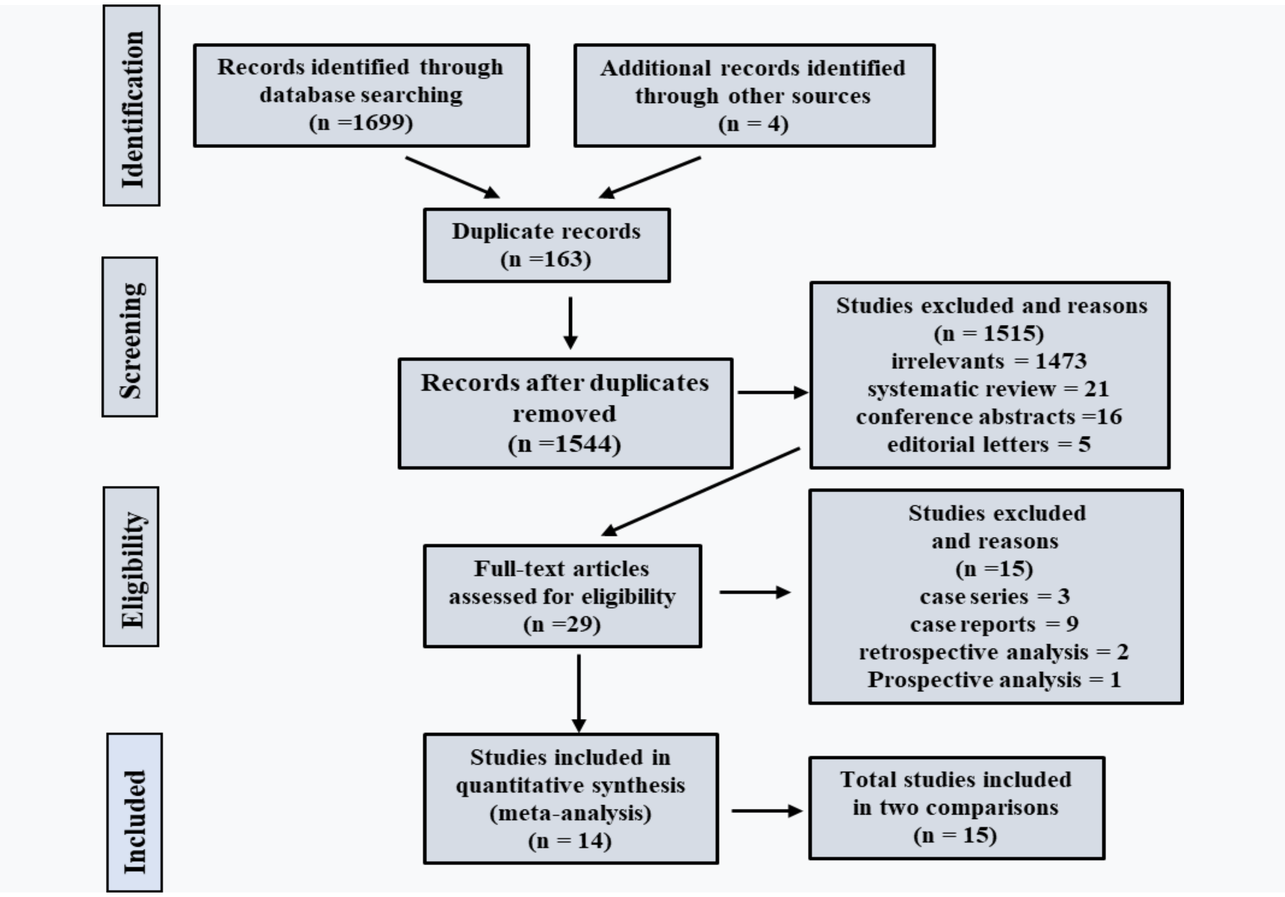

Fig. 1 – Flowchart of the selection of studies included in the review.

Bias assessment and quality of included studies

The review authors' judgments about each risk of bias item, presented as percentages across all included studies, and a summary for each included study in this review are in Figure 2. Performance bias was of high risk in all studies, once there was no attempt to blind participants and personnel in any trials. Selection bias was observed in eight studies; in three studies[21, 24, 27], the method of random sequence generation was unclear, and in five studies[19, 21, 23, 24, 27], the method to conceal the allocation of participants and personnel was not described. In two studies, there were incomplete data,[14, 17], and in three others, there was selective reporting.[18, 23, 27] In one study[19], there was possibly a conflict of interest. Because of this, the authors of this review judged the quality of evidence as low.

Table 1: Characteristics of the studies included in the meta-analysis.

Authors	Study type	Procedures	Patients	Year	Country
Bansal[14]	RCT	LC+LCBDE Pre-ERCP/S+LC	15 15	2010	India
Bansal[15]	RCT	LC+LCBDE Pre-ERCP/S+LC	84 84	2014	India
Cuschieri[16]	RCT	LC+LCBDE Pre-ERCP/S+LC	150 150	1999	Scotland
Ding[17]	RCT	LC+LCBDE Pre-ERCP/S+LC	110 111	2014	China
Elgeidie[18]	RCT	LC+LCBDE Intra- ERCP/S+LC	112 107	2011	Egypt
Ferulano[19]	RCT	LC+LCBDE Pre-ERCP/S+LC	62 62	2011	Italy
González[20]	RCT	LC+LCBDE Pre-ERCP/S+LC Intra- ERCP/S+LC	100 101 99	2016	Cuba
Hong[21]	RCT	LC+LCBDE Intra- ERCP/S+LC	141 93	2006	China
Koc[22]	RCT	LC+LCBDE Pre-ERCP/S+LC	57 54	2013	Turkey
Lv[23]	RCT	LC+LCBDE Pre-ERCP/S+LC	29 24	2016	China
Mohamed[24]	RCT	LC+LCBDE Pre-ERCP/S+LC	75 75	2015	Egypt
Poh[25]	RCT	LC+LCBDE Intra- ERCP/S+LC	52 52	2016	Australia
Rogers[26]	RCT	LC+LCBDE Pre-ERCP/S+LC	61 61	2010	USA
Sgourakis[27]	RCT	LC+LCBDE Pre-ERCP/S+LC	36 42	2002	Greece

Abbreviations: *RCT- randomized controlled trial, LC+LCBDE – laparoscopic cholecystectomy plus common bile duct exploration, Pre-ERCP/S+LC– preoperative endoscopic retrograde cholangiopancreatography plus sphincterotomy followed by laparoscopic cholecystectomy, intra-ERCP/S+LC - intraoperative endoscopic retrograde cholangiopancreatography plus sphincterotomy followed by laparoscopic cholecystectomy.*

Patient characteristics

Overall, there were no significant differences in demographic, clinical, and laboratory characteristics among the study groups, although some data were missing in some studies, particularly in those comparing LC+LCBDE vs. intra-ERCP/S+LC. Women had a higher prevalence of cholelithiasis associated with choledocholithiasis, but the difference among groups was not quite statistically significant (LC+LCBDE vs. pre-ERCP/S+LC, P = 0.0579; LC+LCBDE vs. intra-ERCP/S+LC, P = 0.0421). Biliary symptoms, such as right upper quadrant and/or epigastric pain, biliary colic, nausea, and vomiting, with or without jaundice, were frequently observed in all three study groups. About 9 to 50% of patients presented with complications such as pancreatitis, cholecystitis, and cholangitis at admission. Most of the study patients had changes in liver function tests, particularly in total bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase, but there were no statistically significant differences in clinical or laboratory changes among the three treatment modalities.

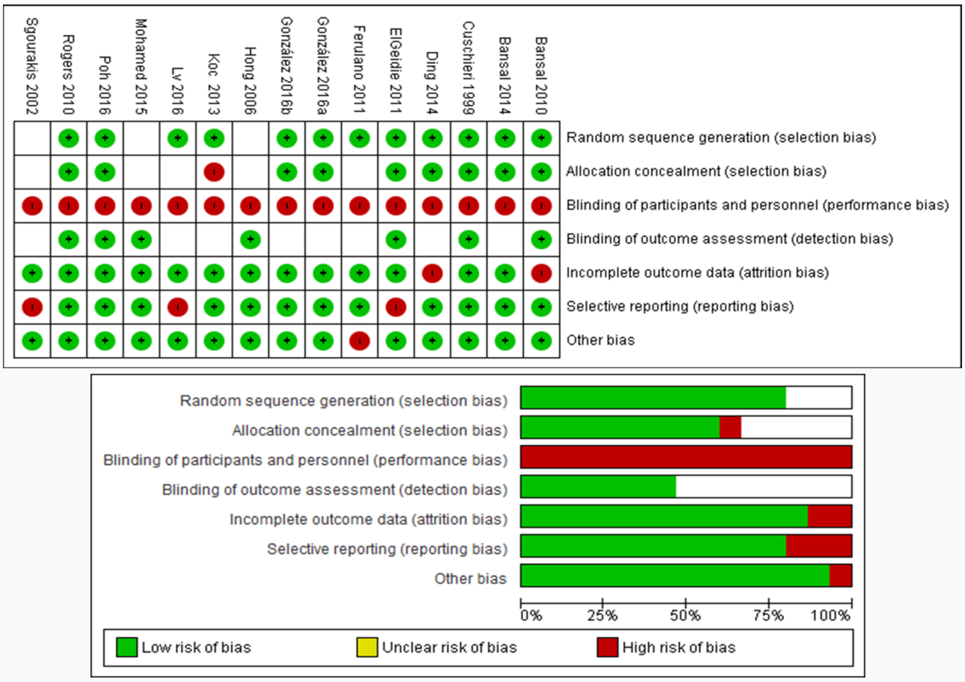

Fig. 2 – Risk of bias summary in the included studies in meta-analysis. Captions: (+ green) low risk; (- red) high risk; (blank) unclear risk of bias.

Effects of interventions

Primary outcome

The meta-analysis included 609 patients in the LC+LCBDE group and 606 patients in the pre-ERCP/S+LC group for CBD stone clearance, with success rates of ductal clearance of 91.3% and 90.1%, respectively. In the LC+LCBDE and intra-ERCP/S+LC groups, there were 348 and 298 patients, respectively, with success rates of ductal clearance of 88.5% and 91.6%. However, the meta-analysis showed no statistically significant differences among the three treatment modalities, as observed in the forest plot using risk ratio and random-effect model (P= 0.83 for LC+LCBDE vs. pre-ERCP/S+LC; P = 0.54 for LC+LCBDE vs. intra-ERCP/S+LC) (Fig. 3).

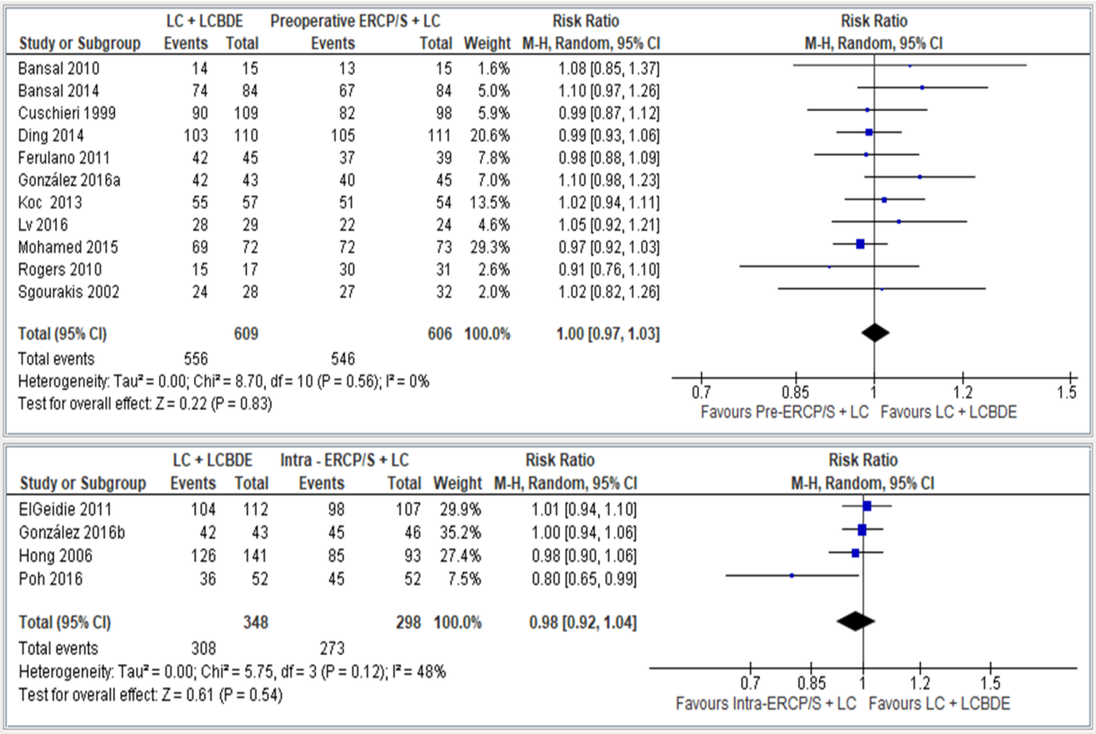

Fig. 3 – Forest plot of comparisons: LC+LCBDE vs pre- or intraoperative ERCP/S+LC for common bile duct stone clearance.

Secondary outcomes

For the comparison between LC+LCBDE and pre-ERCP/S+LC the rates of retained stones, failure of procedure, and cross over to other procedure were lower in laparoscopic arm compared to endoscopic arm. In contrast, the rate of conversion to open surgery was higher in laparoscopic group when compared to pre-endoscopic group. However, in the meta-analysis no statistically significant differences were detected for any of the secondary outcomes, as observed in the forest plot using the risk ratio and random-effect model. For LC+LCBDE vs. pre-ERCP/S+LC arm we observed, respectively: retained stones (8.4% vs. 9.9%, P = 0.36); failure of procedure (3.9% vs. 5.3%, P = 0.29); cross over to other procedure (7.1% vs. 8.5%, P = 0.44); conversion to open surgery (4.6% vs. 2.2%, P = 0. 17).

In contrast, the rates of retained stones, failure of procedure, cross over to other procedure, and conversion to open surgery were lower in intra-ERCP/S+LC compared to LC+LCBDE. However, in the meta-analysis, there were no statistically significant differences between the two groups for all these secondary outcomes, as observed in the forest plot using the risk ratio and random-effect model. For LC+LCBDE vs. intra-ERCP/S+LC arm, we observed, respectively: retained stones (11.5% vs. 8.4%, P = 0.18); failure of procedure (5.92% vs. 5.91%, P = 0.98); cross over to other procedure (6.7% vs. 6.2%, P = 0.98); conversion to open surgery (4.9% vs. 3.4%, P = 0.55). Forest plots of the comparisons between LC+ LCBDE vs. pre-ERCP/S+ LC and LC+LCBDE vs. intra-ERCP/S+LC for all outcomes mentioned above are illustrated in Figs. 4 to 7.

Postoperative morbidity

Total morbidity was lower in the LC+LCBDE group than in the pre-ERCP/S+LC group, but it was higher when compared to the intra-ERCP/S+LC group. However, the meta-analysis showed that there were no statistically significant differences among the three treatment modalities as observed in the forest plot comparisons (10.5% for LC+LCBDE vs. 11.8% for pre-ERCP/S+LC, P = 0.55) and (9.6% for LC+LCBDE vs. 9.3% for intra-ERCP/S+LC, P = 0.84). Nonetheless, it was observed that the occurrence of pancreatitis episodes was higher in both endoscopic groups than in the laparoscopic group, with statistically significant differences in pre-ERCP/S+LC (0.6% for LC+LCBDE vs. 3.6% for pre-ERCP/S+LC, P = 0.002) and non-significant for LC+LCBDE vs. intra-ERCP/S+LC (1.7% vs. 3.9%, P = 0.07). On the other hand, bile leakage was more frequent in the laparoscopic group than in the endoscopic groups, with statistically significant differences between LC+ LCBDE vs. pre-ERCP/S+ LC (4.9% vs. 0.9%, P = 0.001) and non-significant for LC+LCBDE vs. intra-ERCP/S+LC (2.0% vs. 0.6%, P = 0.17). Figures 8 to 10 illustrate the comparisons among groups for total morbidity and the occurrence of pancreatitis and bile leakage.

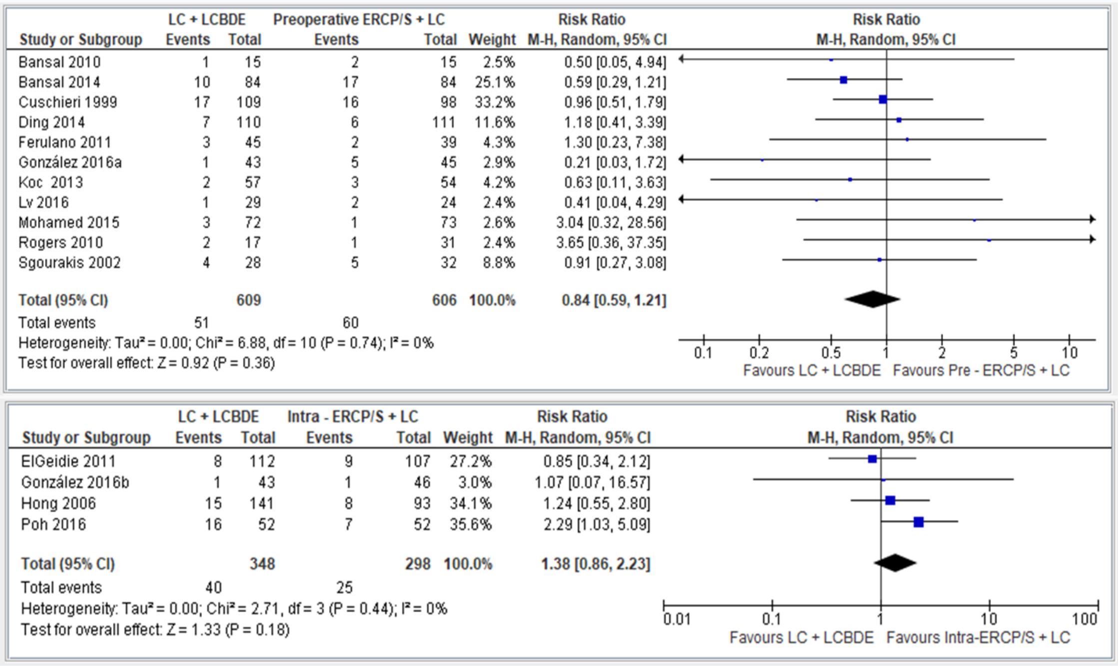

Fig. 4 – Forest plot of comparisons: LC+LCBDE vs pre- or intraoperative ERCP/S+LC for retained stones.

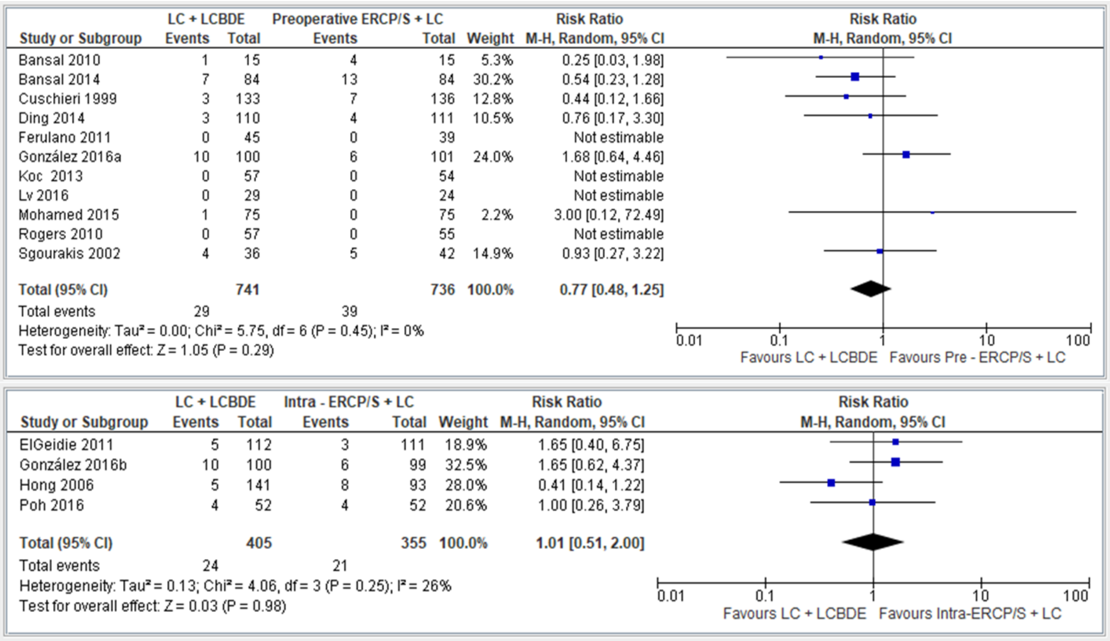

Fig. 5 – Forest plot of comparisons: LC+LCBDE vs pre- or intraoperative ERCP/S+LC for failure of procedure.

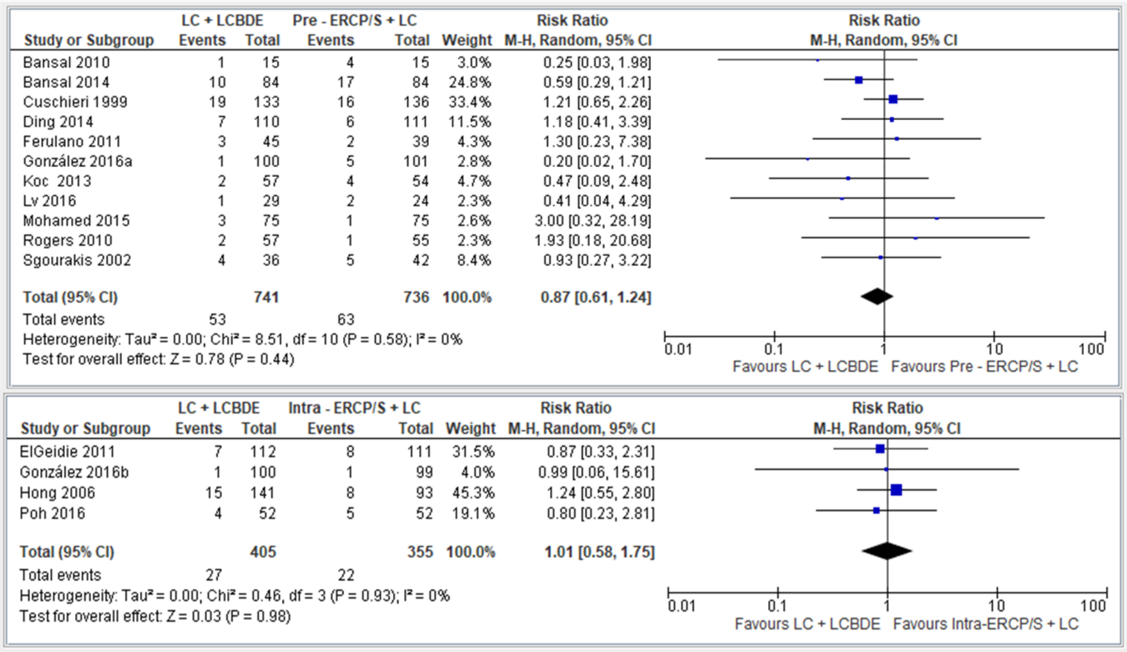

Fig. 6 – Forest plot of comparison: LC+LCBDE vs pre- or intraoperative ERCP/S+LC for cross over to other procedure.

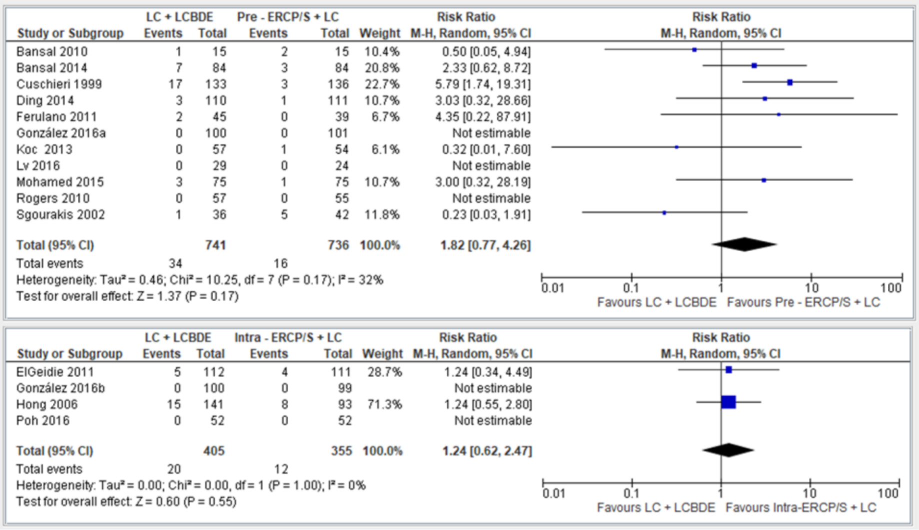

Fig. 7 – Forest plot of comparison: LC+LCBDE vs pre- or intraoperative ERCP/S+LC for conversion to open surgery.

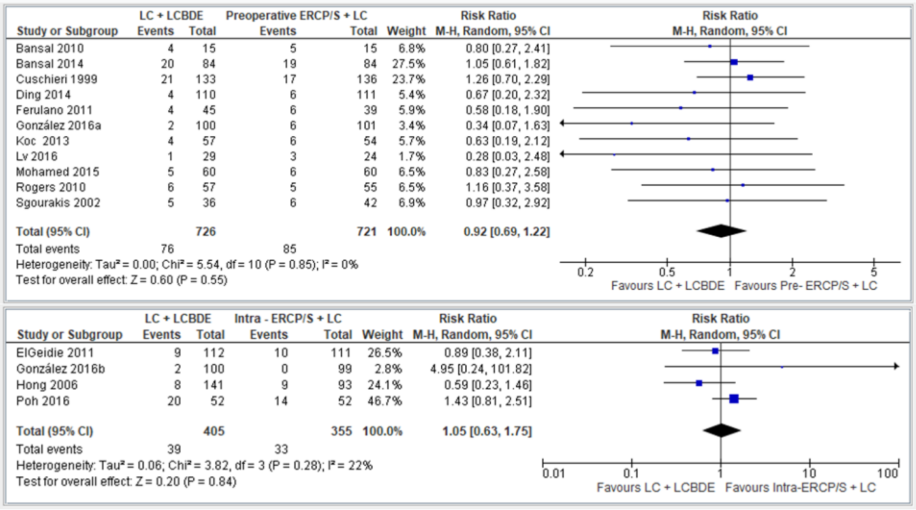

Fig. 8 – Forest plot of comparisons: LC+LCBDE vs pre- or intraoperative ERCP/S+LC for total morbidity.

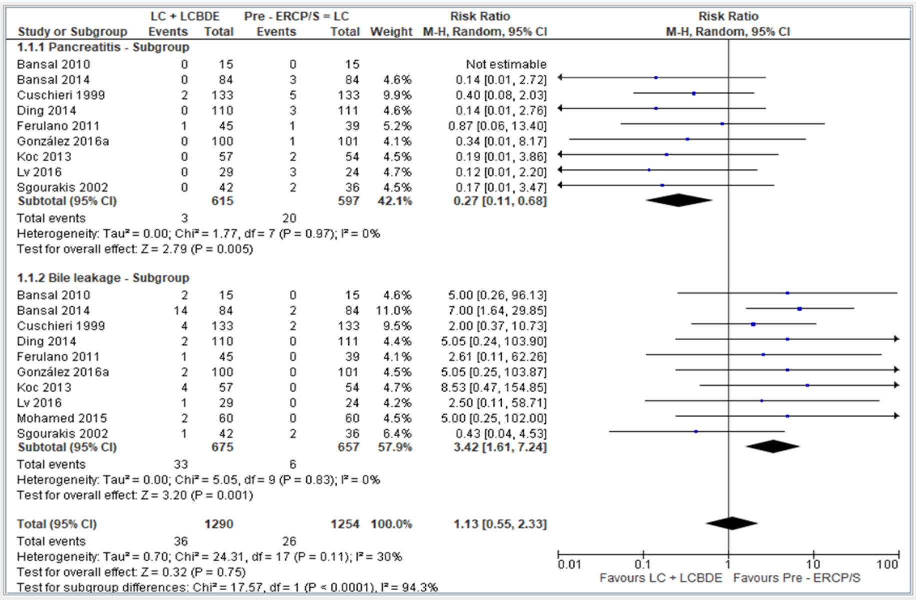

Fig. 9 – Forest plot of comparisons: LC+LCBDE vs pre-ERCP/S+LC for occurrence of pancreatitis and bile leakage.

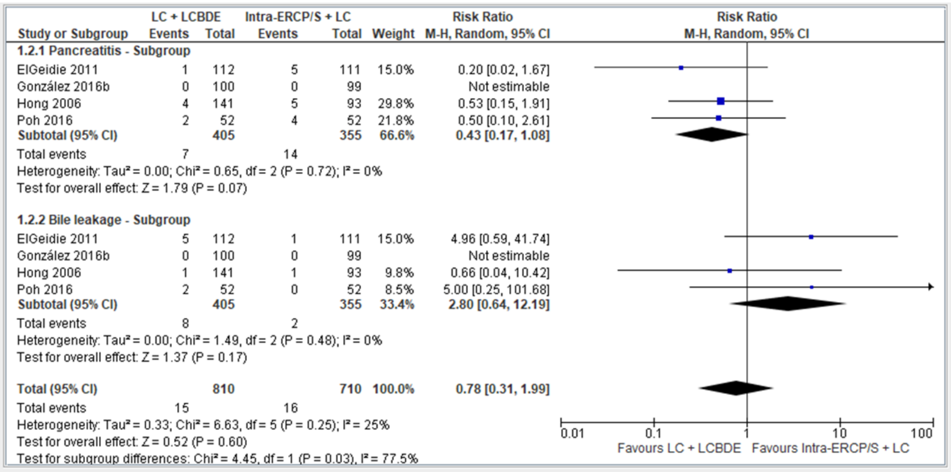

Fig. 10 – Forest plot of comparisons: LC+LCBDE vs. intra-ERCP/S+LC for occurrence of pancreatitis and bile leakage.

Mortality

The mortality rate was lower in the LC+LCBDE group than in pre-ERCP/S+LC, but with statistically non-significant differences (0.3% vs. 0.8%, P = 0.33). On the other hand, there were no deaths in the LC+LCBDE group nor the intra-ERCP/S+LC group (Fig. 11).

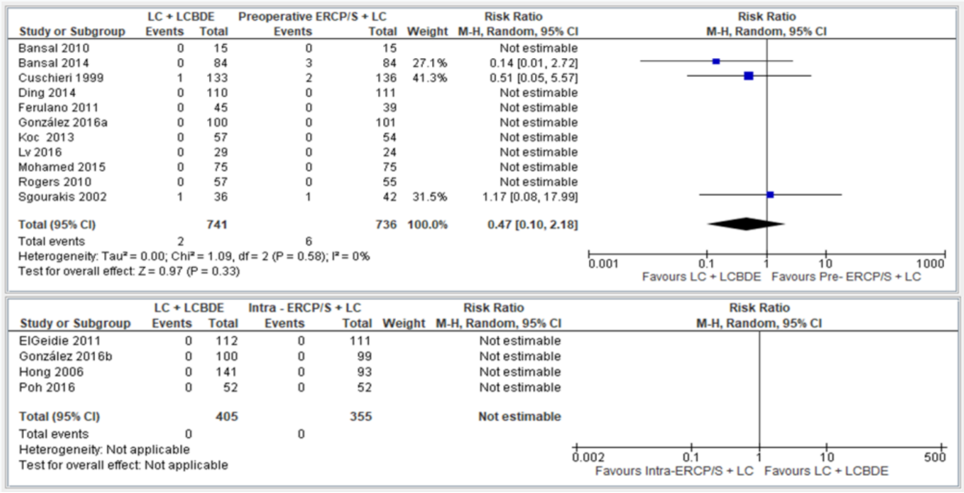

Fig. 11 – Forest plot of comparisons: LC+LCBDE vs pre- or intraoperative ERCP/S+LC for mortality.

Operative time and length of hospital stay

For LC+LCBDE vs. pre-ERCP/S+LC operative time was not assessed in three out of 11 trials,[16, 17, 23] and in one trial,[14] this outcome was not mentioned for the pre-ERCP/S+LC arm. Except for one trial,[17] all studies reported the length of hospital stay. For LC+LCBDE vs. intra-ERCP/S+LC, all trials reported operative time and length of hospital stay. However, we observed that the data for these two outcomes were either given as parametric data, as a mixture of parametric and non-parametric data or in a non-parametric data format (only as a median and interquartile range). Therefore, the data for these outcomes were not included in the meta-analysis of this review. However, observing statistical results reported by the study authors (or, when not available, those calculated by us), we observed that operative time was significantly higher in LC+LCBDE than in pre-ERCP/S+LC in three trials,[15, 19, 20] but significantly lower in two other trials.[22, 24] Operative time also was lower in the laparoscopic group in two other trials.[26, 27] Nonetheless, there were no statistically significant differences between groups. For LC+LCBDE vs. intra-ERCP/S+LC, operative time was lower in the former group in three out of four trials,[18, 21, 25] but no statistically significant differences existed between groups. In contrast, operative time was significantly lower in the intra-ERCP/S+LC than in the LC+LCBDE group in only one of four trials.[20]

The length of hospital stay was significantly lower in the LC+LCBDE group than in the pre-ERCP/S+LC group in six trials,[15, 16, 20, 22, 23, 27] and higher in one trial.[19] In another trial, the length of hospital stay was not assessed,[17] and in three trials,[14, 24, 26] there was no statistically significant difference between the two groups. Length of hospital stay was higher in the LC+LCBDE arm than in the intra-ERCP/S+LC arm in three out of four trials,[20, 21, 25] with statistically significant differences in two of these.[20, 25]

Overall, operative time was significantly higher in the LC+LCBDE group than in the pre-ERCP/S+LC group but lower when compared to the intra-ERCP/S+LC group, although significant in only one trial.[20] The length of hospital stay was shorter in the laparoscopic arm than in the pre-endoscopic arm but longer when compared to the intra-endoscopic group. Table 2 shows the operative time and length of hospital stay findings for the two comparisons.

Table 2: Operative time and length of hospital stay findings for LC+LCBDE vs. Pre-ERCP/S+LC and LC+LCBDE vs. Intra-ERCP/S+LC.

Operative time (min)			
Authors	**LC + LCBDE**	**Pre – ERCP/S + LC**	**P value**
Bansal 2010§	153.0 (120 - 240)	Not mentioned	not estimated
Bansal 2014#	135.7 ± 36.6	72.4 ± 27.6	P < 0.001*
Cuschieri 1999	Not evaluated	Not evaluated	-
Ding 2014	Not evaluated	Not evaluated	-
Ferulano 2011#	160 (100 - 280)	70	P = 0.0004*
González 2016a#	117.0 (40 - 270)	98.0 (30 - 240)	P = 0.0055*
Koc 2013#	93.47 ± 32.06	113.33 ± 36.07	P = 0.0027*
Lv 2016	Not evaluated	Not evaluated	-
Mohamed 2015#	93.0 ± 12.45	117.0 ± 15.76	P < 0.05*
Rogers 2010#	175.0 ± 9.2	182.0 ± 5.4	P = 0.540
Sgourakis 2002#	90.0 ± 60.0	105.0 ± 48.75	P = 0.2270
Authors	**LC + LCBDE**	**Intra -ERCP/S + LC**	**P value**
ElGeidie 2011#	57 (45 - 145)	68 (45 - 160)	P = 0.857
González 2016b#	117.0 (40 - 270)	94.2 (45 - 300)	P = 0.0042*
Hong 2006#	133.83 ± 58.24	140.32 ± 56.55	P = 0.460
Poh 2016§	110 (95 - 140)	112 (102 - 125)	P = 0.590
Length of hospital stay (days)			
Authors	**LC + LCBDE**	**Pre – ERCP/S + LC**	**P value**
Bansal 2010§	4.2 (3 – 9)	4 (2 – 11)	P = 0.9210
Bansal 2014#	4.6 ± 2.4	5.3 ± 6.2	P < 0.03*
Cuschieri 1999§	6 (4.24 – 12)	9 (5.5 – 14)	P < 0.05*
Ding 2014	Not evaluated	Not evaluated	-
Ferulano 2011#	7.1	3.5	P < 0.001*
González 2016a#	2.1	3.1	P < 0.004*
Koc 2013#	3.0	6.0	P < 0.0014*
Lv 2016#	6.72 ± 1.3	10.91 ± 1.6	P < 0.01*
Mohamed 2015#	2.0 ± 0.53	2.0 ± 0.57	P = 0.999
Rogers 2010#	5.3 ± 3.2	6.6 ± 4.0	P = 0.08
Sgourakis 2002#	7.4	9.0	P < 0.0041*
Authors	**LC + LCBDE**	**Intra – ERCP/S + LC**	**P value**
ElGeidie 2011#	2.2 (1 – 9)	3.1 (1 – 7)	P = 0.638
González 2016b#	2.1	1.2	P < 0.0061*
Hong 2006#	4.66 ± 3.07	4.25 ± 3.46	P = 0.3430
Poh 2016§	3.0 (2 – 4)	2 (2 – 3)	P < 0.015*

Abbreviations and symbols: *LC+LCBDE - laparoscopic cholecystectomy plus laparoscopic common bile duct exploration; Pre-ERCP/S+LC-preoperative endoscopic retrograde cholangiopancreatography/sphyncterotomy plus laparoscopic cholecystectomy; intra-ERCP/S+LC – intraoperative endoscopic retrograde cholangiopancreatography/sphyncterotomy plus laparoscopic cholecystectomy. # Mean ± SD or interquartile range or only mean; § median and interquartile range; *differences considered statistically significant as reported by the study authors or calculated for us when not available.*

DISCUSSION

Approximately 5-15% of patients diagnosed with cholelithiasis also have stones located within the CBD.[4] Currently, this complication may be treated laparoscopically, through LC+LCBDE, or endoscopic via, through pre-ERCP/S+LC or intra-ERCP/S+LC. However, it is still unclear which of these three interventions is the most effective therapeutic option for choledocholithiasis.

According to this systematic review, which analyzed 14 randomized controlled trials with 15 comparison arms, LC+LCBDE was found to be superior to pre-ERCP/S+LC in terms of CBD stone clearance and reducing rates of retained stones, failure of procedure, cross over to other procedure, total morbidity, and mortality. However, the only outcome in which pre-ERCP/S+LC was superior was the conversion to open surgery. On the other hand, patients treated with intra-ERCP/S+LC had better success rates than LC+LCBDE for all outcomes. Nevertheless, the meta-analysis found no significant differences between laparoscopic and endoscopic treatments, either in the pre- or intraoperative periods.

These findings are generally consistent with other systematic reviews on this topic.[28-32, 34-39] However, a meta-analysis study by Pan et al.[33] reported that LC+LCBDE was significantly better than pre-ERCP/S+LC regarding CBD stone clearance, reducing morbidity and mortality, retained stones, stone recurrence, and cross-over to other procedures. In contrast, a recent meta-analysis by Lei et al.[38] found results similar to ours but observed that intra-ERCP/S+LC treatment was significantly more effective than LC+LCBDE in terms of reducing the rate of retained stones.

It is important to note that our review focused on two separate comparisons: LC+LCBDE versus pre-ERCP/S+LC and LC+LCBDE versus intra-ERCP/S+LC. This differs from most previous systematic reviews, which evaluated studies comparing vastly different interventions, including LC+LCBDE, pre-, intra-, post-ERCP/S+LC, and conventional surgery, in the same meta-analysis. In our opinion, this approach is inappropriate, even when using subgroup and/or sensitivity analyses.

It is also important to emphasize that a cautious interpretation of the results is recommended, as many of the trials included in our review and others lack uniformity in the techniques used during the procedures. The technical expertise and preferences of endoscopists and laparoscopic surgeons can vary widely, and the human and material resources available in their units can also differ significantly.

Another important issue to consider is that variables related to the diameter of the CBD and cystic duct and the number and size of gallstones may influence the success rates of CBD stone clearance. However, only two clinical trials in this review examined the correlation between these variables and the success rates of CBD stone clearance. Ferulano et al.[19], while studying LC+LCBDE versus pre-ERCP/S+LC, found a significant increase in the risk of failure among patients with stones greater than 5mm in diameter compared to patients with stones 5mm or smaller. In contrast, Hong et al.[21], while studying LC+LCBDE versus intra-ERCP/S+LC, did not observe a significant difference in the success rates of ductal stone clearance among patients with stone sizes ranging from 4–40 mm compared to patients with stones ranging from 5–15 mm. These findings suggest that other factors, such as the route and technique for stone extraction from the CBD, the availability of materials, and the experience level of the professional performing the procedure, may also impact the results.

It is worth noting that there is often inadequate reporting of the methodology in clinical trials. Moreover, while blinding participants and the medical team is practically impossible during surgical interventions, the studies included in our review had issues with random sequence generation, allocation concealment, and blinding of outcome assessment, which are considered important factors according to the Cochrane Collaboration methodology for systematic reviews. As a result, our review has an overall high risk of bias.

Our review excluded non-randomized controlled trials,[40-44] which could have further increased the risk of bias and heterogeneity. However, our analysis did not identify significant differences among the three modalities of interventions, either for CBD stone clearance or for most of the secondary outcomes of interest. This approach has also been used in other reviews, including subgroup studies or sensitivity analysis, but no evidence of a significant difference between laparoscopic and endoscopic interventions was identified.[33]

It is recommended that the randomization process occur when CBD stones are suspected, rather than after the performance of ERCP, in order to avoid exposing the patient and surgical team to the procedure's risks without the potential benefits.[35] In our review, we observed that in some studies, the randomization process took place in participants with suspected CBD stones, diagnosed by ultrasound and/or imaging in the preoperative period,[16, 19, 20, 26, 27] while in other studies, it occurred after the diagnosis of CBD stones was confirmed by intraoperative cholangiogram.[14, 15, 22, 23]

As a result, we found that patients without stones in the CBD were included in the success rates of CBD stone clearance. In our review, one of the trials[18] comparing LC+LCBDE versus intra-ERCP/S+LC included eight patients, two in the laparoscopic group and six in the endoscopic group, who had no stones in the CBD. In another trial[27] comparing LC+LCBDE versus pre-ERCP/S+LC, eight patients in the laparoscopic arm and ten patients in the endoscopic arm had no stones in the CBD. Furthermore, there were misinterpretations in reporting CBD stone clearance in patients who had cross over to other procedures, such as endoscopic treatment to laparoscopic or conversion to open surgery.[16, 18, 25]

We understand that the trials were designed on an intention-to-treat basis and that an attempt was made to reflect the clinical situation as realistically as possible. However, this type of bias makes it challenging to obtain the best evidence to recommend or refute one intervention compared to another regarding choledocholithiasis. Therefore, our review aimed to eliminate these biases by considering CBD stone removal success rates only concerning patients with confirmed bile duct stones treated with the initially planned procedure.

Despite this, our review found no significant differences among the three intervention modalities for CBD stone removal or for most secondary outcomes of interest. However, Singh and Kilambi[32] reported significantly lower rates of technical failure in ductal stone clearance in patients with and without confirmed CBD stones undergoing LCBDE+LC than those undergoing pre-ERCP/S+LC. The authors also confirmed that the test for overall effect of the laparoscopic treatment did not change even after performing a sensitivity analysis separating studies that included patients with confirmed CBD stones from those without confirmed CBD stones.

Our study found that the operative time was significantly longer in the LC+LCBDE group than in the pre-ERCP/S+LC group but shorter than in the intra-ERCP/S+LC group. Additionally, the length of hospital stay was significantly shorter in the laparoscopic arm than in the pre-ERCP/S+LC group but longer than in the intra-ERCP/S+LC group. However, these findings were limited due to the lack of a standard format for reporting results by the study authors, which did not allow for meta-analysis. Dasari et al.[35] also observed these limitations in a comprehensive review comparing surgical versus endoscopic treatment of bile duct stones. Nevertheless, some studies that performed a meta-analysis, even with a few studies contrary to ours, observed a shorter operative time in patients treated with LC+LCBDE compared to endoscopic treatments.[31,33,34,37]

Despite the limitations mentioned, our review found that the length of hospital stay was significantly higher in patients treated with pre-ERCP/S+LC compared to LC+LCBDE or intra-ERCP/S+LC. This finding is consistent with other studies that used meta-analysis comparing one-stage laparoscopic treatment versus two-stage endoscopic treatments,[30, 32, 33, 34, 37] but conflicts with others that did not identify significant differences among the three groups.[29, 31, 36, 39]

CONCLUSION

In conclusion, our systematic review with meta-analysis showed that LC+LCBDE and pre- and intra-ERCP/S+LC were safe and highly effective in removing CBD stones. However, the results suggest that single-step interventions seem to be the option for treating choledocholithiasis. Nevertheless, this choice needs to be made individually for each type of patient, taking into account the resources of the health service and the experience of the professional who will perform it.

Acknowledgments: We wish to thank Miss Marluci Betini of the Central Library of the Campus of UNESP, Faculty of Medicine, Botucatu, Sao Paulo, Brazil, for her essential assistance in the process of identifying and screening the studies included in this review.

Disclosure of interest: The authors declare that they have no conflicts of interest concerning this article.

REFERENCES

1. Marshall HU, Einarsson C. Gallstone disease. J Intern Med, 2007; 261: 529-542.
2. Stinton LM, Myers RP, Shaffer EA. Epidemiology of gallstones. Gastroenterology Clinics of North America, 2010; 39(2): 157-169.
3. Gracie WA, Ransohoff DF. The natural history of silent gallstones: the innocent gallstone is not a myth. N Engl J Med, 1982; 307: 798-800.
4. Cianci P, Tartaglia N, Alberto F, Antonio A, Vincenzo N. Management of choledocholithiasis: current opinions and personal experience. Surg Chron, 2018; 23(3): 157-161.
5. Argueta LFA, Toncel SMR, Sandoval SFC, Gracia DFI, Gómez JMV. Complications from cholelithiasis and its management: key points for diagnosis. Rev. Colomb. Radiol, 2017; 28(3): 4717-4724.
6. Duncan CB, Riall TS. Evidence-based current surgical practice: calculous gallbladder disease. J Gastrointest Surg, 2012; 16(11): 2011 – 2025.
7. Sureka B, Mukund A. Review of imaging in post-laparoscopy cholecystectomy complications. Indian J Radiol Imaging, 2017; 27(4): 470-481.
8. Rogers SJ, Cello JP, Horn JK, Siperstein AE, Schecter WP, Campbell AR, Mackersie RC, Rodas A, Kreuwel HTC, Harris HW. Prospective randomized trial of LC+LCBDE vs. ERCP/S + LC for common bile duct stone disease. Arch Surg, 2010; 145(1): 28-33.
9. Darrien JH, Connor K, Janeczko A, Casey JJ, Paterson-Brown S. The surgical management of concomitant gallbladder and common bile duct stones. HPB Surgery, 2015; Article ID 165068: 1-5.
10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluate healthcare interventions: explanation and elaboration. BMJ *on line*, 2009; 339: 1-27.
11. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst, 1959; (22): 719-748.

12. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed., Chichester (UK); John Wiley and Sons: 2019.
13. Savovic J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, Als-Nielsen B, Balk EM, Gluud C, Gluud LL, Ionnidis JPA, Schulz KF, Beynon R, Welton N, Wood L, Moher D, Deeks JJ, Sterne JAC. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Ann Intern Med, 2012; 157(6): 429-38.
14. Bansal VK, Misra MC, Garg P, Prabhu M. A prospective randomized trial comparing two-stage versus single-stage management of patients with gallstone disease and common bile duct stones. Surg Endosc, 2010; 24(8): 1986-9.
15. Bansal VK, Misra MC, Rajan K, Kilambi R, Kumar S, Krishna A, Kumar A, Pandav CS, Subramaniam R, Arora MK, Garg PK. 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, 2014; 28(3): 875-85.
16. Cuschieri A, Lezoche E, Morino M, Croce E, Lacy A, Toouli J, Faggioni A, Ribeiro VM, Jakimowicz J, Visa J, Hanna GB. 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, 1999; 13(10): 952-7.
17. Ding G, Cai W, Qin M. Single-stage vs. two-stage management for concomitant gallstones and common bile duct stones: a prospective randomized trial with long-term follow-up. J Gastrointest Surg, 2014; 18(5): 947-51.
18. ElGeidie AA, ElShobary MM, Naeem YM. Laparoscopic exploration versus intraoperative endoscopic sphincterotomy for common bile duct stones: a prospective randomized trial. Dig Surg, 2011; 28(5-6): 424-31.
19. Ferulano GP, Dilillo S, D'Ambra M, Lionetti R, Di Silverio P, Capasso S, Pelaggi D, Rutigliano M. Laparoscopic one-tage vs endoscopic plus laparoscopic management of common bile duct stones. A Prospective Randomized Study. Adv Endosc Surg, 2011; 291-306.
20. González JEB, Torres Pena RT, Torres JR, Alfonso MAM, Quintanilla RB, Perez MM. Endoscopic versus laparoscopic treatment for choledocholithiasis: a prospective randomized controlled trial. Endosc Int Open, 2016; 4(11): E1188–E1193.
21. Hong DF, Xin Y, Chen DW. Comparison of laparoscopic cholecystectomy combined with intraoperative endoscopic sphincterotomy and laparoscopic exploration of the common bile duct for cholecystocholedocholithiasis. Surg Endosc, 2006; 20(3): 424-427.
22. Koc B, Karahan S, Adas G, Tutal F, Guven H, Ozsoy A. Comparison of laparoscopic common bile duct exploration and endoscopic retrograde cholangiopancreatography plus laparoscopic cholecystectomy for choledocholithiasis: a prospective randomized study. Am J Surg, 2013; 206(4): 457-63.
23. Lv F, Zhang S, Ji M, Wang Y, Li P, Han W. Single-stage management with combined tri-endoscopic approach for concomitant cholecystolithiasis and choledocholithiasis. Surg Endosc, 2016; 30: 5615–20.
24. Mohamed MA, Bahram MA, Ammar MS, Nassar AH. One-session laparoscopic management of combined common bile duct and gallbladder stones versus sequential ERCP followed by laparoscopic cholecystectomy. J Laparoendosc Adv Surg Tech A, 2015; 25(6): 482-5.
25. Poh BR, Ho SPS, Sritharan M, Yeong CC, Swan M, Devonshire, Cashin P, Croagh DG. Randomized clinical trial of intraoperative endoscopic retrograde cholangiopancreatography versus laparoscopic bile duct exploration in patients with choledocholithiasis. Br J Surg, 2016; 103(9): 1117-24.
26. Rogers SJ, Cello JP, Horn JK, Siperstein AE, Schecter WP, Campbell AR, Machersie RC, Rodas A, Kreuwel HTC, Harris HW. Prospective randomized trial of LC+LCBDE vs ERCP/S+LC for common bile duct stone disease. Arch Surg, 2010; 145(1): 28-33.
27. Sgourakis G, Karaliotas K. Laparoscopic common bile duct exploration and cholecystectomy versus endoscopic stone extraction and laparoscopic cholecystectomy for choledocholithiasis. A prospective randomized study. Minerva Chir, 2002; 57(4): 467-74.
28. Alexakis N, Connor S. Meta-analysis of one- vs. two-stage laparoscopic/endoscopic management of common bile duct stones. HPB, 2012; 14: 254–259.
29. Lu J, Cheng Y, Xiong X-Z, Lin Y-X, Wu S-J, Cheng N-S. Two-stage vs single-stage management for concomitant gallstones and common bile duct stones. W J Gastroenterol, 2012; 18(24): 3156-3166.
30. Kenny R, Richardson J, McGlone ER, Reddy M, Khan AO. Laparoscopic common bile duct exploration versus pre or post-operative ERCP for common bile duct stones in patients undergoing cholecystectomy: Is there any difference? Intern J Surg, 2014; 12: 989-993.
31. Ajayi O, Dimitrov BD, Barry M, Kell MR. Meta-analysis of the efficacy of a single stage laparoscopic management versus two-stage endoscopic management of symptomatic gallstones with common bile duct stones. Acta Chir Croat, 2015; 12: 19–28.
32. 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: 3763–76.

33. Pan L, Chen M, Ji L, Zheng L, Yan P, Fang J, Zhang B, Cai X. The safety and efficacy of laparoscopic common bile duct exploration combined with cholecystectomy for the management of cholecysto-choledocholithiasis: an up-to-date meta-analysis. Ann Surg, 2018; 268: 247–53.
34. Zhu HY, Xu M, Shen HJ, Yang C, Li F, Li KW, Shi WJ, Ji F. A meta-analysis of single-stage versus two-stage management for concomitant gallstones and common bile duct stones. Clin Res Hepatol Gastroenterol, 2015; 39: 584–93.
35. Dasari BV, Tan CJ, Gurusamy KS, Martin DJ, Kirk G, McKie L, et al. Surgical versus endoscopic treatment of bile duct stones. Cochrane Database Syst, 2013; 12: CD003327.
36. Schacher FC, Giongo SM, Teixeira FJP, Mattos AZ. Endoscopic retrograde cholangiopancreatography versus surgery for choledocholithiasis – A meta-analysis. Annals of Hepatol, 2019; 18: 595–600.
37. Gao Y-C, Chen J, Qin Q, Chen H, Wang W, Zhao J, Miao F, Shi X. Efficacy and safety of laparoscopic bile duct exploration versus endoscopic sphincterotomy for concomitant gallstones and common bile duct stones. A meta-analysis of randomized controlled trials. Medicine, 2017; 96(37): e7925.
38. Lei C, Lu T, Yang W, Yang M, Tian H, Song S, Gong S, Yang J, Jiang W, Yang K, Guo T. Comparison of intraoperative endoscopic retrograde cholangiopancreatography and laparoscopic common bile duct exploration combined with laparoscopic cholecystectomy for treating gallstones and common bile duct stones: a systematic review and meta-analysis. Surgical Endoscopy, 2021; 35: 5918–5935.
39. Santos AS, Oliveira AJF, Nogueira JLS, Noronha KVMS, Andrade MV. Endoscopic retrograde cholangiopancreatography for common bile duct calculi: overview of systematic reviews and economic assessments. J Bras Econ Saúde, 2019; 11(2): 170-210.
40. Guan G, Sun C, Ren Y, Zhao Z, Ning S. Comparing a single-staged laparoscopic cholecystectomy with common bile duct exploration versus a two-staged endoscopic sphincterotomy followed by laparoscopic cholecystectomy. Surgery, 2018; 164(5):1030-1034.
41. Piñeres G, Yamakawa T, Kasugai, H, Fukuda N, Ishiyama J, Sakai S, Maruno K, Miyajima N, Sunpaweravong S. Common bile duct stones: management strategies in the laparoscopic era. J Hep Bil Pancr Surg, 1998; 5: 97–103.
42. Wei Q, Wang JG, Li LB, Li JD. Management of choledocholithiasis: comparison between laparoscopic common bile duct exploration and intraoperative endoscopic sphincterotomy. World J Gastroenterol, 2003; 9(12):2856-2858.
43. Heili MJ, Wintz NK, Fowler DL. Choledocholithiasis: endoscopic versus laparoscopic management. Am Surg, 1999; 65(2):135-138.
44. Zhou Y, Wen-Zhang Zha, Xu-Dong Wu, Ren-Gen Fan, Biao Zhang, Yong-Hua Xu, Cheng-Lin Qin, Jing Jia. Three modalities on management of choledocholithiasis: A prospective cohort study. Int J of Surg, 2017; 44: 269-273.