

# 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

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### Abstract

**Background:** The purpose of this study was to compare the efficacy and safety of laparoscopic cholecystectomy (LC) plus laparoscopic common bile duct (CBD) stones exploration (LCBDE) with LC plus endoscopic sphincterotomy (EST) in the treatment of patients with gallstones and CBD stones.

**Methods:** The authors searched PubMed, Web of Science, and Embase to identify relevant studies. Risk ratios (RRs) were pooled to compare stone clear, retained stone, conversion to other procedures, and complications. Weighted mean differences (WMDs) were pooled to compare operative time, and length of hospital stay. A fixed-effects model or random-effects model was used to pool the estimates, according to the heterogeneity among the included studies.

**Results:** A total of 11 randomized controlled trials (RCTs) involving 1663 patients were included in this meta-analysis. The pooled estimate suggested that LC-LCBDE had comparable effects with LC-EST in terms of CBD stone clear rate (RR = 1.02, 95% CI: 0.95, 1.09;  $P = .583$ ), retained stones rate (RR = 1.27, 95% CI: 0.51, 3.19;  $P = .607$ ), and length of hospital stay (WMD = -0.96 days, 95% CI: -2.20, 0.28). In addition, LC-LCBDE was associated with significantly higher conversion rate (RR = 1.59, 95% CI: 1.08, 2.35;  $P = .019$ ) and less operative time (WMD = -11.55 minutes, 95% CI: -16.68, -6.42;  $P < .001$ ) than LC-EST. The incidence of complications was not significant difference between the 2 surgical approaches (RR = 1.07, 95% CI: 0.86, 1.34;  $P = .550$ ).

**Conclusion:** Based on the current evidence, both LC-LCBDE and LC-EST were highly effective in detecting and removing CBD stones and were equivalent in complications. However, our results might be biased by the limitations. Large-scale well-designed RCTs are needed to confirm our findings.

**Abbreviations:** CBD = common bile duct, CIs = confidence intervals, ERCP = endoscopic retrograde cholangiopancreatography, EST = endoscopic sphincterotomy, GRADE = Grading of Recommendations Assessment, Development and Evaluation, LC = laparoscopic cholecystectomy, LCBDE = laparoscopic common bile duct stones exploration, LC-LCBDE = LC combined with laparoscopic CBD exploration, RCTs = randomized controlled trials, RRs = risk ratios, WMD = weight mean difference, WMDs = weighted mean differences.

**Keywords:** cholecystectomy, common bile duct exploration, endoscopic sphincterotomy, laparoscopy, meta-analysis

## 1. Introduction

Concomitant gallstones and common bile duct stones (CBD) are detected in approximately 10% of patients, which are associated

with serious complications, such as cholangitis and pancreatitis.<sup>[1]</sup> The open CBD exploration, used as the conventional approach, has been proven as an effective treatment option.<sup>[2-4]</sup> In the past decades, with the development of new surgical techniques, more and more options and alternatives have been used in the management of gallstones. These approaches include endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and laparoscopic cholecystectomy (LC) with the possibility to explore and clear the CBD.

There are several approaches that used for the treatment of preoperatively suspected choledocholithiasis. These options include preoperative ERCP, endoscopic sphincterotomy (EST), and stone extraction followed by LC<sup>[5,6]</sup>; transcystic cholangiography followed by transcystic or direct CBD exploration<sup>[7,8]</sup>; postoperative ERCP with EST and stone extraction<sup>[9,10]</sup>; LC plus intraoperative ERCP, EST, and stone extraction<sup>[11,12]</sup>; and conversion to open cholecystectomy and CBD exploration.<sup>[13,14]</sup>

The previous study reported that, single-session management of gallstones and CBD stones is effective, safe and less costly than staged procedures.<sup>[15]</sup> And it is still controversial whether LC combined with laparoscopic CBD exploration (LC-LCBDE) is

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superior to LC with EST (LC-EST). Therefore, we conducted this meta-analysis to compare the efficacy and safety between the 2 minimally invasive techniques in the treatment of patients with gallstones and CBD stones.

## 2. Materials and methods

The ethical approval and patient consent was not applicable for meta-analysis.

### 2.1. Literature search for identifying related studies

We conducted this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>[16]</sup> A comprehensive systematic search was performed for relevant literature in PubMed, Web of Science, and Embase from inception through May 10, 2017. The search terms included: (concomitant[All Fields] AND (“common bile duct”[MeSH Terms] OR (“common”[All Fields] AND “bile”[All Fields] AND “duct”[All Fields]) OR “common bile duct”[All Fields]) AND (“calculi”[MeSH Terms] OR “calculi”[All Fields] OR “stones”[All Fields])) AND (“cholecystectomy, laparoscopic”[MeSH Terms] OR (“cholecystectomy”[All Fields] AND “laparoscopic”[All Fields]) OR “laparoscopic cholecystectomy”[All Fields] OR (“laparoscopic”[All Fields] AND “cholecystectomy”[All Fields])) AND (“sphincterotomy, endoscopic”[MeSH Terms] OR (“sphincterotomy”[All Fields] AND “endoscopic”[All Fields]) OR “endoscopic sphincterotomy”[All Fields] OR (“endoscopic”[All Fields] AND “sphincterotomy”[All Fields])) AND (“sphincterotomy, endoscopic”[MeSH Terms] OR (“sphincterotomy”[All Fields] AND “endoscopic”[All Fields]) OR “endoscopic sphincterotomy”[All Fields] OR (“endoscopic”[All Fields] AND “sphincterotomy”[All Fields]))). The search was limited to human subjects and no language restriction was applied. We also identified additional references by manually searching for publications that cited in the included articles and related reviews.

### 2.2. Study selection

Two reviewers independently assessed the eligibility of each article. After screening the title/abstract and the full-text information, these studies were determined as inclusion or exclusion in this study. Disagreements between the reviewers were resolved by discussion and consensus. To be included in this meta-analysis, the study must meet the following inclusive selection criteria: *study design*: randomized controlled trials (RCTs); *study population*: patients with confirmed or suspected CBD stones with gallstones; *intervention*: LC + LCBDE, or LC + EST; *outcomes measure*: stone clear, retained stone, conversion to other procedures, operative time, length of hospital stay, and complications.

### 2.3. Data extraction

Data extraction was conducted by 2 independent investigators. For each included study, the following information was collected: first author's name, year of publication, country, number of patients in each group, median age of patients, gender composition, stone clear rate, retained stone rate, conversion to other procedures, operative time, length of hospital stay, and complications.

### 2.4. Assessment for risk of bias and grading the quality of evidence

We conducted the assessment for risk of bias in accordance with guidelines outlined in the *Cochrane handbook for systematic*

*reviews of interventions* (version 5.1.0).<sup>[17]</sup> Each study was assigned a value of “high,” “low,” or “unclear” according to the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias.<sup>[18]</sup>

The quality of evidence for the outcome measures was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.<sup>[19]</sup> A summary table was established with the GRADE profiler (GRADE pro, version 3.6).

### 2.5. Statistical analysis

We estimated the pooled risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous outcomes and the pooled weight mean difference (WMD) with 95% CI for continuous outcomes. Heterogeneity across the studies was tested using the Cochran Q statistic and quantified with the  $I^2$  statistic, in which  $I^2 > 50\%$  indicated significant heterogeneity.<sup>[20]</sup> A fixed-effects model<sup>[21]</sup> was used to pool the results when heterogeneity was  $< 50\%$ , while a random-effects model<sup>[22]</sup> was chosen when heterogeneity was  $> 50\%$ . We also investigated the influence of a single study on the overall pooled estimate by deleting one study in each turn. If one study reported the result that was significantly different with others or out of the range of others, we would search for the likely reasons and perform a sensitivity analysis by deleting this study. The presence of publication bias was evaluated using the Begg and Egger test.<sup>[23,24]</sup> Results were considered as statistically significant for  $P < .05$ , except otherwise stated. All statistical analyses were performed using STATA, version 12.0 (Stata Corporation, College Station, TX).

## 3. Results

### 3.1. Study selection

The initial search yielded 764 publications, of which 528 were eliminated because of duplicate records. Then 236 were left for title/abstract and full-text information review, and 214 and 11 were excluded, respectively, because they were case reports, non-RCTs, sing-arm trials, or unrelated with our topic. Finally, 11 RCTs<sup>[25–35]</sup> studies met the inclusion criteria and were included in this meta-analysis. The flow chart for study selection is shown in Fig. 1.

### 3.2. Study characteristics

The baseline characteristics of these included studies are summarized in Table 1. The trials were published between 1996 and 2016. And 2 of the 11 trials were conducted in multicenter countries,<sup>[27,31]</sup> and the others were conducted in Egypt,<sup>[25]</sup> China,<sup>[26]</sup> UK,<sup>[28,32]</sup> India,<sup>[29,35]</sup> USA,<sup>[30]</sup> Australia,<sup>[33]</sup> and Turkey.<sup>[34]</sup> The sample size of the enrolled patients ranged from 30 to 300, with a total number of 1663. Among the included studies, 3 trials<sup>[25,26,33]</sup> used 1-stage EST and LC for patients with gallstones and CBD stones; whereas the remaining 8 trials<sup>[27–32,34,35]</sup> used 2-stage EST followed by LC. Notably, in the trial conducted by Noble et al<sup>[32]</sup> patients enrolled were with higher medical risk; whereas, in other studies, patients were with a good-risk.

### 3.3. Risk of bias and quality assessment of outcomes

The details of risk of bias assessment are presented in Fig. 2. Among the 11 trials, 8<sup>[27,29–35]</sup> adequately reported the methods

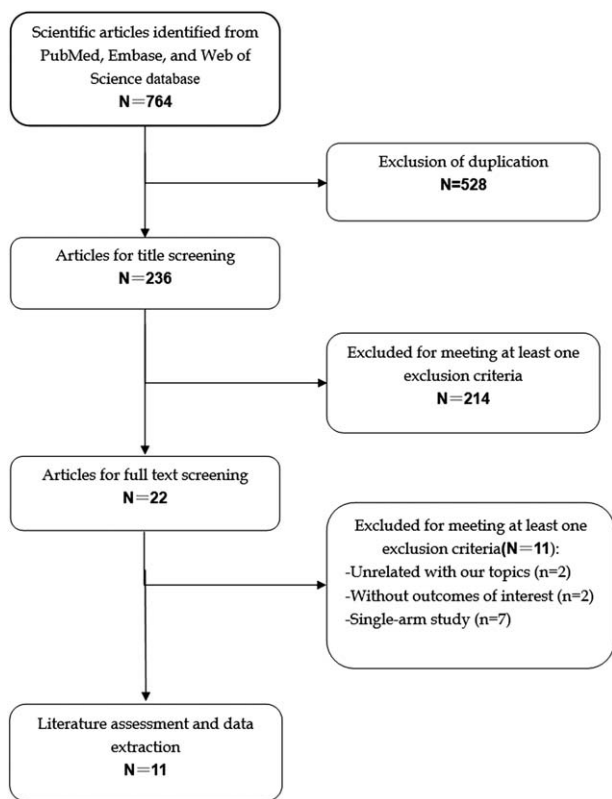


Figure 1. Eligibility of studies for inclusion in meta-analysis.

for randomized sequence and allocation sequence concealment. However, none of the included studies reported in detail the methods for blinding of participants and personnel, and blinding of outcome assessment. Although the double-blinding was

difficult to implement due to the nature of the surgeries, assessment for surgical outcomes was unlikely to be influenced by the knowledge of trial allocations. Thus, we considered the 2 items to be unclear risk of bias. For other 3 items (incomplete outcome data, selective reporting, and other bias), we did not find these bias in all the included studies. Therefore, all the included trials were judged to be at unclear risk of bias.

The GRADE evidence profiles for the outcomes are shown in Table 2. Because there was substantial heterogeneity for CBD stone clear rate and length of hospital stay, the inconsistency of these 2 outcomes was regarded as serious and the quality of evidence was downgraded. Then since all the studies reported data for the 2 outcomes, and the pooled estimates were calculated based on a large sample size. The quality of evidence was upgraded. As shown in Table 2, the GRADE level of evidence was high for all these outcomes, which indicated that the results were reliable.

### 3.4. CBD stone clear rate

All the studies reported the data of CBD stone clear rate.<sup>[25–35]</sup> The success rates of CBD clearance in the LC-LCBDE and LC-EST groups were 88.61% and 87.1%, respectively. Pooled estimates using a random-effects model showed that, there was no significant difference between the 2 groups (RR=1.02, 95% CI: 0.95, 1.09;  $P = .583$ ) (Fig. 3). There was significant heterogeneity ( $I^2 = 71.9%$ ,  $P < .001$ ) among the included studies. Thus, we conducted sensitivity to explore the potential sources of heterogeneity. When we excluded the trial conducted by Noble et al<sup>[32]</sup> the pooled estimate did not change substantially (RR=0.99, 95% CI: 0.95, 1.04,  $P = .756$ ), but no significant heterogeneity was found among the remaining studies ( $I^2 = 46.8%$ ,  $P = .050$ ).

### 3.5. Retained stones rate

Six studies reported the data on retained stones rate.<sup>[25,26,28,33–35]</sup> The rates of retained stones in the LC-LCBDE and LC-EST

**Table 1**  
Baseline characteristics of patients in the trials included in the meta-analysis.

| Study                           | Year | Country            | Intervention | No. of patients | Male/female | Age (mean ± SD, y) |
|---------------------------------|------|--------------------|--------------|-----------------|-------------|--------------------|
| Elgeidie et al <sup>[25]</sup>  | 2011 | Egypt              | LC-LCBDE     | 115             | 29/86       | 32.5 (19–64)       |
|                                 |      |                    | LC-EST       | 111             | 31/102      | 29.2 (20–67)       |
| Hong et al <sup>[26]</sup>      | 2006 | China              | LC-LCBDE     | 141             | 28/65       | 48 (15–82)         |
|                                 |      |                    | LC-EST       | 93              | NR          | NR                 |
| Cuschieri et al <sup>[27]</sup> | 1999 | Multiple countries | LC-LCBDE     | 150             | 60/90       | 19–88              |
|                                 |      |                    | LC-EST       | 150             | 42–108      | 18–89              |
| Rhodes et al <sup>[28]</sup>    | 1998 | UK                 | LC-LCBDE     | 40              | 12/28       | 62 (24–83)         |
|                                 |      |                    | LC-EST       | 40              | 14/26       | 68 (28–84)         |
| Bansal et al <sup>[29]</sup>    | 2010 | India              | LC-LCBDE     | 15              | 5/10        | 39.07 (23–64)      |
|                                 |      |                    | LC-EST       | 15              | 4/11        | 47.1 (34–72)       |
| Rogers et al <sup>[30]</sup>    | 2010 | USA                | LC-LCBDE     | 57              | 17/40       | 39.9 ± 1.9         |
|                                 |      |                    | LC-EST       | 55              | 16/39       | 44.6 ± 1.9         |
| Cuschieri et al <sup>[31]</sup> | 1996 | Multiple countries | LC-LCBDE     | 101             | 40/61       | 19–88              |
|                                 |      |                    | LC-EST       | 106             | 30/76       | 18–89              |
| Noble et al <sup>[32]</sup>     | 2009 | UK                 | LC-LCBDE     | 44              | 16/28       | 75.9 (70–80.8)     |
|                                 |      |                    | LC-EST       | 47              | 22/25       | 74.3 (70–78.9)     |
| Poh et al <sup>[33]</sup>       | 2016 | Australia          | LC-LCBDE     | 52              | 23/29       | 53.4 ± 19.7        |
|                                 |      |                    | LC-EST       | 52              | 21/31       | 53.9 ± 22.6        |
| Koc et al <sup>[34]</sup>       | 2013 | Turkey             | LC-LCBDE     | 57              | 20/37       | 51.5 ± 16.6        |
|                                 |      |                    | LC-EST       | 54              | 18/36       | 54.9 ± 17.9        |
| Bansal et al <sup>[35]</sup>    | 2014 | India              | LC-LCBDE     | 84              | 23/61       | 45.1 ± 15.1        |
|                                 |      |                    | LC-EST       | 84              | 34/50       | 43 ± 13.7          |

EST=endoscopic sphincterotomy, LC=laparoscopic cholecystectomy, LCBDE=laparoscopic common bile duct stones exploration, NR=not reported, SD=standard deviation.

|                  | 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 reporting (reporting bias) | Other bias |
|------------------|---|---|---|---|--|--------------------------------------|------------|
| Bansal VK 2010   | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Bansal VK 2014   | +   | +                                       | ?   | +   | +  | +                                    | +          |
| Cuschieri A 1996 | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Cuschieri A 1999 | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Elgeidie AA 2011 | ?   | ?                                       | ?   | ?   | +  | +                                    | +          |
| Hong DF 2006     | ?   | ?                                       | ?   | ?   | +  | +                                    | +          |
| Koc B 2013       | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Noble H 2009     | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Poh BR 2016      | +   | +                                       | ?   | ?   | +  | +                                    | +          |
| Rhodes M 1998    | ?   | ?                                       | ?   | ?   | +  | +                                    | +          |
| Rogers SJ 2010   | +   | +                                       | ?   | ?   | +  | +                                    | +          |

Figure 2. Risk of bias summary.

groups were 8.43% and 6.98%, respectively. The summarized estimate suggested that the rate of retained stones between the 2 groups was not significantly different (RR=1.27, 95% CI: 0.51, 3.19;  $P=.607$ ) (Fig. 4). There was significant heterogeneity among the included studies ( $I^2=58.5%$ ,  $P=.034$ ).

### 3.6. Conversion to other procedure

Eight studies reported the data on conversion.<sup>[125–27,29,31,32,34,35]</sup> The conversion rate in the LC-LCBDE and LC-EST groups were 8.95% and 5.51%, respectively. The aggregated results showed that conversion rate was significantly higher in LC-LCBDE group than in the LC-EST group (RR=1.59, 95% CI: 1.08, 2.35;  $P=.019$ ) (Fig. 5). There was no significant heterogeneity among the included studies ( $I^2=0.0%$ ,  $P=.648$ ).

### 3.7. Operative time

Eight studies reported data on operative time.<sup>[25,26,28–30,33–35]</sup> The mean operative time in patients treated with LC-LCBDE was 119.5 minutes, and 129.0 minutes for patients treated with LC-EST. LC-LCBDE was associated with a significant less operative time than LC-EST (WMD=−11.55 minutes, 95% CI: −16.68, −6.42;  $P<.001$ ) (Fig. 6). No significant heterogeneity was observed among the included studies ( $I^2=12.6%$ ,  $P=.332$ ).

Subgroup analysis based on stage procedure of LC-EST showed that, LC-LCBDE had a less operative time than 1-stage (WMD=−9.42 minutes, 95% CI: −15.57, −3.27;  $P=.003$ ) and 2-stage LC-EST (WMD=−14.46 minutes, 95% CI: −21.14, −7.79;  $P<.001$ ).

### 3.8. Length of hospital stay

Length of hospital stay was reported in all the included studies.<sup>[25–35]</sup> The mean hospital stay was 4.13 days in the LC-LCBDE group and 5.11 days in the LC-EST group, respectively. LC-LCBDE had a shorter length of hospital stay than LC-EST (WMD=−0.96 days, 95% CI: −2.20, 0.28) (Fig. 7), however, the difference did not reach statistical significance ( $P=.129$ ). There was substantially significant heterogeneity among the included studies ( $I^2=97.2%$ ,  $P<.001$ ).

Subgroup analysis based on stage procedure of LC-EST showed that, LC-LCBDE was associated with a similar length of hospital stay with 1-stage LC-EST (WMD=0.14 days, 95% CI: −0.16, 0.44;  $P=.368$ ), and a shorter length of hospital stay than 2-stage LC-EST (WMD=−1.41 days, 95% CI: −1.68, −1.15;  $P<.001$ ).

Among these included studies, the trial conducted by Cuschieri et al<sup>[27]</sup> reported 3 days more of length of hospital stay in the LC-LCBDE group than in the LC-EST group. Therefore, we conducted sensitivity analysis by excluding this trial. After excluding this trial, the pooled data did not change substantially (WMD=−0.74 days, 95% CI: −1.95, 0.47;  $P=.231$ ), but significant heterogeneity was still present ( $I^2=96.2%$ ,  $P<.001$ ). We further excluded a single trial at one time. However, the heterogeneity was still present, and the overall combined WMD altered slightly (data not shown).

### 3.9. Complication

All the studies reported the data on complications.<sup>[25–35]</sup> The complication rates in the LC-LCBDE and LC-EST groups were 10.25% and 9.15%, respectively. There was no significant difference between the 2 groups (RR=1.07, 95% CI: 0.86, 1.34;  $P=.550$ ). The test for heterogeneity was not significant ( $I^2=0.0%$ ,  $P=.771$ ).

LC-LCBDE was associated with a significantly higher rate of bile leakage than LC-EST (RR=2.66, 95% CI: 1.23, 5.77;  $P=.013$ ). Whereas, for other complications, including pancreatitis, pneumonia, hemorrhage, surgical-site infection, and cholangitis, the rates between the 2 treatment procedures were not significant (Table 3).

### 3.10. Publication bias

Assessment of publication bias using Begg and Egger tests showed that, there was no potential publication bias among the included studies (Begg test,  $P=.350$ ; Egger test,  $P=.210$ ).

**Table 2**

**GRADE evidence profile.**

| Quality assessment |   | Effect                  |                          |                         |                        |                     |                      |                     |   |           |           |
|--------------------|---|-------------------------|--------------------------|-------------------------|------------------------|---------------------|----------------------|---------------------|---|-----------|-----------|
|                    |   | Design                  | Risk of bias             | Inconsistency           | Indirectness           | Imprecision         | Other considerations | No. of patients     | Relative (95% CI)                               | Absolute  | Quality   |
| 8                  | CBD stone clear rate<br>Randomized trials   | No serious risk of bias | Serious*                 | No serious indirectness | No serious imprecision | Strong association† | 739/634 (88.6%)      | RR 1.02 (0.95–1.09) | 26 more per 1000 (from 44 fewer to 105 more)    | ⊕⊕⊕⊕ HIGH | CRITICAL  |
|                    |   |                         |                          |                         |                        |                     | 86.5%                |                     | 26 more per 1000 (from 43 fewer to 104 more)    |           |           |
| 3                  | Retained stones rate<br>Randomized trials   | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | None                | 41/486 (8.43%)       | RR 1.27 (0.51–3.19) | 10 more per 1000 (from 3 fewer to 63 more)      | ⊕⊕⊕⊕ HIGH | IMPORTANT |
|                    |   |                         |                          |                         |                        |                     | 5.56%                |                     | 14 more per 1000 (from 4 fewer to 81 more)      |           |           |
| 6                  | Conversion to other procedure<br>Randomized trials  | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | None                | 63/704 (8.94%)       | RR 1.59 (1.08–2.35) | 36 more per 1000 (from 3 more to 86 more)       | ⊕⊕⊕⊕ HIGH | IMPORTANT |
|                    |   |                         |                          |                         |                        |                     | 5.3%                 |                     | 31 more per 1000 (from 3 more to 74 more)       |           |           |
| 5                  | Operative time (range of scores: –16.68 to 6.42; Better indicated by lower values)<br>Randomized trials | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | None                | 558                  | —                   | WMD –11.55 lower (–16.68 higher to –6.42 lower) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
|                    |   |                         |                          |                         |                        |                     | 550                  |                     |   |           |           |
| 8                  | Length of hospital stay (better indicated by lower values)<br>Randomized trials                         | No serious risk of bias | Serious‡                 | No serious indirectness | No serious imprecision | Strong association† | 853                  | —                   | WMD –0.96 lower (–2.2 to 0.28 higher)           | ⊕⊕⊕⊕ HIGH | IMPORTANT |
|                    |   |                         |                          |                         |                        |                     | 801                  |                     |   |           |           |
| 8                  | Complication<br>Randomized trials   | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | Strong association† | 50/488 (10.2%)       | RR 1.07 (0.86–1.34) | 1 more per 1000 (from 31 fewer to 44 more)      | ⊕⊕⊕⊕ HIGH | IMPORTANT |
|                    |   |                         |                          |                         |                        |                     | 9.35%                |                     | 1 more per 1000 (from 22 fewer to 32 more)      |           |           |

CBD = common bile duct, CI = confidence interval, RR = risk ratio, WMD = weight mean difference.

\* Substantial heterogeneity ( $I^2 = 71.9\%$ ) was found.

† A total of 1663 patients were enrolled.

‡ Substantial heterogeneity ( $I^2 = 97.2\%$ ) was found.

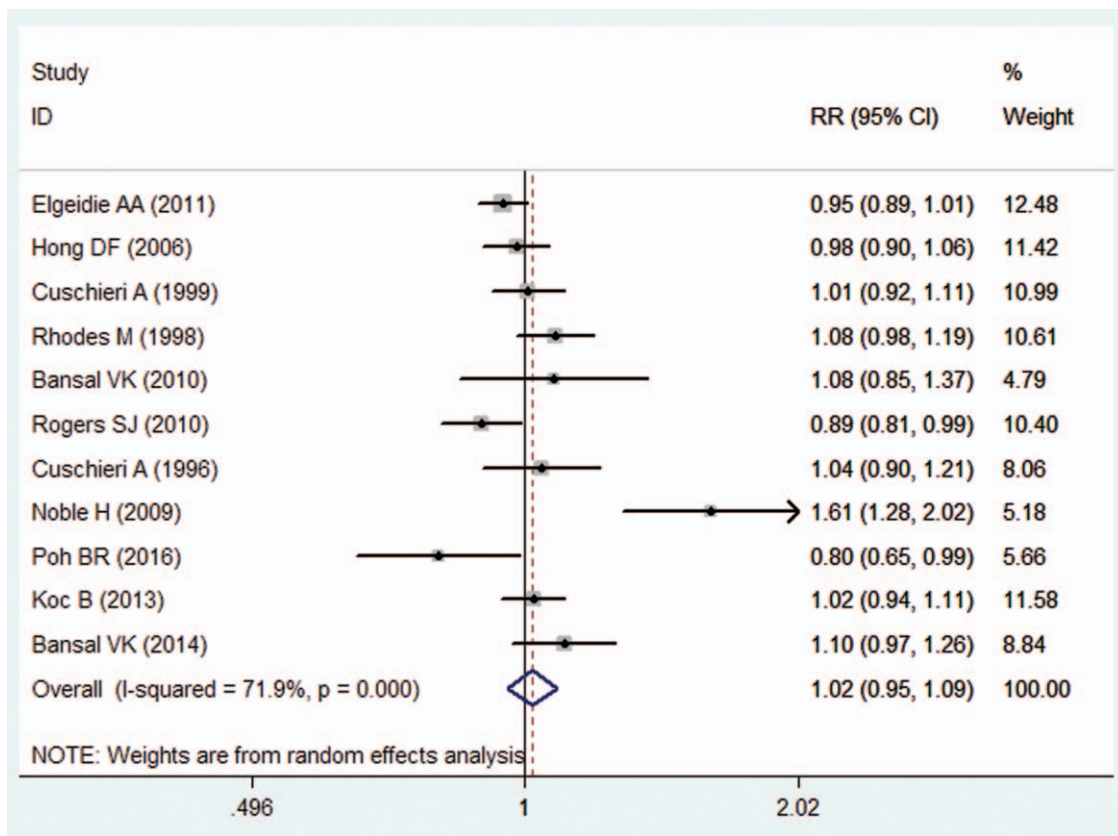


Figure 3. Forest plot showing the comparison between LC-LCBDE and LC-EST in CBD stone clear rate.

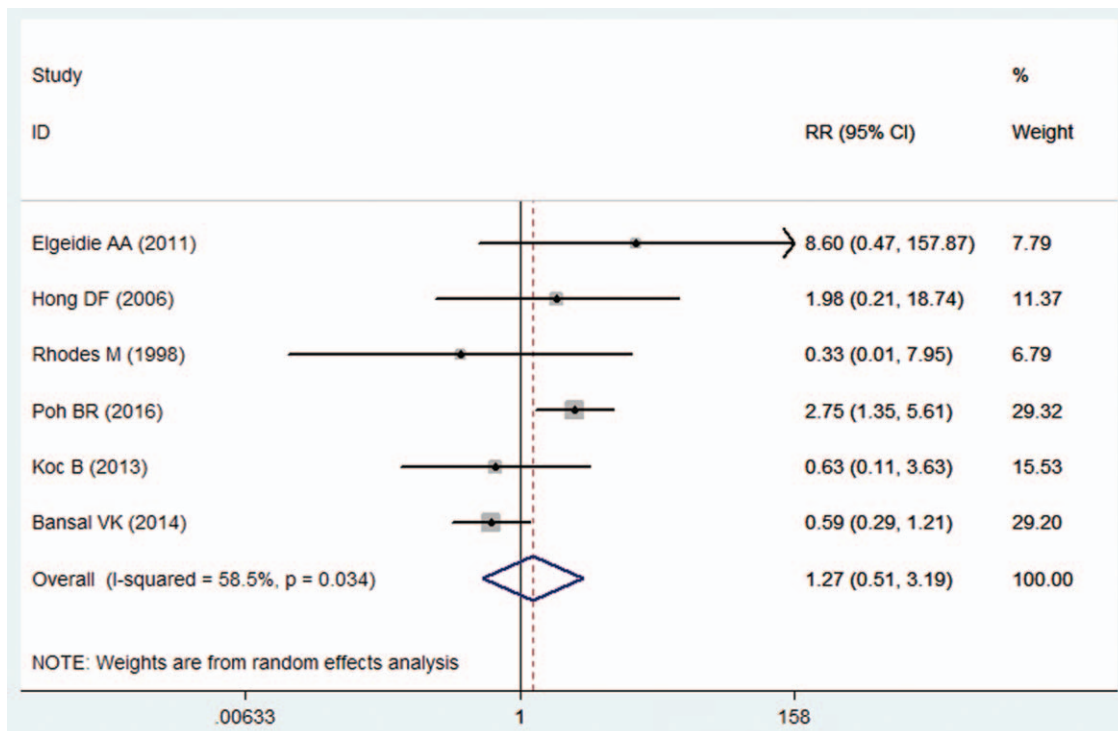


Figure 4. Forest plot showing the comparison between LC-LCBDE and LC-EST in retained stones rate.

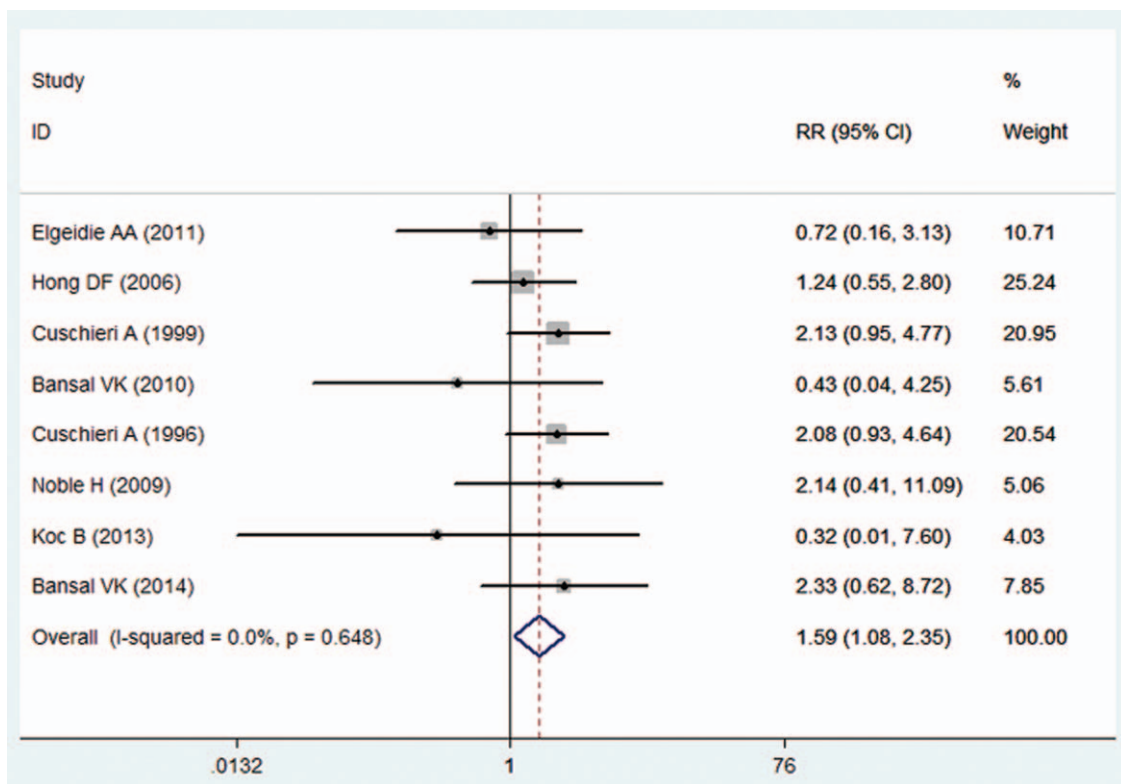


Figure 5. Forest plot showing the comparison between LC-LCBDE and LC-EST in conversion rate.

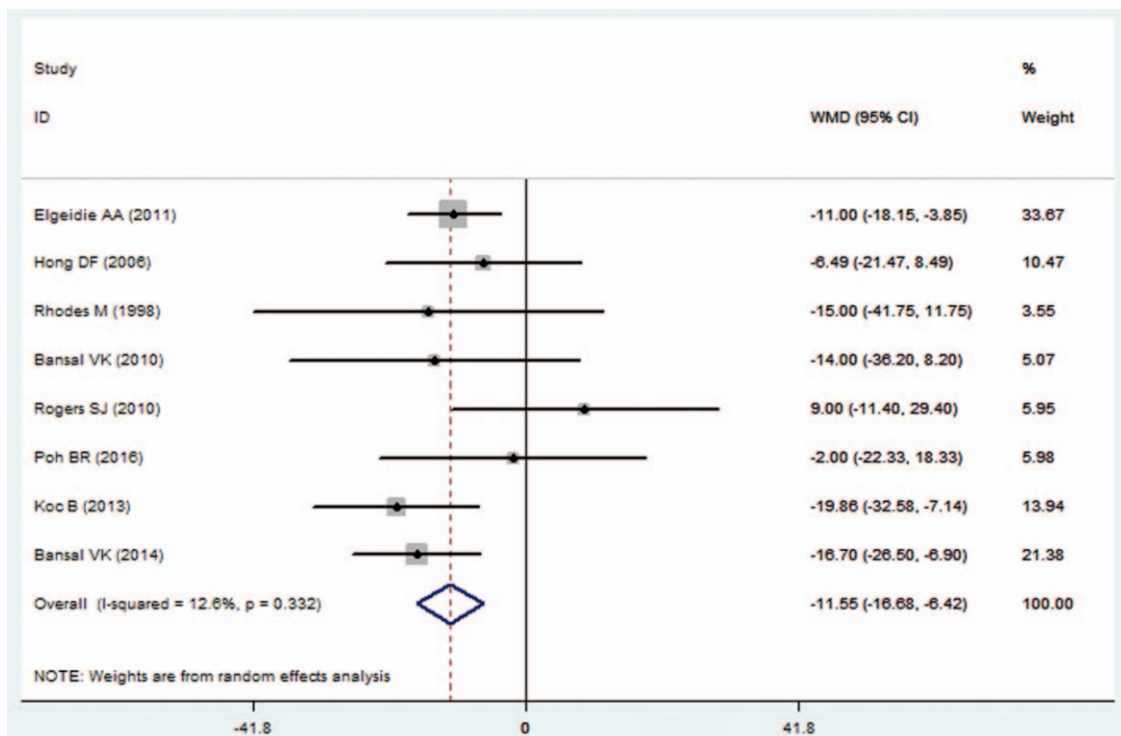


Figure 6. Forest plot showing the comparison between LC-LCBDE and LC-EST in operative time.

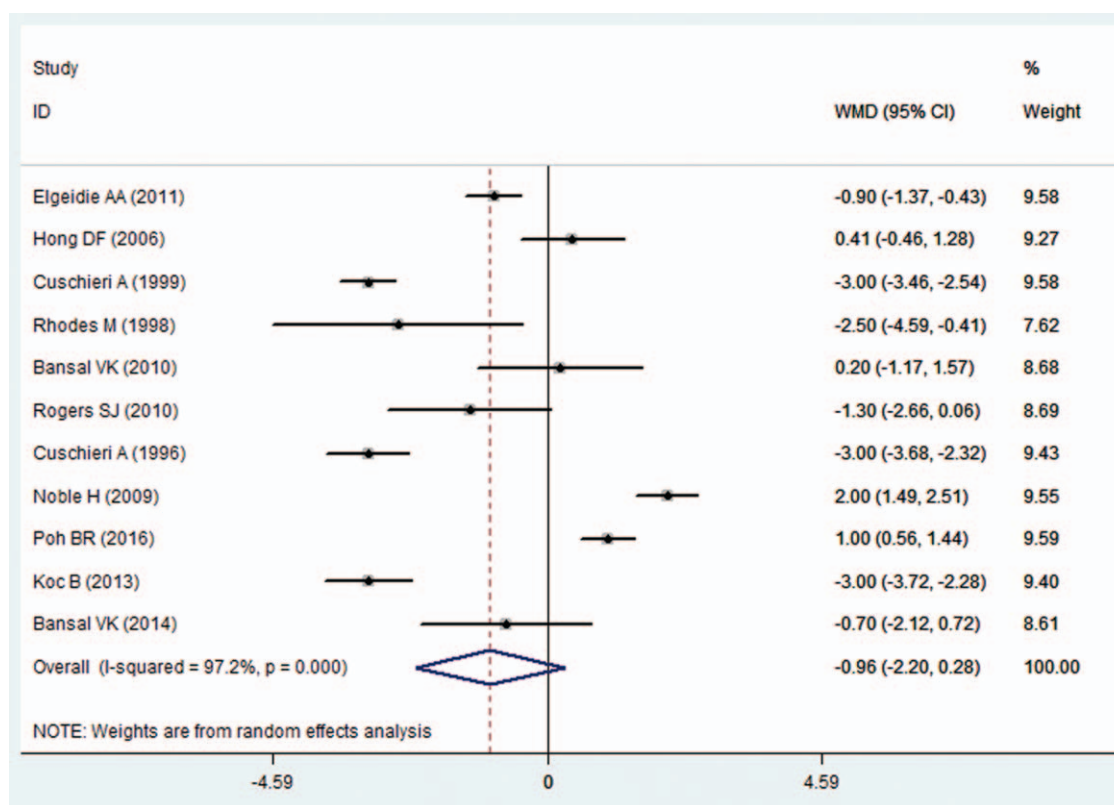


Figure 7. Forest plot showing the comparison between LC-LCBDE and LC-EST in length of hospital stay.

#### 4. Discussion

The purpose of this meta-analysis was to compare the efficacy and safety of LC-LCBDE with LC-EST in patients with gallstones and concomitant CBD stones. Our study showed that, LC-LCBDE was associated with comparable effects with LC-EST in terms of CBD stone clear rate, retained stones rate, and length of hospital stay. In addition, LC-LCBDE resulted in significantly higher conversion rate and less operative time than LC-EST. The incidence of complications between the 2 surgical approaches was not significant difference.

To the best of our knowledge, this study is the first meta-analysis to compare the effects and safety of LC-LCBDE with LC-EST in patients with gallstone and CBD stones. LC-LCBDE and LC-EST are the most ideal of mini-invasive procedures, which are widely used in patients with cholelithiasis and choledocholithiasis.<sup>[36,37]</sup> There has been one recently published systematic review and meta-analysis,<sup>[38]</sup> which compared ERCP with open or

laparoscopic surgery. In that study, the authors reported of 8 trials with 760 patients that compared ERCP with open surgical clearance.<sup>[38]</sup> They found that ERCP was less effective than open surgery in CBD stone clear (odds ratio, OR = 2.89, 95% CI: 1.81, 4.61).<sup>[38]</sup> The mortality seemed to be higher (risk difference, RD = 1%, 95% CI: -1%, 4%), but the difference did not reach a statistical significance.<sup>[38]</sup>

In this met-analysis, we found the success rates of CBD clearance was 88.6% for LC-LCBDE and 87.1% for LC-EST, which was in consistent with the previous studies.<sup>[27,39]</sup> There was no significant difference in success rate between the 2 surgical approaches. Among the included studies, LC-LCBDE was reported to have better CBD stone clearance than LC-EST, despite the difference was not significant. However, in the trial conducted by Elgeidie et al,<sup>[25]</sup> a higher success rate of CBD clearance in LC-EST group was reported. In that study, 112 and 107 patients were randomly assigned to LC-LCBDE and LC-EST groups, respectively; and the success rate of stone clearance in the 2 groups was 92.0% and 97.2%, respectively.<sup>[25]</sup> Similarly, Rogers et al<sup>[30]</sup> also reported a higher stone clearance for LC-EST. In that study, the stone clearance rate for patients undergoing LC-LCBDE was 88%, compared to 98% for patients with LC-EST.<sup>[30]</sup> The authors assumed that the higher stone clearance rate for LC-EST in their studies might be the result of a type II error.<sup>[30]</sup> Given the stone detected in 17 of 57 LC-LCBDE patients and 31 of 55 LC-EST patients, the power to detect a significant difference ( $\alpha = 0.05$ ) in clearance should be approximately 0.82.<sup>[30]</sup>

Regarding to the conversion to an open procedure, patients undergoing LC-LCBDE had a significantly higher conversion rate than those with LC-EST. The corresponding values for these

Table 3

Summary of the risk ratio (RR) of complications in patients with concomitant gallstones and CBD stones.

| Adverse events          | RR   | 95% CI    | P    |
|-------------------------|------|-----------|------|
| Pancreatitis            | 0.60 | 0.24–1.46 | .26  |
| Bile leakage            | 2.66 | 1.23–5.77 | .013 |
| Pneumonia               | 1.21 | 0.28–5.28 | .802 |
| Hemorrhage              | 0.57 | 0.20–1.66 | .303 |
| Surgical-site infection | 1.80 | 0.41–7.91 | .436 |
| Cholangitis             | 0.32 | 0.03–2.97 | .315 |

CBD = common bile duct, CI = confidence interval.



patients were 8.95% and 6.98%, respectively. The time interval between endoscopic papillotomy and LC remains controversial. In the multicenter trial of European Association of Endoscopic Surgery (E.A.E.S.), the time interval for the 2-stage procedures was not specified. While in the trial conducted by Sgourakis and Karaliotas,<sup>[39]</sup> LC was performed within 2 days after the stones were removed by endoscopic surgery. de Vries et al<sup>[40]</sup> reported a higher conversion rate when LC was performed more than 2 weeks after endoscopic papillotomy. They found that the conversion rate was 31% when cholecystectomy was done between 2 and 6 weeks, 4% within 2 weeks, and 16% after 6 weeks.<sup>[40]</sup>

In this study, the mean operative time was significantly less for patients undergoing LC-LCBDE than those with LC-EST. Our result was in consistent with the findings from the included studies. It has been reported that, the prolonged operative time for LCBDE may increase the incidence of complications for higher risk patients.<sup>[41]</sup> However, this result was not found in the trial conducted by Paganini et al,<sup>[42]</sup> who reported a similar morbidity or mortality between patients over 70 and less than 70 years. Mover, in the trial of Noble et al<sup>[32]</sup> they did not find any increased complications because of longer operative time. In that study, 91 high-risk patients with median age of 74.56 years were randomly assigned into LC-LCBDE or LC-EST groups. The authors concluded that, the 2 approaches had comparable results in terms of postoperative hospital stay, conversion, and complications in high-risk patients, but LC-LCBDE was more effective and efficient, and avoided unnecessary procedures.<sup>[32]</sup> Since there was only one study reporting LCBDE in high-risk patients, we could not perform subgroup analysis to identify whether LCBDE would lead to increased complications in these patients. Further well-conducted RCTs are needed to address this issue.

There were several potential limitations in this study which should be considered. First, there was moderate heterogeneity among the included studies. However, one should not be surprising given the variation in characteristics of populations (age, female/male, stone number, stone size), time intervention between endoscopic papillotomy and LC, laparoscope device and operator experience between the 2 approaches. All these factors contributed to the heterogeneity and had potential impacts on our results. Second, all included trials were not performed with double-blinded method, which might lead to performance and detection bias. Third, our meta-analysis is based on 11 RCTs, and 3 of them have a relatively small sample size (less than 100). Studies with small sample size are more likely to result in an overestimated treated effect than large studies. Fourth, we were unable to assess the effects and safety of LCBDE in high-risk patients due to the sparse reporting across studies.

In conclusion, the current meta-analysis suggested that both LC-LCBDE and LC-EST were highly effective in detecting and removing CBD stones and were equivalent in complications. However, the conversion rate was higher and operative time was less for LC-LCBDE. More large-scale, well-designed RCTs are needed to confirm our findings. In the future studies, the effects and safety of LCBDE in patients with high-risk should be given more attention.

## References

[1] Tazuma S. Gallstone disease: epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). *Best Pract Res Clin Gastroenterol* 2006;20:1075–83.

- [2] Targarona EM, Ayuso RM, Bordas JM, et al. Randomised trial of endoscopic sphincterotomy with gallbladder left in situ versus open surgery for common bile duct calculi in high-risk patients. *Lancet* 1996;347:926–9.
- [3] Hammarstrom LE, Holmin T, Stridbeck H, et al. Long-term 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* 1995;82: 1516–21.
- [4] Neoptolemos JP, Carr-Locke DL, Fossard DP. Prospective randomised study of preoperative endoscopic sphincterotomy versus surgery alone for common bile duct stones. *Br Med J (Clin Res Ed)* 1987;294:470–4.
- [5] Rabago LR, Vicente C, Soler F, et al. Two-stage treatment with preoperative endoscopic retrograde cholangiopancreatography (ERCP) compared with single-stage treatment with intraoperative ERCP for patients with symptomatic cholelithiasis with possible choledocholithiasis. *Endoscopy* 2006;38:779–86.
- [6] Enochsson L, Lindberg B, Swahn F, et al. Intraoperative endoscopic retrograde cholangiopancreatography (ERCP) to remove common bile duct stones during routine laparoscopic cholecystectomy does not prolong hospitalization: a 2-year experience. *Surg Endosc* 2004;18: 367–71.
- [7] Ricciardi R, Islam S, Canete JJ, et al. Effectiveness and long-term results of laparoscopic common bile duct exploration. *Surg Endosc* 2003;17: 19–22.
- [8] Berthou JC, Drouard F, Charbonneau P, et al. Evaluation of laparoscopic management of common bile duct stones in 220 patients. *Surg Endosc* 1998;12:16–22.
- [9] Coppola R, D'Ugo D, Ciletti S, et al. ERCP in the era of laparoscopic biliary surgery. Experience with 407 patients. *Surg Endosc* 1996;10: 403–6.
- [10] Park AE, Mastrangelo MJ Jr. Endoscopic retrograde cholangiopancreatography in the management of choledocholithiasis. *Surg Endosc* 2000;14:219–26.
- [11] Ghazal AH, Sorour MA, El-Riwini M, et al. Single-step treatment of gall bladder and bile duct stones: a combined endoscopic-laparoscopic technique. *Int J Surg* 2009;7:338–46.
- [12] Lella F, Bagnolo F, Rebuffat C, et al. Use of the laparoscopic-endoscopic approach, the so-called “rendezvous” technique, in cholecystocholedocholithiasis: a valid method in cases with patient-related risk factors for post-ERCP pancreatitis. *Surg Endosc* 2006;20:419–23.
- [13] Vellacott KD, Powell PH. Exploration of the common bile duct: a comparative study. *Br J Surg* 1979;66:389–91.
- [14] McSherry CK, Glenn F. The incidence and causes of death following surgery for nonmalignant biliary tract disease. *Ann Surg* 1980;191: 271–5.
- [15] Susana Estevez M, Abele D, Puntarulo S. Lipid radical generation in polar (*Laternula elliptica*) and temperate (*Mya arenaria*) bivalves. *Comp Biochem Physiol B Biochem Mol Biol* 2002;132:729–37.
- [16] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- [17] Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. The Cochrane Collaboration, Oxford:2011.
- [18] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- [19] Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- [20] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- [21] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719–48.
- [22] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
- [23] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
- [24] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- [25] ElGeidie AA, ElShobary MM, Naeem YM. Laparoscopic exploration versus intraoperative endoscopic sphincterotomy for common bile duct stones: a prospective randomized trial. *Dig Surg* 2011;28:424–31.
- [26] 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;20:424–7.
- [27] Cuschieri A, Lezoche E, Morino M, et al. 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;13:952–7.
- [28] Rhodes M, Sussman L, Cohen L, et al. Randomised trial of laparoscopic exploration of common bile duct versus postoperative endoscopic retrograde cholangiography for common bile duct stones. *Lancet* 1998;351:159–61.
- [29] Bansal VK, Misra MC, Garg P, et al. A prospective randomized trial comparing two-stage versus single-stage management of patients with gallstone disease and common bile duct stones. *Surg Endosc* 2010;24:1986–9.
- [30] Rogers SJ, Cello JP, Horn JK, et al. Prospective randomized trial of LC+LCBDE vs ERCP/S+LC for common bile duct stone disease. *Arch Surg* 2010;145:28–33.
- [31] Cuschieri A, Croce E, Faggioni A, et al. EAES ductal stone study. Preliminary findings of multi-center prospective randomized trial comparing two-stage vs single-stage management. *Surg Endosc* 1996;10:1130–5.
- [32] Noble H, Tranter S, Chesworth T, et al. A randomized, clinical trial to compare endoscopic sphincterotomy and subsequent laparoscopic cholecystectomy with primary laparoscopic bile duct exploration during cholecystectomy in higher risk patients with choledocholithiasis. *J Laparoendosc Adv Surg Tech A* 2009;19:713–20.
- [33] Poh BR, Ho SP, Sritharan M, et al. Randomized clinical trial of intraoperative endoscopic retrograde cholangiopancreatography versus laparoscopic bile duct exploration in patients with choledocholithiasis. *Br J Surg* 2016;103:1117–24.
- [34] Koc B, Karahan S, Adas G, et al. Comparison of laparoscopic common bile duct exploration and endoscopic retrograde cholangiopancreatography plus laparoscopic cholecystectomy for choledocholithiasis: a prospective randomized study. *Am J Surg* 2013;206:457–63.
- [35] Bansal VK, Misra MC, Rajan K, et al. 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;28:875–85.
- [36] Lauter DM, Froines EJ. Laparoscopic common duct exploration in the management of choledocholithiasis. *Am J Surg* 2000;179:372–4.
- [37] Memon MA, Hassaballa H, Memon MI. Laparoscopic common bile duct exploration: the past, the present, and the future. *Am J Surg* 2000;179:309–15.
- [38] Martin DJ, Vernon DR, Toouli J. Surgical versus endoscopic treatment of bile duct stones. *Cochrane Database Syst Rev* 2006;Cd003327.
- [39] 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;57:467–74.
- [40] de Vries A, Donkervoort SC, van Geloven AA, et al. Conversion rate of laparoscopic cholecystectomy after endoscopic retrograde cholangiography in the treatment of choledocholithiasis: does the time interval matter? *Surg Endosc* 2005;19:996–1001.
- [41] Noble H, Spratt M, Norton S, et al. Risk factors associated with a poor outcome following laparoscopic bile duct exploration. *Surg Endosc* 2006;20:S253.
- [42] Paganini AM, Feliciotti F, Guerrieri M, et al. Laparoscopic cholecystectomy and common bile duct exploration are safe for older patients. *Surg Endosc* 2002;16:1302–8.