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Common Bile Duct Stones Management: A Network Meta-analysis

--Manuscript Draft--

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Abstract:	Background Timely management is critical for treating symptomatic common bile duct (CBD) stones; however, a single optimal management strategy has yet to be defined in the acute care setting. Consequently, this systematic review and network meta-analysis, comparing 1-stage (CBD exploration or intraoperative ERCP with simultaneous cholecystectomy) and 2-stage (pre- or post-cholecystectomy ERCP) procedures, was undertaken with the main outcomes of interest being post-procedural complications and hospital length of stay (LOS). Methods PubMed, SCOPUS, MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were methodically queried for articles from 2010 to 2021. The search terms were a combination of medical subject headings terms and the subsequent terms: Gallstone, Common Bile Duct (stone), Choledocholithiasis, Cholecystitis, Endoscopic Retrograde Cholangiography/ERCP, Common Bile Duct Exploration, Intra-, Pre-, Peri-, and Post-operative Endoscopic Retrograde Cholangiography, Stone Extraction, One-stage- & Two-stage-procedure. Studies that compared ≥2 procedures were included, whereas

	studies not recording complications (bile leak, hemorrhage, pancreatitis, perforation, intraabdominal infections, and other infections) or LOS were excluded. A network meta-analysis was conducted to compare the four different approaches for managing CBD stones. Results A total of 16 studies (8,644 participants) addressing the LOS and 41 studies (19,756 participants) addressing post-procedural complications were included in the analysis. The 1-stage approaches were associated with a decrease in LOS compared to the 2-stage approaches. CBD exploration demonstrated a lower overall risk of complications compared to preoperative ERCP, but there were no differences in the overall risk of complications in the remaining comparisons. However, differences in specific post-procedural complications were detected between the four different approaches managing CBD stones. Conclusion This network meta-analysis suggests that both laparoscopic CBDE and intraoperative ERCP have equally good outcomes and provide a preferable single-anesthesia patient pathway with a shorter overall length of hospital stay compared to the 2-stage approaches.

July 18, 2022

To:

Journal of Trauma and Acute Care Surgery

Deputy Editor Deborah M. Stein, MD, MPH, MD

Editor-in-Chief Raul Coimbra, MD, PhD, FACS

Re: Common Bile Duct Stones Management: A Network Meta-analysis (JT-D-22-00605)

Dear Professor Stein,

Thank you for the review of our manuscript "Common Bile Duct Stones Management: A Network Meta-analysis". We appreciate the questions and comments made by the peer reviewers of The Journal of Trauma and Acute Care Surgery, as well as your Editorial assessment.

The issues raised have been addressed point by point in the "answer to reviewer" document, and highlighted changes have been introduced in the attached revised manuscript. I, Shahin Mohseni, have reviewed and edited the submission to omit any identifying information. I hereby submit this self-blinded manuscript for consideration in The Journal of Trauma and Acute Care Surgery.

We look forward to your final decision on our work.

Respectfully,

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ABSTRACT

Background

Timely management is critical for treating symptomatic common bile duct (CBD) stones; however, a single optimal management strategy has yet to be defined in the acute care setting. Consequently, this systematic review and network meta-analysis, comparing 1-stage (CBD exploration or intraoperative ERCP with simultaneous cholecystectomy) and 2-stage (pre- or post-cholecystectomy ERCP) procedures, was undertaken with the main outcomes of interest being post-procedural complications and hospital length of stay (LOS).

Methods

PubMed, SCOPUS, MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were methodically queried for articles from 2010 to 2021. The search terms were a combination of medical subject headings terms and the subsequent terms: Gallstone, Common Bile Duct (stone), Choledocholithiasis, Cholecystitis, Endoscopic Retrograde Cholangiography/ERCP, Common Bile Duct Exploration, Intra-, Pre-, Peri-, and Post-operative Endoscopic Retrograde Cholangiography, Stone Extraction, One-stage- & Two-stage-procedure. Studies that compared ≥2 procedures were included, whereas studies not recording complications (bile leak, hemorrhage, pancreatitis, perforation, intraabdominal infections, and other infections) or LOS were excluded. A network meta-analysis was conducted to compare the four different approaches for managing CBD stones.

Results

A total of 16 studies (8,644 participants) addressing the LOS and 41 studies (19,756 participants) addressing post-procedural complications were included in the analysis. The 1-stage approaches were associated with a decrease in LOS compared to the 2-stage approaches. CBD exploration demonstrated a lower overall risk of complications compared to preoperative ERCP, but there were no differences in the overall risk of complications in the remaining comparisons. However, differences in *specific* post-procedural complications were detected between the four different approaches managing CBD stones.

Conclusion

This network meta-analysis suggests that both laparoscopic CBDE and intraoperative ERCP have equally good outcomes and provide a preferable single-anesthesia patient pathway with a shorter overall length of hospital stay compared to the 2-stage approaches.

Key words: Common Bile Duct Stone, Choledocholithiasis, ERCP, Common Bile Duct Exploration, one- and two-stage procedure.

Level of Evidence: Level II, Systemic review and network meta-analysis

Running title: *CBD Stone Management in acute care surgery*

Common Bile Duct Stones Management: A Network Meta-analysis

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Author Contributions:

Study design: SM, GAB, BS, and RC came up with the initial idea for the study. All authors have discussed and agreed before the start of the study on the study inclusion and exclusion criteria, analysis, and the main outcomes of interest.

Abstract review: All authors have voted on the abstracts for further review.

Manuscripts reviewed for inclusion in analysis: SM, GAB, MPF.

Data extraction and analysis: SM, GAB, MPF, YC.

Interpretation of data and results: All authors.

Drafting manuscript: SM, GAB, MPF, YC, RC.

Revision of manuscript: All authors have critically reviewed and accepted the final version of manuscript submitted.

Responses to reviewers' comments and questions

Reviewer #1

The authors performed a systematic review in an effort to determine optimal management of CBD stones as it relates to length of stay and procedural complications. Long story short, pancreatitis was decreased with CBDE as well as LOS and some other associated complications.

I found this article to be fairly novel, wonderfully well-written, and enjoyable to read. I feel the impact is sufficient to warrant publication and I feel it adds to the knowledge base.

Response: *We thank the reviewer for their time to critically review our work and their kind words.*

Two minor things to consider:

Small grammatical issue on p10 line 17. "that majority of these stones" should probably read "the majority of these stones"

Response: *Thank you for bringing this typo to our attention.*

Figures 2-6. When I read Forest plots I'm used to seeing a "favors CBD exploration" or "favors ERCP" indication on either side of the Forest plot to make it more readable.

Response: *Thank you for this comment. Since the analysis compares pre-, peri- and post cholecystectomy ERCP both with CBDE and between peri-ERCP (one-stage approach) to pre-and post-ERCP (two-stage approach), it would give the wrong impression if would use the term "favors ERCP" in the figures.*

Reviewer #2

The authors submit a well-written and thorough meta-analysis manuscript which reviewed articles related to the treatment of common bile duct stones from an Acute Care Surgeon perspective. As the authors point out, the trends in treatment of this clinical problem have shifted over several decades and, as technology has changed, we are left trying to determine what the current standard of care should be. The authors identified important primary and secondary outcomes which are all of importance to an acute care surgery model including length of stay as well as intraoperative and postoperative complications. The literature search they describe sounds like it was appropriately comprehensive in nature and they excluded historical articles that included patients from greater than 25 years ago.

The title is appropriately broad, indicating that this is applicable to physicians with operative abilities and those who are not surgeons. The abstract is concise and attracts interest in reading the full manuscript. The conclusions are clear, given the limitations of this type of study. This manuscript outlines the various clinical technique and performs a comparative analysis which acute care surgeons can use to guide management and, perhaps, consider adding to their own skillset and Lap CBDE exploration is not commonly performed in many large centers.

I have just a few minor comments for the authors to consider.

1. Can you describe the method by which you assigned a study quality score to the manuscripts you reviewed?

Response: *Thank you for this question. The quality score was calculated as the sum of the number of Cochrane Suggested Risk of Bias criteria that were classified as low risk. If a criterion couldn't be definitively classified as high or low risk, they received half a point*

instead. The following has been added to the methods section under the headline "Quality Assessment":

"A quality score was calculated for each study as the sum of the number of criteria that were classified as low risk. If a criterion could not be definitively classified as high or low risk, it was counted as half a point instead."

2. In Figure 1, is the LOS missing in the first bar for the pre-ERCP group?

Response: *No, it is not missing; however, due to its value being very small, the bar cannot be seen in the figure. We have added this information under Figure 1 accordingly.*

"*Due to the low value calculated for preoperative ERCP in regard to length of stay, this bar is not visible in the figure."

3. In comparing the CBDE vs ERCP groups in terms of bile leak and the risk being higher in the CBDE group...Was there consideration that the post-ERCP group may have included patients undergoing ERCP specifically for bile leak?

Response: *Thank you for this question. This scenario is highly unlikely since the studies included specifically reported that the ERCP was carried out for CBD stone removal and not for other conditions such as post-cholecystectomy bile leak.*

4. Is the confounding factor of preoperative knowledge of a CBD stone vs finding a, unexpected stone intraoperatively a concern? Is this a limitation?

Response: *Thank you for this valid question. Although out of the scope of the current manuscript, the authors did comment on this scenario under the section "watchful waiting".*

"Unfavorable outcomes have also been reported in 16%-36% of patients when no intervention was undertaken for CBD stones diagnosed by intraoperative cholangiogram (IOC), depending on the size of the calculi.[17]"

The current manuscript is meant for acute care surgeons, who care for patients with symptomatic CBD stones, i.e. stones are either highly suspected pre-operatively, or detected intra-operatively, and constitute the indication for admission and surgery. Consequently, the primary focus of the discussion is active intervention in these instances.

"Nevertheless, most patients with CBD calculi admitted to acute care surgical services present with one or more symptoms and conditions related to the presence of CBD stone(s), such as abdominal pain, jaundice, cholecystitis, cholangitis, and pancreatitis, which necessitates an active rather than a "wait-and-see" approach."

I feel this is a strong manuscript overall and should be published.

Response: *The authors thank the reviewer for their time to critically review our work.*

Background

Common bile duct (CBD) stones are frequently encountered in the surgical practice of acute care surgeons. Up to 20% of patients requiring urgent cholecystectomy for acute cholecystitis have been found to have concomitant CBD stones.[1–3] Despite being a common surgical condition, the optimal management of CBD stones in the acute setting has been highly debated. In the last several decades, the surgical approach for treating complicated biliary calculous diseases has fundamentally changed from open to laparoscopic.[4,5] With the introduction of endoscopic retrograde cholangiopancreatography (ERCP) in 1968, the interventional approach to CBD stones shifted in favor of a 2-stage approach, either pre-cholecystectomy (preERCP) or post-cholecystectomy (postERCP).[4,5] More recently the 1-stage approach with intraoperative ERCP (iERCP) or laparoscopic CBD exploration (CBDE) by choledochoscopy and cholecystectomy has become a strong contender to the 1-stage open surgical CBDE, i.e., choledochotomy plus cholecystectomy.[6,7]

Since acute care surgeons commonly manage CBD stone-related conditions, it is important to establish evidence-based best practice for this patient population to improve resource allocation and training, decrease disease- and procedural-specific complications, as well as improve overall patient throughput in the hospital. Moreover, it is important to understand the application and associated outcomes of multiple different approaches to a complicated disease process such as choledocholithiasis so therapy can also be tailored to an individual center, surgeon, or patient.

To this end, we undertook a systematic review and network meta-analysis comparing the different treatment options for CBD stones. The main outcomes of interest were postoperative complications and hospital length of stay (LOS), when comparing the 1-stage and 2-stage approaches.

Methods

Eligibility criteria

This study was conducted according to the PRISMA guidelines (Supplementary Table 1).[8] No protocol was used for the systemic review. We included studies that met the following inclusion criteria: a) the study design was either an observational cohort study, case-control, or randomized control trial (RCT) investigating the management of choledocholithiasis; b) patients were managed using CBDE, iERCP, preERCP, or postERCP; c) the experimental group(s) and the control group received different treatments; d) the study recorded complications and/or LOS in all groups. Studies were excluded based on the following criteria: a) irrelevant studies; b) duplicate studies; c) unavailable data in the manuscript; d) studies unavailable in English or English-translation; e) studies for which a full-text was unavailable; f) studies not indexed by MEDLINE; g) previous systematic reviews and meta-analyses as well as reviews, letters, and case reports; h) the mean LOS was reported without a standard deviation (SD), or the median LOS was reported without an interquartile range (IQR).

Search methodology

PubMed, SCOPUS, MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were methodically searched from January 2010 to December 2021. The initial search was from 2000; however, since many of the studies included patients from the end of 1900's or very early in the 2000's, the decision was made to concentrate on the studies published from 2010 and beyond. The search terms were a combination of medical subject headings terms and the subsequent terms: Gallstone, Common Bile Duct (stone), Choledocholithiasis, Cholecystitis, Endoscopic Retrograde Cholangiography/ERCP, Common

Bile Duct Exploration, Intra-, Pre-, Peri-, and Post-operative Endoscopic Retrograde Cholangiography, Stone Extraction, One-stage- & Two-stage-procedure.

Study selection

Using the web-based software platform Covidence®, several investigators screened the original studies independently based on the previously mentioned inclusion and exclusion criteria. An initial review was performed of the article abstracts and titles, after which each reviewer would cast a vote using the software platform to include or exclude the study from further review. Votes from two independent investigators were required to include or exclude a study. Investigators performed a full-text review of the remaining articles after the initial screening. Studies that received votes for inclusion from two independent investigators were retained for the final analysis. Any discrepancies in voting were addressed by discussion or third- party consensus.

Data extraction

All data were extracted from eligible studies using a standardized protocol. The following information was retrieved: PubMed unique identifier; authors' names; publication year; the country where the study was conducted; study design; study subjects; the number of participants; the number of male and female participants; the range of years covered by the study; case and control procedure; the number of patients who underwent the case and control procedure; the number of patients lost to further analysis; the number of patients with and without any complication for the case and control procedures; the number of patients with and without a specific complication for the case and control procedures (these included bile leak, hemorrhage, pancreatitis, perforation, intraabdominal infections, and other infections); mean and standard deviation (SD) or median and interquartile range (IQR) for LOS.

Quality assessment

The risk of bias was evaluated in conjunction with the data extraction using the Cochrane Suggested Risk of Bias criteria for EPOC reviews: random sequence generation, allocation concealment, baseline outcome measurements similar, baseline characteristics similar, incomplete outcome data, knowledge of the allocated interventions adequately prevented during the study, protection against contamination, selective outcome reporting, and other risks of bias. A quality score was calculated for each study as the sum of the number of criteria that were classified as low risk. If a criterion could not be definitively classified as high or low risk, it was counted as half a point instead.

Outcomes

The primary outcomes of interest were the overall risk of complications and the total hospital LOS. The secondary outcomes of interest were the risk of bile leak, hemorrhage, pancreatitis, perforation, intraabdominal infections, and other infections.

Statistical analysis

The mean difference (MD) for LOS and corresponding standard error (SE) of MD were calculated using the following formulae:

$$MD = mean_1 - mean_2$$

$$SE_{MD} = \sqrt{\left(\frac{N_1 s_1^2 + N_2 s_2^2}{N_1 + N_2 - 2}\right)\left(\frac{N_1 + N_2}{N_1 N_2}\right)}$$

where *mean*, *s*, and *N* correspond to the mean LOS, SD of LOS, and number of patients, respectively. According to the Cochrane Handbook, if the median and IQR were provided

instead of the mean and SD, the mean and SD were estimated using the median and IQR.[9] An MD <0 indicates that treatment 1 has a shorter mean LOS than treatment 2. If the 95% confidence interval (CI) for the MD contains 0, there is no statistically significant difference between the treatment groups.

The risk ratio (RR) and corresponding SE of the natural log-transformed RR [log(RR)] were calculated using the extracted numbers according to the formulae below for all complications and specific complications:

$$RR = \frac{n_1/N_1}{n_2/N_2}$$

$$SE_{\log(RR)} = \sqrt{\frac{N_1 - n_1}{N_1 n_1} + \frac{N_2 - n_2}{N_2 n_2}}$$

where n_1 is the number of patients with complications in treatment group 1, N_1 is the total number of patients in treatment group 1, n_2 is the number of patients with complications in treatment group 2, and N_2 is the total number of patients in treatment group 2. According to the Cochrane Handbook, if n_1 or n_2 were 0, they were replaced by 0.5.[9] An RR < 1 indicates that treatment 1 had a lower risk for complication(s) than treatment 2. If the 95% CI for the RR contains 1 there is no statistically significant difference between the treatment groups.

The direct effect for every potential pair of treatments was evaluated using conventional meta-analyses. The Q test and I^2 index were used to evaluate the heterogeneity of each effect size. An I^2 index <50% indicates that the studies have good homogeneity, and the fixed-effects model was used; otherwise, a random- effects model was used. If an indirect effect between two treatments existed, it was derived using the method described by Dias et al. Subsequently,

a network meta-analysis was used to combine both the direct and indirect effects for comparison.[10]

The net splitting method was used to diagnose inconsistency between the direct and indirect effects.[11] The direct, indirect, and combined effects were presented using forest plots. The comparison-adjusted funnel plots were used to visualize the risk of publication bias in the network meta-analyses; the numerical Egger's test for publication bias was also employed where possible.[12] A ranking probability plot was used to rank the treatments (a high value indicates that the treatment might be better). The rank probability was calculated according to the method suggested by Rücker et al.[13]

The statistical analyses were completed in R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using packages meta, metaphor, and netmeta.[11,14,15]

Results

Study selection outcome and characteristics

The search identified 1,920 potential articles for inclusion, after excluding duplicates. 348 studies remained after the initial review of titles and abstracts. Finally, 16 studies (N= 8,644) addressing the LOS and 41 studies (N = 19,756) addressing post-procedural complications were retained for the analysis (Supplemental figure 1 and 2). The average ages of the participants included in these studies were 54.2 and 54.1 years for the LOS and post-procedural complications studies, respectively.

Study quality assessment

The quality of the included studies varied in terms of quality score (the total score is 10 with 10 reflecting the highest quality study) from 2.5 to 7.5, with a median score of 5.5.

Laparoscopic CBD Exploration compared to pre- or post-cholecystectomy ERCP

According to the rank probabilities, for overall complications and specific complications including bleeding, pancreatitis, and perforation, CBDE was better than pre- and postERCP (Figure 1). Regarding LOS, although the point estimate for CBDE indicated a longer LOS than postERCP, the difference was not statistically significant (MD=0.36; 95% CI: -1.26, 1.98; Figure 2). However, there was a significantly reduced LOS in the CBDE cohort compared to the preERCP cohort (MD= -2.02; 95 CI%: -3.04, -1.01; Figure 2). The relative risk of all complications was also reduced in the CBDE cohort compared to the preERCP group (RR=0.77; 95% CI: 0.59, 0.99; Figure 3), whereas no difference was observed compared to the postERCP group. The risk of bile leak was 3 times higher in the CBDE group compared to preERCP (RR=3.31; 95% CI: 2.00, 5.46; Figure 4), while no difference was found when comparing CBDE to postERCP (RR=1.37; 95% CI: 0.68, 2.78; Figure 4). The risk of pancreatitis was reduced by almost 80% in the CBDE group compared to both preERCP (RR=0.22; 95% CI: 0.12, 0.40; Figure 5) and postERCP (RR=0.24; 95% CI: 0.13, 0.46; Figure 5). No difference was detected in the risk of iatrogenic perforation (Figure 6), hemorrhage (Supplemental Figure 3), intraabdominal infections (Supplemental Figure 4), or other infections (Supplemental Figure 5) between pre- or postERCP and CBDE.

Intraoperative ERCP compared to pre- and post-cholecystectomy ERCP

Regarding LOS and the overall risk of complications, iERCP was superior to both pre- and postERCP according to the rank probabilities (Figure 1). According to the rank probabilities,

iERCP was also better than pre- or postERCP for intraabdominal infections (Figure 1). The network meta-analysis demonstrated a significantly reduced LOS in the iERCP cohort compared to the preERCP cohort (MD=-3.12; 95% CI: -3.91, -2.32; Figure 2), but no statistical difference compared to postERCP group (Figure 2). Although the point estimates for the iECRP cohort indicated a lower overall risk of complications compared to pre- and postERCP, the results were not statistically significant (Figure 3). The risk of bile leak was almost halved in the iERCP cohort compared to the postERCP group (RR=0.56; 95% CI: 0.37, 0.84; Figure 4); however, no statistically significant difference was detected when iERCP was compared to the preERCP (RR=1.35; 95% CI: 0.80, 2.27; Figure 4). The risk of intraabdominal infections was lower after iERCP compared to postERCP (RR=0.65; 95% CI: 0.44, 0.94; Supplemental figure 4). There was no statistically significant difference detected in the risk of pancreatitis (Figure 5), iatrogenic perforation (Figure 6), hemorrhage (Supplemental figure 3), or other infections (Supplemental figure 5) when comparing iECRP with pre- and postERCP cohorts.

Laparoscopic CBD exploration compared to Intraoperative ERCP

iERCP demonstrated a higher probability of being better than CBDE in terms of LOS (Figure 1), with a significantly lower LOS than CBDE (MD=-1.09; 95% CI: -2.15, -0.04; Figure 2). Regarding the overall risk of complications, CBDE was better than iERCP based on the rank probabilities (Figure 1). However, the difference was not statistically significant (RR=0.94; 95% CI: 0.70, 1.26; Figure 3). For specific complications, CBDE was superior to iERCP regarding the risk of hemorrhage, pancreatitis, and perforation (Figure 1). CBDE was associated with twice the risk of bile leak compared to iERCP (RR=2.45; 95% CI: 1.33, 4.52; Figure 4). The relative risk of pancreatitis was reduced by 78% in the CBDE cohort compared to the iERCP cohort (RR=0.22; 95% CI: 0.12, 0.41; Figure 5). The risk of iatrogenic perforation was reduced by 86% in patients who underwent CBDE (RR =0.14; 95% CI: 0.02, 0.93; Figure

6); however, this was only based on the indirect comparison. There was no statistically significant difference detected in the risk of hemorrhage (Supplemental figure 3), intraabdominal infections (Supplemental figure 4), or other infections (Supplemental figure 5), when comparing CBDE and iERCP.

Publication bias

Funnel plots of all the studies included as a part of the network meta- analysis were created to graphically determine the presence of publication bias (Supplemental figure 6-13). In general, studies were distributed within or close to the 95% confidence interval for all outcomes, which indicated a homogenous distribution of the study results. The non-significant p-values derived from Egger's test further support this conclusion. Collectively, these results indicate no statistically significant publication bias in the included articles that would impact the meta-analysis estimates of effect size.

Discussion

There is consensus that timely management is critical for treating CBD stones, particularly those that are symptomatic, while improving patient throughput in the hospital. However, a single optimal management strategy has yet to be defined in the acute care setting.

Watchful waiting

It is important to recognize that even asymptomatic CBD stones confer a high risk of complications. In a cohort of patients with incidental CBD stones diagnosed by imaging in

asymptomatic patients, biliary complications developed in 6.1% of patients after one year, 11% after three years, and 17% after five years.[16] Unfavorable outcomes have also been reported in 16%-36% of patients when no intervention was undertaken for CBD stones diagnosed by intraoperative cholangiogram (IOC), depending on the size of the calculi.[17] These results are in line with a recent population-based registry study from Sweden conducted by Johansson et al. comparing surveillance to intervention for CBD stones found on IOC.[18] They reported a 5-fold increase in the risk of needing to perform an unplanned postERCP due to retained stone(s) in the surveillance group compared to the intervention group [adjusted HR 5.5 (95% CI: 4.8-6.4), p<0.005]. For smaller stones (<4mm in diameter), the risk of an unplanned postERCP was 3 times higher in the surveillance group [adjusted HR 3.5 (95% CI: 2.4-5.1), p<0.005].[18] However, there is still an ongoing debate about the ideal approach and value to a "wait-and-see" approach for entirely asymptomatic CBD stones that are discovered only on imaging or by intraoperative cholangiography, where multiple series have demonstrated the majority of these stones will pass spontaneously and will not require further intervention or hospitalization.[19–21] Nevertheless, most patients with CBD calculi admitted to acute care surgical services present with one or more symptoms and conditions related to the presence of CBD stone(s), such as abdominal pain, jaundice, cholecystitis, cholangitis, and pancreatitis, which necessitates an active rather than a "wait-and-see" approach.

ERCP without cholecystectomy

Cholecystectomy after ERCP for CBD stones has been widely debated, especially in the elderly.[22] Deferring post-ERCP cholecystectomy has been associated with higher rates of morbidity and readmissions.[23–25] Over 25% of cases eventually require a cholecystectomy.[22,25] In a meta-analysis that included 1,605 patients, 864 (53.8%) had their cholecystectomy deferred following ERCP with sphincterotomy, of whom 26% required a cholecystectomy.[25]

Furthermore, a total of 37% of patients with in-situ gallbladders suffered a complication from remaining stones. Compared to a prophylactic cholecystectomy, deferred cholecystectomy resulted in a significantly increased risk of mortality [odds ratio (OR) 2.56 (95% CI 1.54-4.23), P<0.0001]. Patients who did not undergo a prophylactic cholecystectomy were also more likely to develop recurrent biliary pain and cholecystitis [OR 5.10 (95% CI 3.39-7.67), P<0.0001]. However, the rate of pancreatitis [OR 3.11 (95% CI 0.99-9.83), P=0.053] and cholangitis [OR 1.49 (95% CI 0.74-2.98), P=0.264] was unaffected.[25] These findings favor performing post-ERCP cholecystectomy, preferably during the index admission rather than as a postponed elective operation.

In practice, most patients deferred from an index admission cholecystectomy are older, burdened by comorbidities, and frail, which makes managing CBD stone-related complications even more challenging.[22,24–26] With a growing elderly patient population worldwide, gallstone-related diseases and interventions will also increase; this includes cholecystectomy for acute cholecystitis, which has a 3-fold higher risk of CBD stones than elective cholecystectomy.[27,28] Currently, guidelines do not make a distinction in the optimal timing of acute cholecystectomy for cholecystitis when comparing elderly and younger patients. Instead, surgery during the index admission is recommended for all ages, where no absolute contraindication to surgery exists.[29,30] Even in octogenarians, post-ERCP laparoscopic cholecystectomy has been shown to be safe.[31] Nevertheless, the risks associated with a more technically challenging operation post-ERCP should not be underestimated and decision about surgery versus observation should be tailored to the patient and the individual risk-benefit analysis.[32]

Laparoscopic CBDE versus pre- or post-cholecystectomy ERCP

The use of laparoscopic CBDE has been steadily declining in the US in favor of the 2-stage approach using ERCP and cholecystectomy.[5] Despite both approaches exhibiting comparable

safety and efficacy, the 1-stage CBDE strategy seems superior in terms of shorter LOS, need for fewer procedures, and cost-effectiveness.[1,33,34] The current analyses found a lower overall risk of complications and a reduced LOS in patients undergoing CBDE compared to preERCP; however, CBDE and postERCP did not differ significantly. When comparing specific complications, CBDE had an 80% lower risk of pancreatitis than pre- and postERCP, whereas no differences were observed in the risk of hemorrhage, perforation, or infectious complications. The risk of bile leak was 3 times higher in CBDE patients compared to preERCP; nonetheless, this difference was not present when comparing CBDE to postERCP. The overall LOS was on average 2 days shorter in patients undergoing CBDE compared to preERCP. This is likely due to the logistical challenges of scheduling an ERCP, which is usually performed by gastroenterologists rather than surgeons. In summary, these results support a 1-stage CBDE approach over the 2-stage approaches.

iERCP vs. pre- or post-cholecystectomy ERCP

A Cochrane review from 2018 that included 5 randomized trials with a total of 517 patients (257 patients who underwent a rendezvous-ERCP and cholecystectomy and 260 patients who underwent a 2-stage approach) concluded that there was no difference between iERCP and preERCP in regards to the overall morbidity and mortality rates.[35] This is in line with recent studies comparing the two different approaches,[24] and mirrors the result of the current study. Pancreatitis, a feared complication resulting from accidentally canulating the pancreatic duct or the increased pressure caused by the contrast injection, occurs in up to 7% of ERCP cases.[36,37] However, the use of the rendezvous technique during iERCP is increasing,[6] which may mitigate this risk.[36] In a meta-analysis by Lin et al. that included 1,061 patients, of whom 542 underwent a rendezvous iERCP and 519 underwent a post-cholecystectomy ERCP, the authors reported a 74% decreased odds of post-procedural pancreatitis in patients managed

using the rendezvous technique (OR 0.26, 95% CI 0.12-0.54).[38] They also reported a decrease in overall morbidity (OR 0.41, 95% CI 0.27-0.62) and LOS [MD (days) -3.52, 95% CI: -4.69, -2.35]. Nevertheless, they did not identify any significant differences in bile leak or hemorrhage risk when comparing the two approaches.[38] Another meta-analysis undertaken by Arrezo et al. including 4 randomized studies comparing the rendezvous iERCP to a 2-stage approach, found an almost 50% decrease in the overall odds of complications (OR 0.56, 95% CI: 0.32-0.99, P=0.04) with a decrease in the odds of clinical pancreatitis by over 70% in the iERCP group (OR 0.33, 95% CI: 0.12-0.91, P=0.03).[39] In the current study, we did not observe a difference in the risk of pancreatitis between the iERCP and pre- or postERCP groups. This is likely explained by all types of iERCP being included, i.e., those performed with and without the rendezvous technique. Conversely, there was a decrease in the LOS by 3-days in the iERCP group compared to the preERCP group. These results favor a 1-stage iERCP approach over the 2-stage procedures.

Laparoscopic CBDE versus iERCP

Previous studies have found that the 1-stage CBDE and iERCP procedures are effective in CBD clearance compared to pre- or postERCP.[40] However, in a randomized clinical trial by Poh et al. the rate of retained stones was higher in patients managed using CBDE compared to iERCP (42% vs 15%).[34] In a network meta-analysis by Richi et al. investigating the safety-to-efficacy ratio, expressed as the ratio of morbidity to successful stone clearance, laparoscopic cholecystectomy with rendezvous iERCP was superior to the other three approaches.[40] However, the network geometrics suggested that two main comparisons were lacking: postERCP vs iERCP and preERCP vs. postERCP. Although the current network meta-analysis was unable to establish any differences in the overall rate of complications between CBDE and iERCP, there were significant differences in the risk of three specific complications:

pancreatitis, perforation, and bile leak. iERCP was associated with a higher risk of pancreatitis and perforation. This is expected given the risk of cannulation of the pancreatic duct and sphincterotomy associated perforation when performing an ERCP. Conversely, the risk of bile leak was significantly increased in patients who had undergone CBDE compared to iERCP. It is important to highlight most biliary leaks necessitate additional interventions either with percutaneous drainage or CBD stenting, which is carried out through an ERCP. Granular data on the management of complications were not available in the studies included in the current investigation and were also out of the scope of the current paper.

Studies investigating the LOS have either reported results that favor iERCP or have been unable to find any differences compared to CBDE.[34,41] The network meta-analysis in the current study indicated that iERCP was associated with a decrease in the total LOS by one day, on average, compared to CBDE.

Challenges in clinical practice and implementation

Currently, hospitals and acute care services offer widely different approaches for managing CBD stones, largely based on the logistics involved, the managing physicians' skillsets, and individual provider preference. At most institutions, ERCP is performed by gastroenterologists, which necessitates the coordination of resources between different services which can be time-consuming and incur the risk of delaying treatment. When resources are limited, such as during the COVID-19 pandemic, where most healthcare systems contended with a constant shortage of hospital beds, the 1-stage approach would theoretically have been beneficial in reducing the time from admission to discharge, although this would also need to factor in the potentially increased average operative time required for either iERCP or CBDE. Although out of the scope of the current study, intuitively, the 1-stage approaches could also reduce overall cost

and increase patient satisfaction. The Acute Care Surgery subspeciality in Europe and the United States is still evolving; thus, additional exploration of different approaches to treating CBD stone disease is required to improve patient care.

Limitations

There are several limitations to be highlighted in the current study. There is a risk of selection bias since the included studies were required to have a comparison of ≥2 of the procedures. Studies describing only one procedure were excluded as these descriptive studies lacked a comparison group, which is required for the meta-analysis. Furthermore, no distinction was made between choledocotomy or cholecystoscopy for CBDE, nor between iERCP performed using the rendezvous or traditional technique. Finally, the severity of complications was not available for further analysis. Nevertheless, to the authors' knowledge, this is the first study comparing common post-procedural complications and LOS across all four available interventions used for the management of CBD stones. The network meta-analysis allowed for a larger sample size, strengthening statistical power. Finally, a prospective randomized comparison of all four interventions for CBD stone management would be nearly impossible without introducing institutional biases or organizational and expertise limitations.

Conclusion

Our network meta-analysis suggests that both laparoscopic common bile duct exploration and intraoperative ERCP have equally good outcomes and may provide a preferable single-anesthesia patient pathway with a shorter overall length of hospital stay compared to the 2-stage approaches.

Supplemental Digital Content

Supplemental Digital Content 1: PRISMA checklist

Supplemental Digital Content 2: Supplemental figures not included in the full publication

Supplemental Digital Content 3: Reference list containing all studies included in the meta-analysis

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Figure legends:

Figure 1. Ranking of procedures
*Due to the low value calculated for preoperative ERCP in regard to length of stay, this bar is not visible in the figure.

Figure 2. Network meta-analysis of hospital length of stay

Figure 3. Network meta-analysis of the overall risk of complications

Figure 4. Network meta-analysis of the risk of post-procedure bile leak

Figure 5. Network meta-analysis of the risk of post-procedure pancreatitis

Figure 6. Network meta-analysis of the risk of perforation

Background

Common bile duct (CBD) stones are frequently encountered in the surgical practice of acute care surgeons. Up to 20% of patients requiring urgent cholecystectomy for acute cholecystitis have been found to have concomitant CBD stones.[1–3] Despite being a common surgical condition, the optimal management of CBD stones in the acute setting has been highly debated. In the last several decades, the surgical approach for treating complicated biliary calculous diseases has fundamentally changed from open to laparoscopic.[4,5] With the introduction of endoscopic retrograde cholangiopancreatography (ERCP) in 1968, the interventional approach to CBD stones shifted in favor of a 2-stage approach, either pre-cholecystectomy (preERCP) or post-cholecystectomy (postERCP).[4,5] More recently the 1-stage approach with intraoperative ERCP (iERCP) or laparoscopic CBD exploration (CBDE) by choledochoscopy and cholecystectomy has become a strong contender to the 1-stage open surgical CBDE, i.e., choledochotomy plus cholecystectomy.[6,7]

Since acute care surgeons commonly manage CBD stone-related conditions, it is important to establish evidence-based best practice for this patient population to improve resource allocation and training, decrease disease- and procedural-specific complications, as well as improve overall patient throughput in the hospital. Moreover, it is important to understand the application and associated outcomes of multiple different approaches to a complicated disease process such as choledocholithiasis so therapy can also be tailored to an individual center, surgeon, or patient.

To this end, we undertook a systematic review and network meta-analysis comparing the different treatment options for CBD stones. The main outcomes of interest were postoperative complications and hospital length of stay (LOS), when comparing the 1-stage and 2-stage approaches.

Methods

Eligibility criteria

This study was conducted according to the PRISMA guidelines (Supplementary Table 1).[8] No protocol was used for the systemic review. We included studies that met the following inclusion criteria: a) the study design was either an observational cohort study, case-control, or randomized control trial (RCT) investigating the management of choledocholithiasis; b) patients were managed using CBDE, iERCP, preERCP, or postERCP; c) the experimental group(s) and the control group received different treatments; d) the study recorded complications and/or LOS in all groups. Studies were excluded based on the following criteria: a) irrelevant studies; b) duplicate studies; c) unavailable data in the manuscript; d) studies unavailable in English or English-translation; e) studies for which a full-text was unavailable; f) studies not indexed by MEDLINE; g) previous systematic reviews and meta-analyses as well as reviews, letters, and case reports; h) the mean LOS was reported without a standard deviation (SD), or the median LOS was reported without an interquartile range (IQR).

Search methodology

PubMed, SCOPUS, MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were methodically searched from January 2010 to December 2021. The initial search was from 2000; however, since many of the studies included patients from the end of 1900's or very early in the 2000's, the decision was made to concentrate on the studies published from 2010 and beyond. The search terms were a combination of medical subject headings terms and the subsequent terms: Gallstone, Common Bile Duct (stone), Choledocholithiasis, Cholecystitis, Endoscopic Retrograde Cholangiography/ERCP, Common

Bile Duct Exploration, Intra-, Pre-, Peri-, and Post-operative Endoscopic Retrograde Cholangiography, Stone Extraction, One-stage- & Two-stage-procedure.

Study selection

Using the web-based software platform Covidence®, several investigators screened the original studies independently based on the previously mentioned inclusion and exclusion criteria. An initial review was performed of the article abstracts and titles, after which each reviewer would cast a vote using the software platform to include or exclude the study from further review. Votes from two independent investigators were required to include or exclude a study. Investigators performed a full-text review of the remaining articles after the initial screening. Studies that received votes for inclusion from two independent investigators were retained for the final analysis. Any discrepancies in voting were addressed by discussion or third- party consensus.

Data extraction

All data were extracted from eligible studies using a standardized protocol. The following information was retrieved: PubMed unique identifier; authors' names; publication year; the country where the study was conducted; study design; study subjects; the number of participants; the number of male and female participants; the range of years covered by the study; case and control procedure; the number of patients who underwent the case and control procedure; the number of patients lost to further analysis; the number of patients with and without any complication for the case and control procedures; the number of patients with and without a specific complication for the case and control procedures (these included bile leak, hemorrhage, pancreatitis, perforation, intraabdominal infections, and other infections); mean and standard deviation (SD) or median and interquartile range (IQR) for LOS.

Quality assessment

The risk of bias was evaluated in conjunction with the data extraction using the Cochrane Suggested Risk of Bias criteria for EPOC reviews: random sequence generation, allocation concealment, baseline outcome measurements similar, baseline characteristics similar, incomplete outcome data, knowledge of the allocated interventions adequately prevented during the study, protection against contamination, selective outcome reporting, and other risks of bias. A quality score was calculated for each study as the sum of the number of criteria that were classified as low risk. If a criterion could not be definitively classified as high or low risk, it was counted as half a point instead.

Outcomes

The primary outcomes of interest were the overall risk of complications and the total hospital LOS. The secondary outcomes of interest were the risk of bile leak, hemorrhage, pancreatitis, perforation, intraabdominal infections, and other infections.

Statistical analysis

The mean difference (MD) for LOS and corresponding standard error (SE) of MD were calculated using the following formulae:

$$MD = mean_1 - mean_2$$

$$SE_{MD} = \sqrt{\left(\frac{N_1 s_1^2 + N_2 s_2^2}{N_1 + N_2 - 2}\right)\left(\frac{N_1 + N_2}{N_1 N_2}\right)}$$

where *mean*, *s*, and *N* correspond to the mean LOS, SD of LOS, and number of patients, respectively. According to the Cochrane Handbook, if the median and IQR were provided

instead of the mean and SD, the mean and SD were estimated using the median and IQR.[9] An MD <0 indicates that treatment 1 has a shorter mean LOS than treatment 2. If the 95% confidence interval (CI) for the MD contains 0, there is no statistically significant difference between the treatment groups.

The risk ratio (RR) and corresponding SE of the natural log-transformed RR [log(RR)] were calculated using the extracted numbers according to the formulae below for all complications and specific complications:

$$RR = \frac{n_1/N_1}{n_2/N_2}$$

$$SE_{\log(RR)} = \sqrt{\frac{N_1 - n_1}{N_1 n_1} + \frac{N_2 - n_2}{N_2 n_2}}$$

where n_1 is the number of patients with complications in treatment group 1, N_1 is the total number of patients in treatment group 1, n_2 is the number of patients with complications in treatment group 2, and N_2 is the total number of patients in treatment group 2. According to the Cochrane Handbook, if n_1 or n_2 were 0, they were replaced by 0.5.[9] An RR < 1 indicates that treatment 1 had a lower risk for complication(s) than treatment 2. If the 95% CI for the RR contains 1 there is no statistically significant difference between the treatment groups.

The direct effect for every potential pair of treatments was evaluated using conventional meta-analyses. The Q test and I^2 index were used to evaluate the heterogeneity of each effect size. An I^2 index <50% indicates that the studies have good homogeneity, and the fixed-effects model was used; otherwise, a random- effects model was used. If an indirect effect between two treatments existed, it was derived using the method described by Dias et al. Subsequently,

a network meta-analysis was used to combine both the direct and indirect effects for comparison.[10]

The net splitting method was used to diagnose inconsistency between the direct and indirect effects.[11] The direct, indirect, and combined effects were presented using forest plots. The comparison-adjusted funnel plots were used to visualize the risk of publication bias in the network meta-analyses; the numerical Egger's test for publication bias was also employed where possible.[12] A ranking probability plot was used to rank the treatments (a high value indicates that the treatment might be better). The rank probability was calculated according to the method suggested by Rücker et al.[13]

The statistical analyses were completed in R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using packages meta, metaphor, and netmeta.[11,14,15]

Results

Study selection outcome and characteristics

The search identified 1,920 potential articles for inclusion, after excluding duplicates. 348 studies remained after the initial review of titles and abstracts. Finally, 16 studies (N= 8,644) addressing the LOS and 41 studies (N = 19,756) addressing post-procedural complications were retained for the analysis (Supplemental figure 1 and 2). The average ages of the participants included in these studies were 54.2 and 54.1 years for the LOS and post-procedural complications studies, respectively.

Study quality assessment

The quality of the included studies varied in terms of quality score (the total score is 10 with 10 reflecting the highest quality study) from 2.5 to 7.5, with a median score of 5.5.

Laparoscopic CBD Exploration compared to pre- or post-cholecystectomy ERCP

According to the rank probabilities, for overall complications and specific complications including bleeding, pancreatitis, and perforation, CBDE was better than pre- and postERCP (Figure 1). Regarding LOS, although the point estimate for CBDE indicated a longer LOS than postERCP, the difference was not statistically significant (MD=0.36; 95% CI: -1.26, 1.98; Figure 2). However, there was a significantly reduced LOS in the CBDE cohort compared to the preERCP cohort (MD= -2.02; 95 CI%: -3.04, -1.01; Figure 2). The relative risk of all complications was also reduced in the CBDE cohort compared to the preERCP group (RR=0.77; 95% CI: 0.59, 0.99; Figure 3), whereas no difference was observed compared to the postERCP group. The risk of bile leak was 3 times higher in the CBDE group compared to preERCP (RR=3.31; 95% CI: 2.00, 5.46; Figure 4), while no difference was found when comparing CBDE to postERCP (RR=1.37; 95% CI: 0.68, 2.78; Figure 4). The risk of pancreatitis was reduced by almost 80% in the CBDE group compared to both preERCP (RR=0.22; 95% CI: 0.12, 0.40; Figure 5) and postERCP (RR=0.24; 95% CI: 0.13, 0.46; Figure 5). No difference was detected in the risk of iatrogenic perforation (Figure 6), hemorrhage (Supplemental Figure 3), intraabdominal infections (Supplemental Figure 4), or other infections (Supplemental Figure 5) between pre- or postERCP and CBDE.

Intraoperative ERCP compared to pre- and post-cholecystectomy ERCP

Regarding LOS and the overall risk of complications, iERCP was superior to both pre- and postERCP according to the rank probabilities (Figure 1). According to the rank probabilities,

iERCP was also better than pre- or postERCP for intraabdominal infections (Figure 1). The network meta-analysis demonstrated a significantly reduced LOS in the iERCP cohort compared to the preERCP cohort (MD=-3.12; 95% CI: -3.91, -2.32; Figure 2), but no statistical difference compared to postERCP group (Figure 2). Although the point estimates for the iECRP cohort indicated a lower overall risk of complications compared to pre- and postERCP, the results were not statistically significant (Figure 3). The risk of bile leak was almost halved in the iERCP cohort compared to the postERCP group (RR=0.56; 95% CI: 0.37, 0.84; Figure 4); however, no statistically significant difference was detected when iERCP was compared to the preERCP (RR=1.35; 95% CI: 0.80, 2.27; Figure 4). The risk of intraabdominal infections was lower after iERCP compared to postERCP (RR=0.65; 95% CI: 0.44, 0.94; Supplemental figure 4). There was no statistically significant difference detected in the risk of pancreatitis (Figure 5), iatrogenic perforation (Figure 6), hemorrhage (Supplemental figure 3), or other infections (Supplemental figure 5) when comparing iECRP with pre- and postERCP cohorts.

Laparoscopic CBD exploration compared to Intraoperative ERCP

iERCP demonstrated a higher probability of being better than CBDE in terms of LOS (Figure 1), with a significantly lower LOS than CBDE (MD=-1.09; 95% CI: -2.15, -0.04; Figure 2). Regarding the overall risk of complications, CBDE was better than iERCP based on the rank probabilities (Figure 1). However, the difference was not statistically significant (RR=0.94; 95% CI: 0.70, 1.26; Figure 3). For specific complications, CBDE was superior to iERCP regarding the risk of hemorrhage, pancreatitis, and perforation (Figure 1). CBDE was associated with twice the risk of bile leak compared to iERCP (RR=2.45; 95% CI: 1.33, 4.52; Figure 4). The relative risk of pancreatitis was reduced by 78% in the CBDE cohort compared to the iERCP cohort (RR=0.22; 95% CI: 0.12, 0.41; Figure 5). The risk of iatrogenic perforation was reduced by 86% in patients who underwent CBDE (RR =0.14; 95% CI: 0.02, 0.93; Figure

6); however, this was only based on the indirect comparison. There was no statistically significant difference detected in the risk of hemorrhage (Supplemental figure 3), intraabdominal infections (Supplemental figure 4), or other infections (Supplemental figure 5), when comparing CBDE and iERCP.

Publication bias

Funnel plots of all the studies included as a part of the network meta- analysis were created to graphically determine the presence of publication bias (Supplemental figure 6-13). In general, studies were distributed within or close to the 95% confidence interval for all outcomes, which indicated a homogenous distribution of the study results. The non-significant p-values derived from Egger's test further support this conclusion. Collectively, these results indicate no statistically significant publication bias in the included articles that would impact the meta-analysis estimates of effect size.

Discussion

There is consensus that timely management is critical for treating CBD stones, particularly those that are symptomatic, while improving patient throughput in the hospital. However, a single optimal management strategy has yet to be defined in the acute care setting.

Watchful waiting

It is important to recognize that even asymptomatic CBD stones confer a high risk of complications. In a cohort of patients with incidental CBD stones diagnosed by imaging in

asymptomatic patients, biliary complications developed in 6.1% of patients after one year, 11% after three years, and 17% after five years.[16] Unfavorable outcomes have also been reported in 16%-36% of patients when no intervention was undertaken for CBD stones diagnosed by intraoperative cholangiogram (IOC), depending on the size of the calculi.[17] These results are in line with a recent population-based registry study from Sweden conducted by Johansson et al. comparing surveillance to intervention for CBD stones found on IOC.[18] They reported a 5-fold increase in the risk of needing to perform an unplanned postERCP due to retained stone(s) in the surveillance group compared to the intervention group [adjusted HR 5.5 (95% CI: 4.8-6.4), p<0.005]. For smaller stones (<4mm in diameter), the risk of an unplanned postERCP was 3 times higher in the surveillance group [adjusted HR 3.5 (95% CI: 2.4-5.1), p<0.005].[18] However, there is still an ongoing debate about the ideal approach and value to a "wait-and-see" approach for entirely asymptomatic CBD stones that are discovered only on imaging or by intraoperative cholangiography, where multiple series have demonstrated the majority of these stones will pass spontaneously and will not require further intervention or hospitalization.[19–21] Nevertheless, most patients with CBD calculi admitted to acute care surgical services present with one or more symptoms and conditions related to the presence of CBD stone(s), such as abdominal pain, jaundice, cholecystitis, cholangitis, and pancreatitis, which necessitates an active rather than a "wait-and-see" approach.

ERCP without cholecystectomy

Cholecystectomy after ERCP for CBD stones has been widely debated, especially in the elderly.[22] Deferring post-ERCP cholecystectomy has been associated with higher rates of morbidity and readmissions.[23–25] Over 25% of cases eventually require a cholecystectomy.[22,25] In a meta-analysis that included 1,605 patients, 864 (53.8%) had their cholecystectomy deferred following ERCP with sphincterotomy, of whom 26% required a cholecystectomy.[25]

Furthermore, a total of 37% of patients with in-situ gallbladders suffered a complication from remaining stones. Compared to a prophylactic cholecystectomy, deferred cholecystectomy resulted in a significantly increased risk of mortality [odds ratio (OR) 2.56 (95% CI 1.54-4.23), P<0.0001]. Patients who did not undergo a prophylactic cholecystectomy were also more likely to develop recurrent biliary pain and cholecystitis [OR 5.10 (95% CI 3.39-7.67), P<0.0001]. However, the rate of pancreatitis [OR 3.11 (95% CI 0.99-9.83), P=0.053] and cholangitis [OR 1.49 (95% CI 0.74-2.98), P=0.264] was unaffected.[25] These findings favor performing post-ERCP cholecystectomy, preferably during the index admission rather than as a postponed elective operation.

In practice, most patients deferred from an index admission cholecystectomy are older, burdened by comorbidities, and frail, which makes managing CBD stone-related complications even more challenging.[22,24–26] With a growing elderly patient population worldwide, gallstone-related diseases and interventions will also increase; this includes cholecystectomy for acute cholecystitis, which has a 3-fold higher risk of CBD stones than elective cholecystectomy.[27,28] Currently, guidelines do not make a distinction in the optimal timing of acute cholecystectomy for cholecystitis when comparing elderly and younger patients. Instead, surgery during the index admission is recommended for all ages, where no absolute contraindication to surgery exists.[29,30] Even in octogenarians, post-ERCP laparoscopic cholecystectomy has been shown to be safe.[31] Nevertheless, the risks associated with a more technically challenging operation post-ERCP should not be underestimated and decision about surgery versus observation should be tailored to the patient and the individual risk-benefit analysis.[32]

Laparoscopic CBDE versus pre- or post-cholecystectomy ERCP

The use of laparoscopic CBDE has been steadily declining in the US in favor of the 2-stage approach using ERCP and cholecystectomy.[5] Despite both approaches exhibiting comparable

safety and efficacy, the 1-stage CBDE strategy seems superior in terms of shorter LOS, need for fewer procedures, and cost-effectiveness.[1,33,34] The current analyses found a lower overall risk of complications and a reduced LOS in patients undergoing CBDE compared to preERCP; however, CBDE and postERCP did not differ significantly. When comparing specific complications, CBDE had an 80% lower risk of pancreatitis than pre- and postERCP, whereas no differences were observed in the risk of hemorrhage, perforation, or infectious complications. The risk of bile leak was 3 times higher in CBDE patients compared to preERCP; nonetheless, this difference was not present when comparing CBDE to postERCP. The overall LOS was on average 2 days shorter in patients undergoing CBDE compared to preERCP. This is likely due to the logistical challenges of scheduling an ERCP, which is usually performed by gastroenterologists rather than surgeons. In summary, these results support a 1-stage CBDE approach over the 2-stage approaches.

iERCP vs. pre- or post-cholecystectomy ERCP

A Cochrane review from 2018 that included 5 randomized trials with a total of 517 patients (257 patients who underwent a rendezvous-ERCP and cholecystectomy and 260 patients who underwent a 2-stage approach) concluded that there was no difference between iERCP and preERCP in regards to the overall morbidity and mortality rates.[35] This is in line with recent studies comparing the two different approaches,[24] and mirrors the result of the current study. Pancreatitis, a feared complication resulting from accidentally canulating the pancreatic duct or the increased pressure caused by the contrast injection, occurs in up to 7% of ERCP cases.[36,37] However, the use of the rendezvous technique during iERCP is increasing,[6] which may mitigate this risk.[36] In a meta-analysis by Lin et al. that included 1,061 patients, of whom 542 underwent a rendezvous iERCP and 519 underwent a post-cholecystectomy ERCP, the authors reported a 74% decreased odds of post-procedural pancreatitis in patients managed

using the rendezvous technique (OR 0.26, 95% CI 0.12-0.54).[38] They also reported a decrease in overall morbidity (OR 0.41, 95% CI 0.27-0.62) and LOS [MD (days) -3.52, 95% CI: -4.69, -2.35]. Nevertheless, they did not identify any significant differences in bile leak or hemorrhage risk when comparing the two approaches.[38] Another meta-analysis undertaken by Arrezo et al. including 4 randomized studies comparing the rendezvous iERCP to a 2-stage approach, found an almost 50% decrease in the overall odds of complications (OR 0.56, 95% CI: 0.32-0.99, P=0.04) with a decrease in the odds of clinical pancreatitis by over 70% in the iERCP group (OR 0.33, 95% CI: 0.12-0.91, P=0.03).[39] In the current study, we did not observe a difference in the risk of pancreatitis between the iERCP and pre- or postERCP groups. This is likely explained by all types of iERCP being included, i.e., those performed with and without the rendezvous technique. Conversely, there was a decrease in the LOS by 3-days in the iERCP group compared to the preERCP group. These results favor a 1-stage iERCP approach over the 2-stage procedures.

Laparoscopic CBDE versus iERCP

Previous studies have found that the 1-stage CBDE and iERCP procedures are effective in CBD clearance compared to pre- or postERCP.[40] However, in a randomized clinical trial by Poh et al. the rate of retained stones was higher in patients managed using CBDE compared to iERCP (42% vs 15%).[34] In a network meta-analysis by Richi et al. investigating the safety-to-efficacy ratio, expressed as the ratio of morbidity to successful stone clearance, laparoscopic cholecystectomy with rendezvous iERCP was superior to the other three approaches.[40] However, the network geometrics suggested that two main comparisons were lacking: postERCP vs iERCP and preERCP vs. postERCP. Although the current network meta-analysis was unable to establish any differences in the overall rate of complications between CBDE and iERCP, there were significant differences in the risk of three specific complications:

pancreatitis, perforation, and bile leak. iERCP was associated with a higher risk of pancreatitis and perforation. This is expected given the risk of cannulation of the pancreatic duct and sphincterotomy associated perforation when performing an ERCP. Conversely, the risk of bile leak was significantly increased in patients who had undergone CBDE compared to iERCP. It is important to highlight most biliary leaks necessitate additional interventions either with percutaneous drainage or CBD stenting, which is carried out through an ERCP. Granular data on the management of complications were not available in the studies included in the current investigation and were also out of the scope of the current paper.

Studies investigating the LOS have either reported results that favor iERCP or have been unable to find any differences compared to CBDE.[34,41] The network meta-analysis in the current study indicated that iERCP was associated with a decrease in the total LOS by one day, on average, compared to CBDE.

Challenges in clinical practice and implementation

Currently, hospitals and acute care services offer widely different approaches for managing CBD stones, largely based on the logistics involved, the managing physicians' skillsets, and individual provider preference. At most institutions, ERCP is performed by gastroenterologists, which necessitates the coordination of resources between different services which can be time-consuming and incur the risk of delaying treatment. When resources are limited, such as during the COVID-19 pandemic, where most healthcare systems contended with a constant shortage of hospital beds, the 1-stage approach would theoretically have been beneficial in reducing the time from admission to discharge, although this would also need to factor in the potentially increased average operative time required for either iERCP or CBDE. Although out of the scope of the current study, intuitively, the 1-stage approaches could also reduce overall cost

and increase patient satisfaction. The Acute Care Surgery subspeciality in Europe and the United States is still evolving; thus, additional exploration of different approaches to treating CBD stone disease is required to improve patient care.

Limitations

There are several limitations to be highlighted in the current study. There is a risk of selection bias since the included studies were required to have a comparison of ≥2 of the procedures. Studies describing only one procedure were excluded as these descriptive studies lacked a comparison group, which is required for the meta-analysis. Furthermore, no distinction was made between choledocotomy or cholecystoscopy for CBDE, nor between iERCP performed using the rendezvous or traditional technique. Finally, the severity of complications was not available for further analysis. Nevertheless, to the authors' knowledge, this is the first study comparing common post-procedural complications and LOS across all four available interventions used for the management of CBD stones. The network meta-analysis allowed for a larger sample size, strengthening statistical power. Finally, a prospective randomized comparison of all four interventions for CBD stone management would be nearly impossible without introducing institutional biases or organizational and expertise limitations.

Conclusion

Our network meta-analysis suggests that both laparoscopic common bile duct exploration and intraoperative ERCP have equally good outcomes and may provide a preferable single-anesthesia patient pathway with a shorter overall length of hospital stay compared to the 2-stage approaches.

Supplemental Digital Content

Supplemental Digital Content 1: PRISMA checklist

Supplemental Digital Content 2: Supplemental figures not included in the full publication

Supplemental Digital Content 3: Reference list containing all studies included in the meta-analysis

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Figure legends:

Figure 1. Ranking of procedures
*Due to the low value calculated for preoperative ERCP in regard to length of stay, this bar is not visible in the figure.

Figure 2. Network meta-analysis of hospital length of stay

Figure 3. Network meta-analysis of the overall risk of complications

Figure 4. Network meta-analysis of the risk of post-procedure bile leak

Figure 5. Network meta-analysis of the risk of post-procedure pancreatitis

Figure 6. Network meta-analysis of the risk of perforation

Figure 1

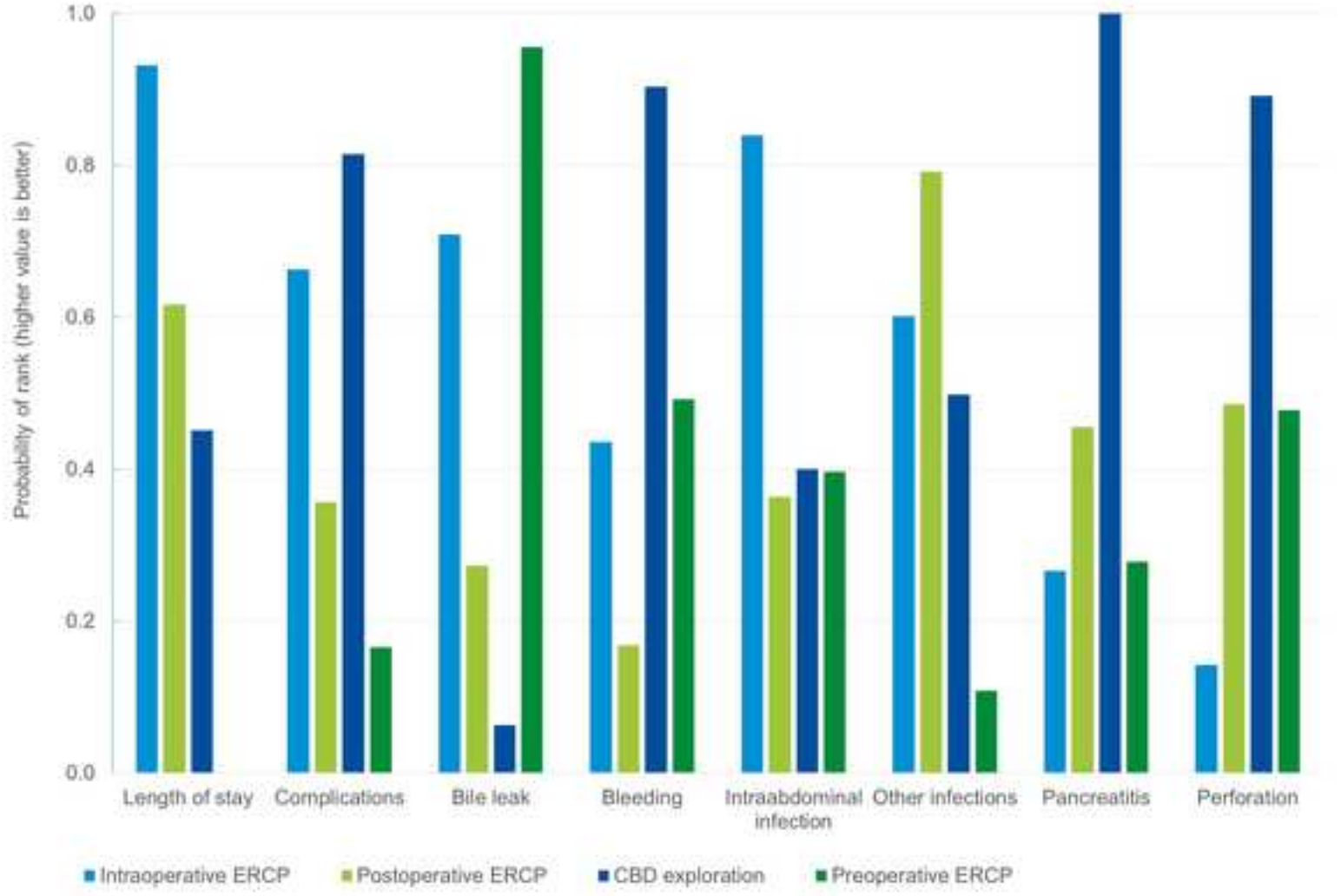


Figure 2

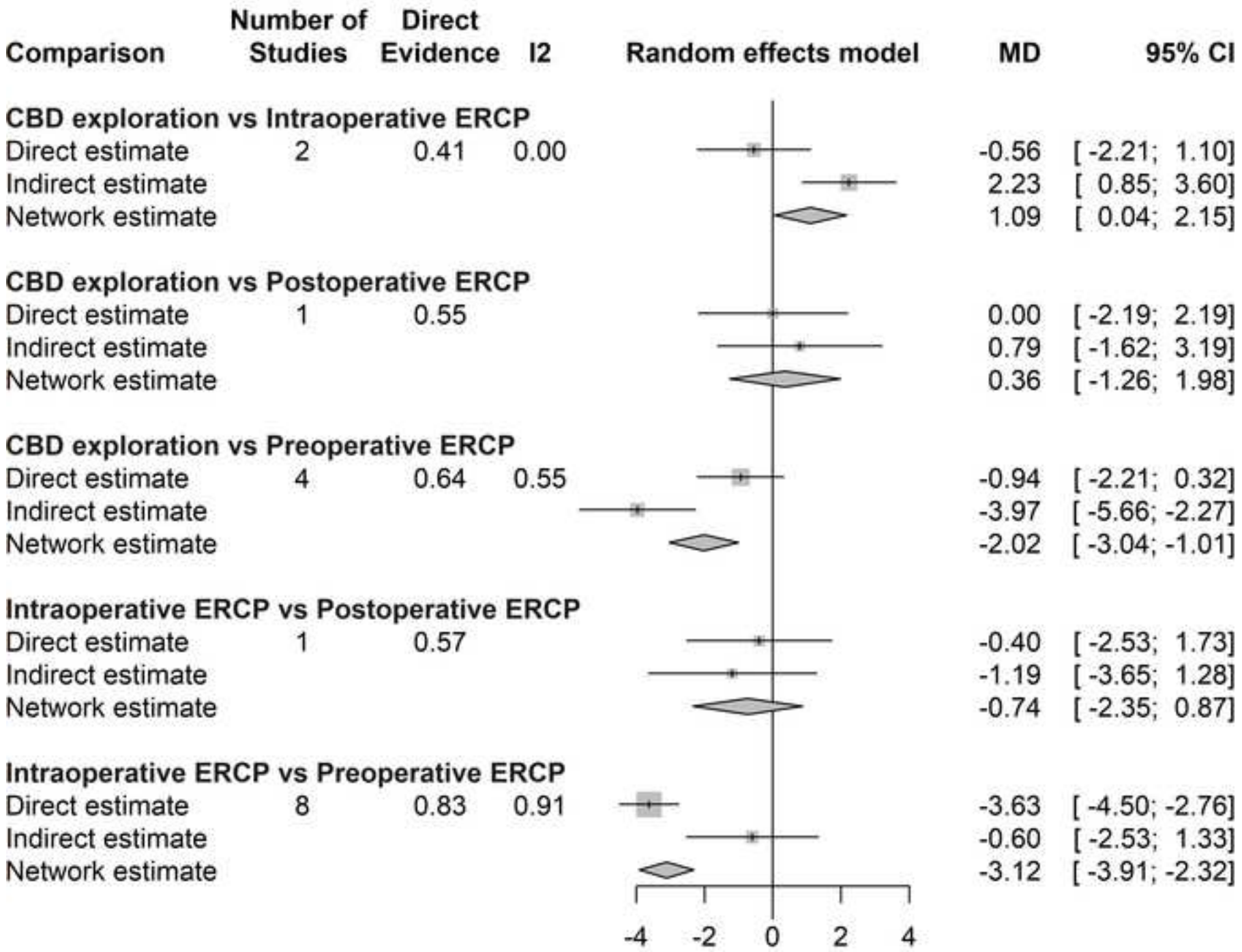


Figure 3

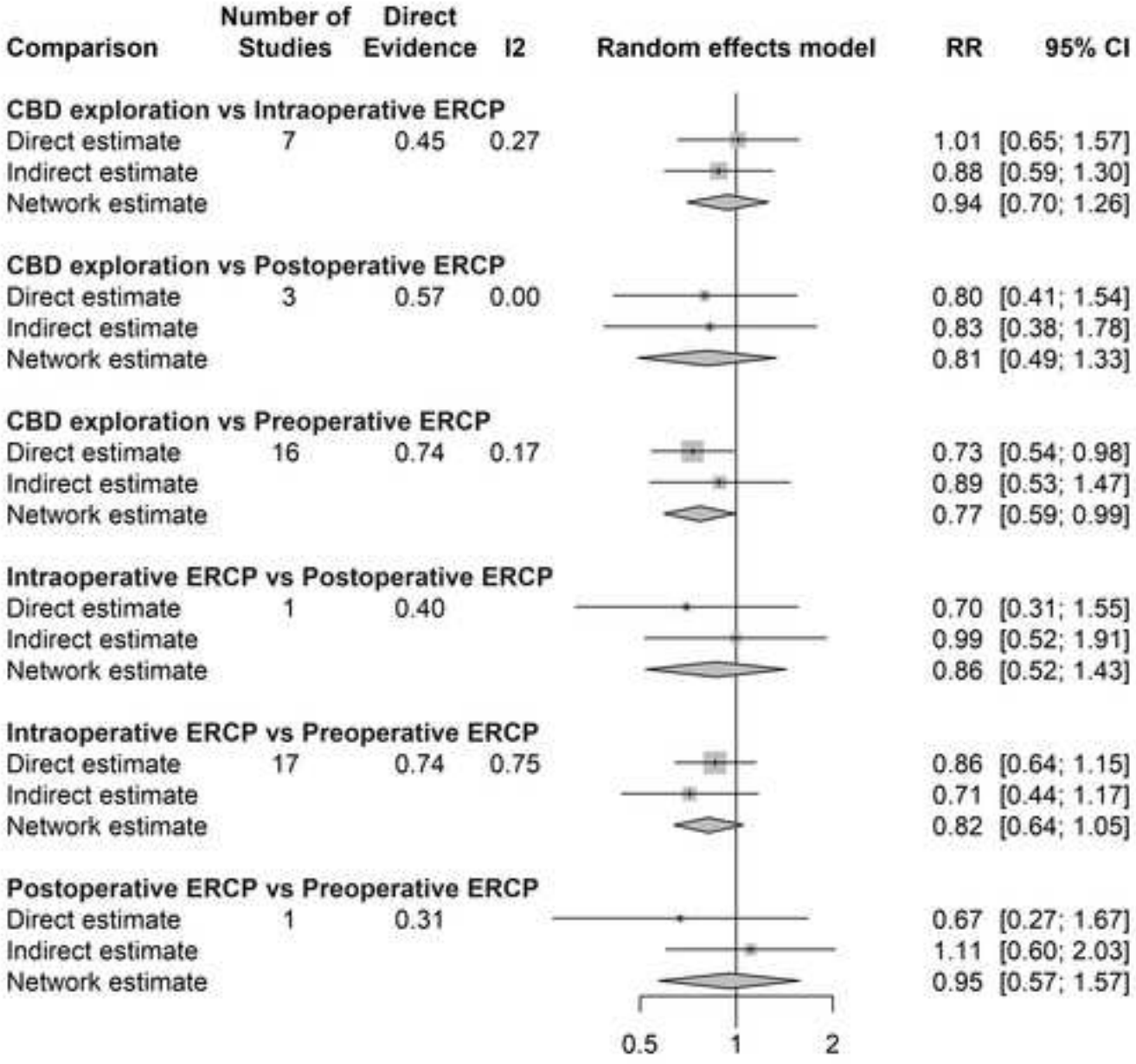


Figure 4

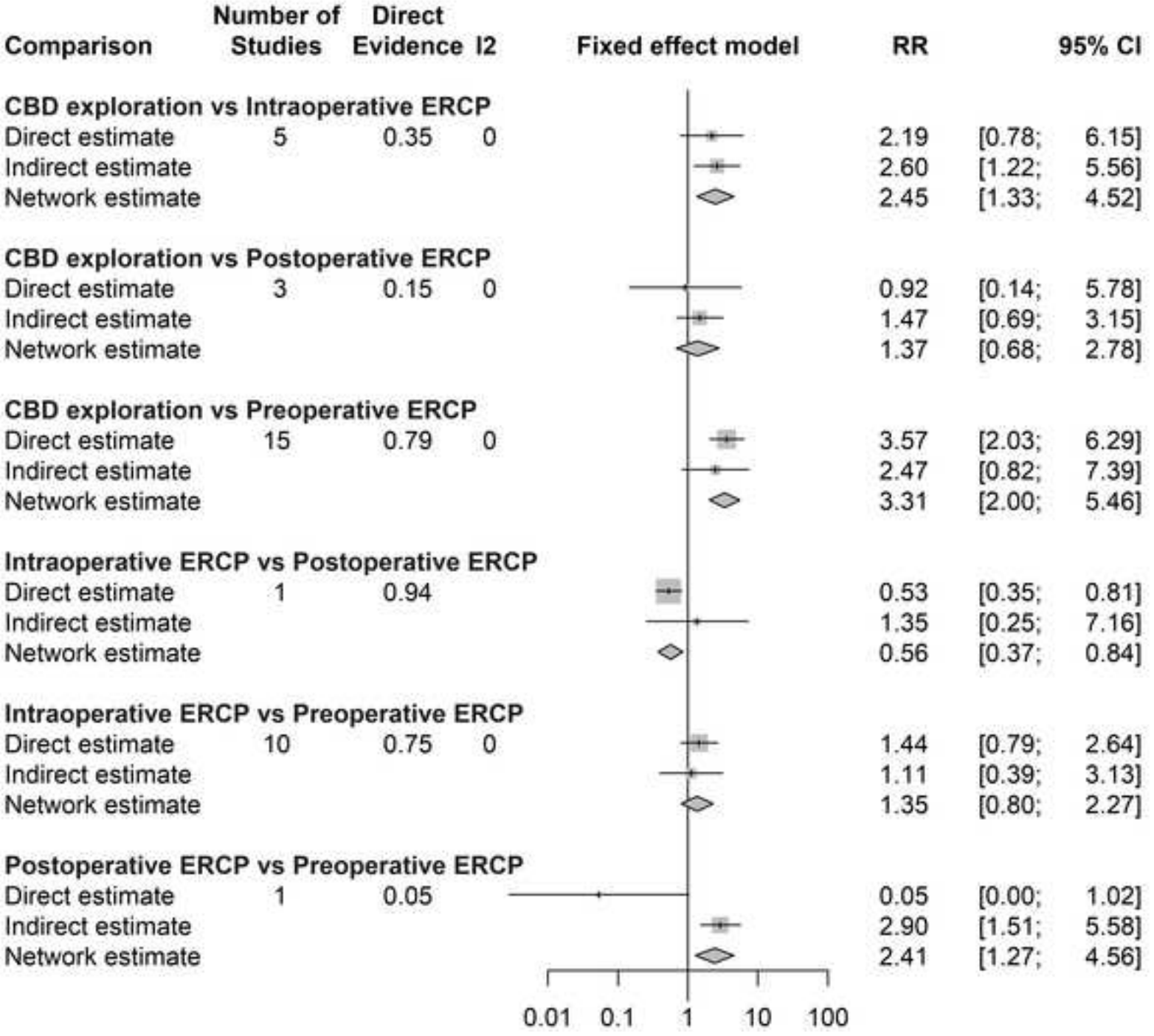


Figure 5

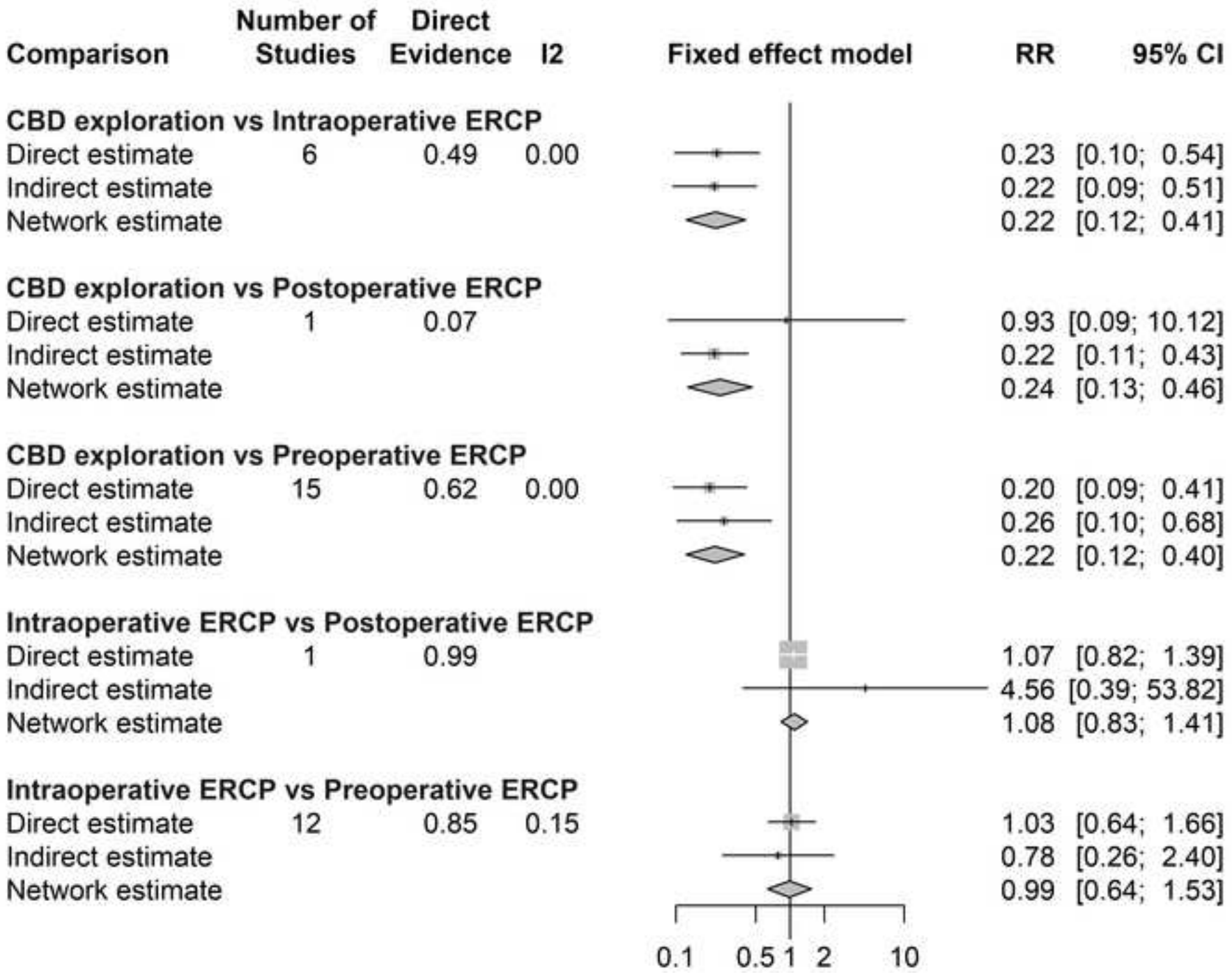
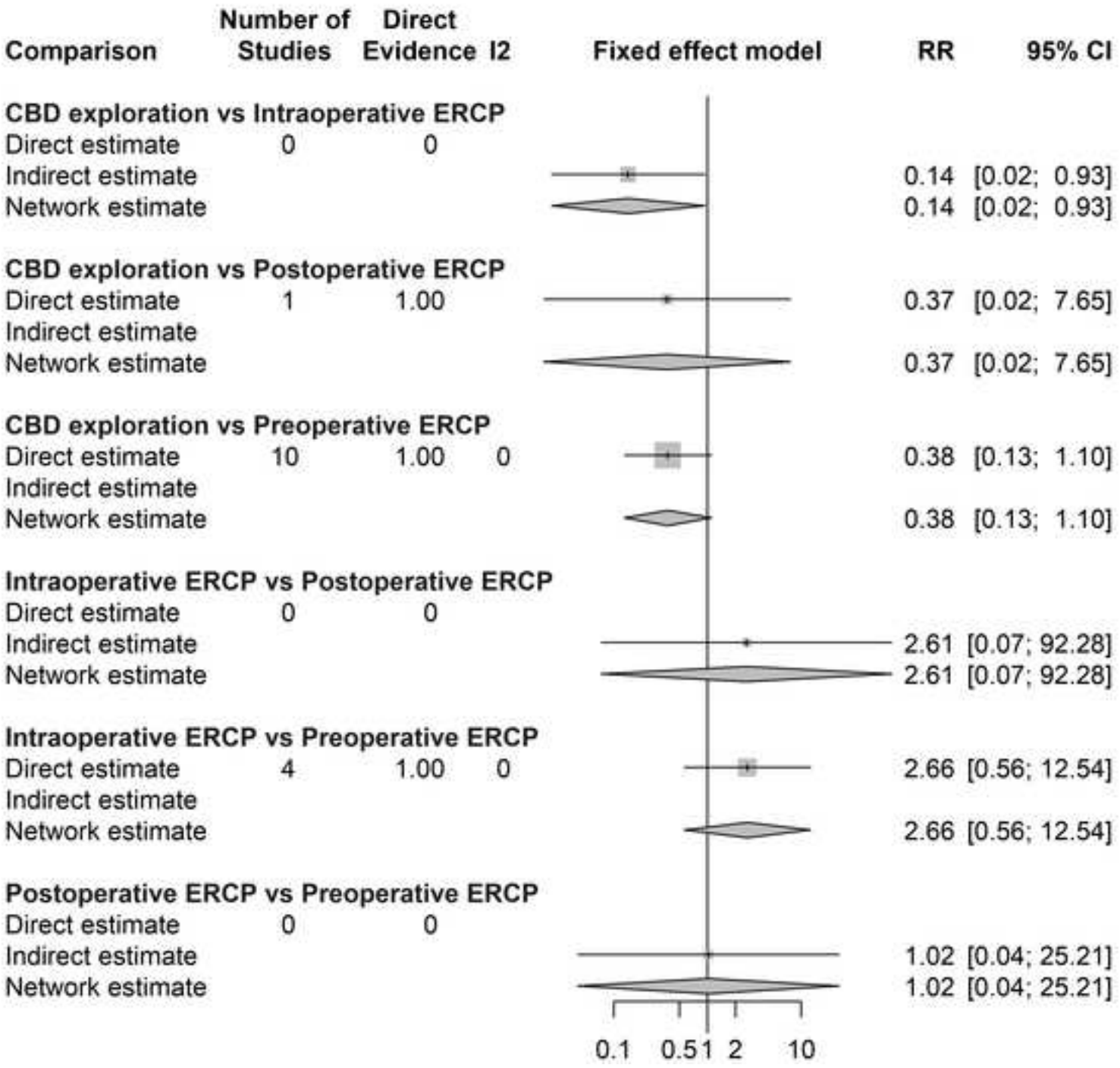


Figure 6



Supplemental Digital Content 3

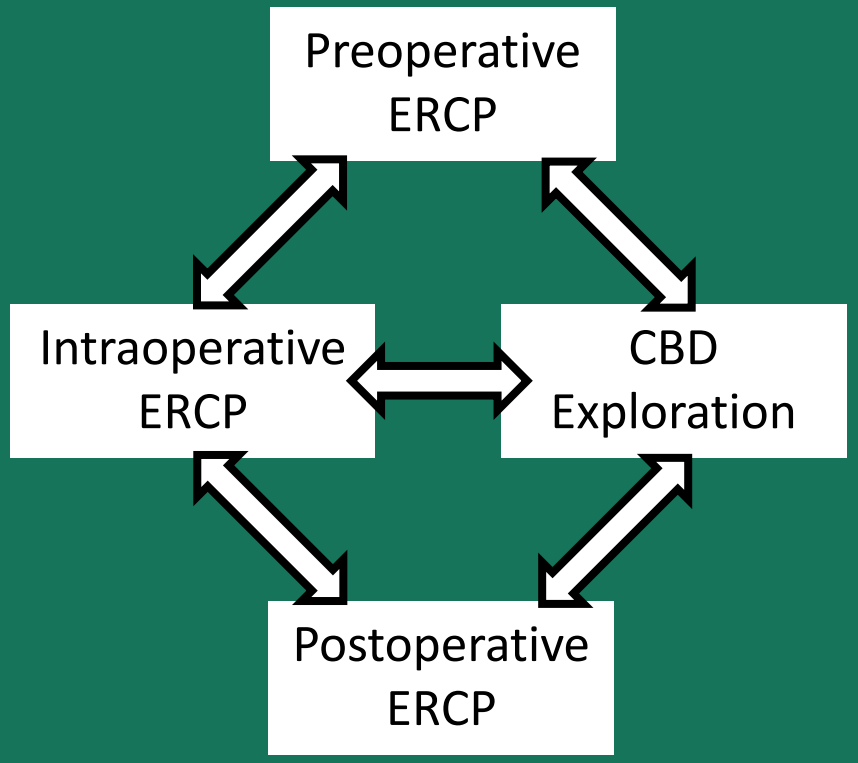
Visual Abstract

Common Bile Duct Stones (CBD) Management: A Network Meta-analysis

Comparing CBD Management

42 studies from 2010-2020

Network Meta-Analysis



*Operative = Laparoscopic Cholecystectomy

Conclusions

Decreased Length of Hospital Stay for 1-stage procedures

Different complication profiles

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