

SYSTEMATIC REVIEWS AND META-ANALYSES

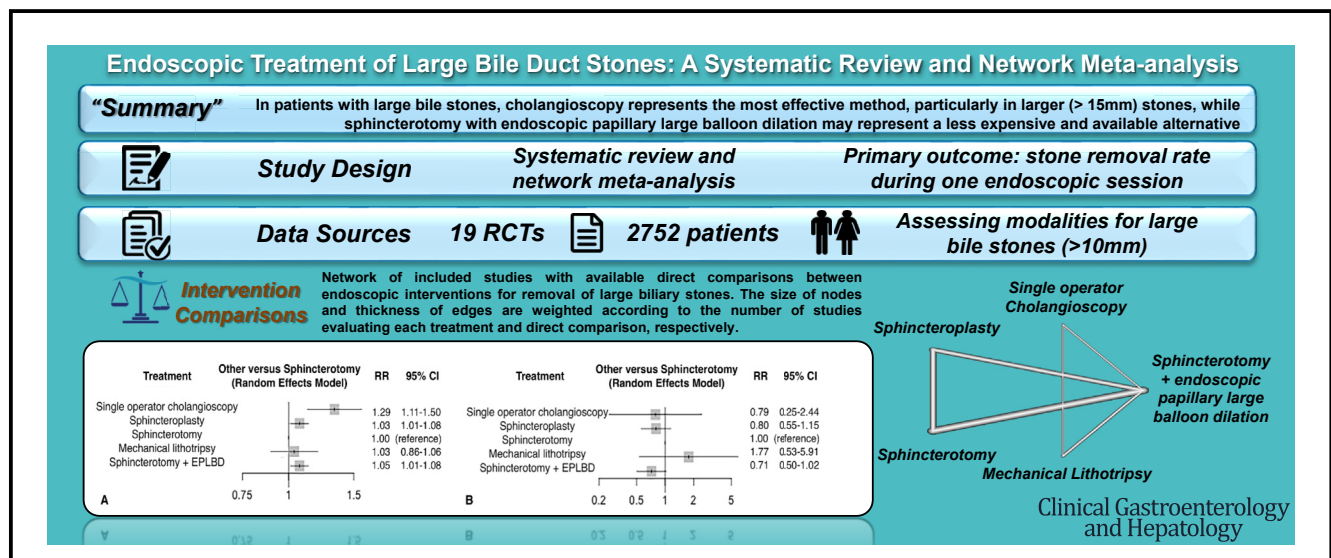
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Endoscopic Treatment of Large Bile Duct Stones: A Systematic Review and Network Meta-Analysis



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BACKGROUND & AIMS:

Several endoscopic methods have been proposed for the treatment of large biliary stones. We assessed the comparative efficacy of these treatments through a network meta-analysis.

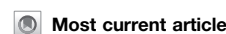
METHODS:

Nineteen randomized controlled trials (2752 patients) comparing different treatments for management of large bile stones (>10 mm) (endoscopic sphincterotomy, balloon sphincteroplasty, sphincterotomy followed by endoscopic papillary large balloon dilation [S+EPLBD], mechanical lithotripsy, single-operator cholangioscopy [SOC]) with each other were identified. Study outcomes were the success rate of stone removal and the incidence of adverse events. We

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Abbreviations used in this paper: AE, adverse event; CBD, common bile duct; EPLBD, endoscopic papillary large balloon dilation; ERCP, endoscopic retrograde cholangiopancreatography; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NNT, number needed to treat; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; RCT, randomized controlled trial; RR,

risk ratio; SOC, single-operator cholangioscopy; S+EPLBD, sphincterotomy plus endoscopic papillary large balloon dilation; SUCRA, surface under the cumulative ranking.



performed pairwise and network meta-analysis for all treatments, and used Grading of Recommendations, Assessment, Development, and Evaluation criteria to appraise the quality of evidence.

RESULTS:

All treatments except mechanical lithotripsy significantly outperformed sphincterotomy in terms of stone removal rate (risk ratio [RR], 1.03–1.29). SOC was superior to other adjunctive interventions (vs balloon sphincteroplasty [RR, 1.24; 95% CIs, 1.07–1.45], vs S+EPLBD [RR, 1.23; range, 1.06–1.42] and vs mechanical lithotripsy [RR, 1.34; range, 1.14–1.58]). Cholangioscopy ranked the highest in increasing the success rate of stone removal (surface under the cumulative ranking [SUCRA] score, 0.99) followed by S+EPLBD (SUCRA score, 0.68). SOC and S+EPLBD outperformed the other modalities when only studies reporting on stones greater than 15 mm were taken into consideration (SUCRA scores, 0.97 and 0.71, respectively). None of the assessed interventions was significantly different in terms of adverse event rate compared with endoscopic sphincterotomy or with other treatments. Post-ERCP pancreatitis and bleeding were the most frequent adverse events.

CONCLUSIONS:

Among patients with large bile stones, cholangioscopy represents the most effective method, in particular in patients with larger (>15 mm) stones, whereas S+EPLBD could represent a less expensive and more widely available alternative.

Keywords: GRADE; ERCP; Biliary; Sphincterotomy; Pancreatitis.

Endoscopic retrograde cholangiopancreatography (ERCP) is the treatment of choice for the management of common bile duct (CBD) stones, usually through biliary sphincterotomy and removal using balloons or baskets.¹ However, difficult bile duct stones (ie, stones >10 mm in diameter, barrel-shaped stones, or stones in patients with a tapered bile duct) represent a challenge, even for highly experienced endoscopists, and are associated with the frequent need for additional interventions such as mechanical lithotripsy or cholangioscopy-assisted lithotripsy for fragmentation and stone retrieval.² Beyond mechanical lithotripsy, endoscopic papillary large balloon dilatation (EPLBD), either with or without previous endoscopic biliary sphincterotomy and single-operator cholangioscopy (SOC) with laser lithotripsy or electrohydraulic lithotripsy, also have been proposed to tackle cases of difficult extraction. Currently, international guidelines recommend a limited sphincterotomy followed by EPLBD as the first-line approach to difficult biliary stones because it decreases the need for mechanical lithotripsy by 30% to 50% with similar success rates compared with endoscopic sphincterotomy alone,^{3–5} but with a lower incidence of adverse events compared with large sphincterotomy.⁶ On the other hand, the development of SOC during the past few years has led to its implementation, combined with laser or electrohydraulic lithotripsy, for the treatment of difficult bile duct stones, with an estimated stone clearance of 88%. This clearance rate can be increased further up to 100% after multiple sessions and the technique is associated with a favorable safety profile.⁷ Mainly because of its costs, SOC + laser lithotripsy/electrohydraulic lithotripsy currently is recommended after failure to achieve complete stone clearance using EPLBD and/or mechanical lithotripsy.⁶ There is still limited evidence on the

comparative efficacy of the aforementioned techniques, based mainly on traditional pairwise meta-analyses, whereas a previous network meta-analysis did not evaluate the specific setting of large/difficult CBD stones,⁸ and randomized-controlled trials (RCTs) on SOC were either not available or not taken into consideration. In contrast to pairwise meta-analyses, network meta-analysis can provide evidence about the comparative effectiveness of multiple interventions and synthesize available data across a network of RCTs, highlighting its utility for gathering comparative clinical data to guide everyday clinical practice. This systematic review and network meta-analysis compared the efficacy and safety of different endoscopic techniques for the management of patients with large CBD stones.

Methods

This systematic review and network meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement⁹ and the report of the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons Good Research Practices.¹⁰

Selection Criteria

Studies included in this meta-analysis were RCTs that met the following inclusion criteria: (1) patients: adults (age, >18 y) undergoing ERCP for removal of large (≥ 10 mm) CBD stones; (2) intervention: endoscopic techniques for stone removal including endoscopic sphincterotomy, balloon sphincteroplasty, sphincterotomy followed by EPLBD (S+EPLBD), mechanical lithotripsy,

and SOC; (3) comparator: another of the earlier-reported methods; and (4) outcomes: the primary outcome was the rate of successful stone removal during 1 endoscopic session, while the incidence of adverse events was the secondary outcome. For the purposes of this study, any trial clearly reporting data on the primary outcome was considered eligible to be included in the analysis. Non-comparative observational and retrospective studies, studies published as abstracts, and trials assessing stone removal in CBD stones smaller than 10 mm or not clearly reporting the primary outcome for stones 10 mm or larger were excluded.

Definitions

Regarding the applied endoscopic techniques, endoscopic sphincterotomy was defined as any cut performed from the papillary orifice up to the duct-duodenal junction, while the same definition applied for sphincterotomy followed by EPLBD. Moreover, balloon sphincteroplasty was defined as any sphincteroplasty performed using a 10-mm or larger controlled radial expansion balloon, while mechanical lithotripsy-assisted and SOC-assisted stone extraction were defined as the use of a mechanical lithotripter and the use of a cholangioscopy-assisted lithotripsy (laser or electrohydraulic) to achieve stone extraction, respectively.

Search Strategy

The search strategy was designed and conducted by an experienced medical librarian (J.L.) with input from study investigators, using various databases with variant-controlled vocabularies, expanded terminology, varying algorithms, and keyword capabilities, for RCTs of different methods for removal of large CBD stones published from inception through May 2021. A complementary manual search was performed on additional databases (Google Scholar, Cochrane library) and by checking the references of all main review articles on this topic to identify possible additional eligible studies. In cases of repetitive publications from the same population, only the most recent and complete article was taken into consideration. Two investigators (A.F. and P.G.) independently evaluated the studies for eligibility and resolved any disagreements through discussion and consensus. When no agreement could be reached, a third investigator (S.F.C.) determined the eligibility. The detailed PubMed search strategy is reported in [Supplementary Table 1](#).

Data Abstraction and Quality Assessment

Data on study-, patient-, and treatment-related characteristics were abstracted onto a standardized form by 3 authors independently (A.F., P.G., and G.T.). The following data were abstracted: first author, year of

What You Need to Know

Background

Management of large biliary stones is challenging, even for experienced endoscopists. Many treatment options exist but it is not clear which technique provides the most effective and safest stone clearance.

Findings

Network meta-analysis concluded that single-operator cholangioscopy was most effective for difficult stone removal, followed by large sphincterotomy plus endoscopic papillary large balloon dilation.

Implications for patient care

Single-operator cholangioscopy is the most effective method for large bile stone management, while sphincterotomy followed by endoscopic papillary large balloon dilation provides an excellent, less expensive, and widely available option, especially for index endoscopic retrograde cholangiopancreatographies.

publication, country in which the study was conducted, study period, number of participants, follow-up period, age and sex of patients, characteristics of the stones (size and number), type of endoscopic technique used, successful stone removal rate, and adverse events, including bleeding, perforation, post-ERCP pancreatitis (PEP), acute cholangitis, and death. The risk of bias of individual studies was assessed using the Cochrane Risk of Bias assessment tool.¹¹

Statistical Analysis

For both outcomes of interest direct meta-analyses were performed using a random-effects model to estimate the pooled relative risk (RR) and 95% CI.¹² We assessed statistical heterogeneity using the I^2 statistic, with values greater than 50% indicating significant heterogeneity, and small study effects were assessed by examining funnel plot asymmetry.¹³ Direct comparisons were performed using RevMan v5.3 (Cochrane Collaboration, Copenhagen, Denmark). Next, we conducted network meta-analyses, for both outcomes, using a multivariate random-effects meta-regression as described elsewhere.¹⁴ We used a frequentist approach based on a random-effects consistency model and provided a point estimate from the network along with 95% CIs from the frequency distribution of the estimate. Moreover, we conducted 2 predefined sensitivity analyses to assess the robustness of findings regarding the primary outcome of the study by repeating the network analysis including only studies reporting success rates of stone removal for stones 15 mm and larger and only studies in which index ERCPs were performed. For all

analyses, the denominator was based on an intention-to-treat analysis as described in each included study. We calculated the relative ranking of the interventions for achieving the primary and the secondary outcome using the surface under the cumulative ranking (SUCRA) curve method. SUCRA values range between 0, when a treatment is certainly the worst, and 1, when a treatment is certainly the best.¹⁵ As such, higher scores correspond to higher ranking for achieving successful stone removal or preventing adverse event (AE) occurrence. Network meta-analysis was conducted with the R package *net-meta* (Foundation for Statistical Computing, Vienna, Austria). Finally, data for single adverse events were pooled from the included trials and pooled rates (95% CI) were reported.

Quality of Evidence

The quality of evidence derived from the pairwise and network meta-analysis was judged using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework.¹⁶ In this approach, direct evidence from RCTs starts at high quality and can be rated down based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity), and/or publication bias, to levels of moderate, low, and very low quality (Supplementary Table 2). When assessing for studies imprecision, evidence was rated down even if the 95% CI did not cross unity if the optimal information size (measure of fragility) was smaller than 200 events of failure to achieve the favorable outcome across all studies.¹⁷

The rating of indirect estimates starts at the lowest rating of the 2 pairwise estimates that contribute as first-order loops to the indirect estimate but can be rated down further for imprecision or intransitivity (dissimilarity between studies in terms of clinical or methodologic characteristics). If direct and indirect estimates were similar (ie, coherent), then the higher of the 2 ratings was assigned to the network meta-analysis estimates. To assess the quality of evidence, when effect estimates from both pairwise meta-analysis (head-to-head comparisons) and network meta-analysis were available, we preferentially used pairwise estimates if the confidence in the estimate was moderate-high; however, if the pairwise estimate provided only low or very low quality of evidence or if there were no pairwise comparisons, then estimates from network meta-analysis were used to rate the quality of evidence.

Results

From 3036 unique studies identified using the search strategy, we ultimately included 19 RCTs in the network meta-analysis, comparing 5 different strategies (sphincterotomy, balloon sphincteroplasty, S+EPLBD, mechanical lithotripsy, and SOC) for patients with large CBD

stones.^{18–36} Supplementary Figure 1 shows the study selection flowchart, and Figure 1 shows the available direct comparisons and network of trials.

Characteristics of Included Studies

Table 1 summarizes the baseline characteristics of the RCTs included in the network meta-analysis. Overall, the included 19 trials included 2732 patients. Eighteen RCTs were 2-arm controlled trials, of which 5 compared balloon sphincteroplasty vs sphincterotomy,^{18,21,22,30,35} 5 compared S+EPLBD vs sphincterotomy,^{19,24–26,29} 1 compared S+EPLBD vs mechanical lithotripsy,²⁰ 3 compared balloon sphincteroplasty vs S+EPLBD,^{23,28,34} 2 compared SOC vs S+EPLBD,^{31,36} 2 compared SOC vs mechanical lithotripsy,^{32,33} and a single 3-arm trial compared balloon sphincteroplasty vs sphincterotomy vs S+EPLBD.²⁷ Among the included studies, the stone diameter was estimated during the intervention based on comparison of the stone size on cholangiography with the diameter of the duodenoscope shaft. Of note, 8 RCTs^{18–20,24,25,27,31,32} provided data for stones 15 mm or larger, and in 4 of these^{19,24,31,32} only patients with stones 15 mm or larger were recruited. The success rate of CBD stone clearance and the rate of adverse events were reported in all studies. The baseline patient characteristics (sex and age) and the treatment-related features were distributed evenly between the active and comparator groups and across different trials (Table 1). The recruitment period ranged from 1995 to 2018 and the mean age was between 42.6 and 81 years. Finally, in 15 studies,^{18–30,34,35} patients were enrolled during their index ERCP. In 1 study,³³ 73% of

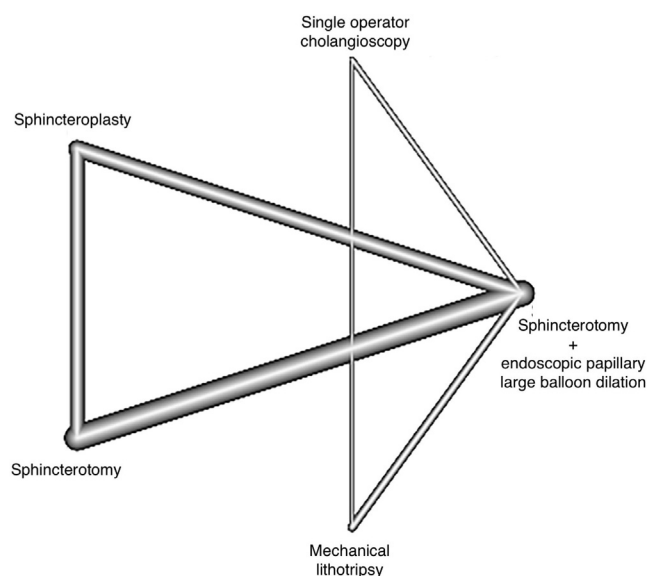


Figure 1. Network of the included trials. Network of included studies with the available direct comparisons between endoscopic interventions for removal of large biliary stones. The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively.

Table 1. Characteristics of Included Randomized Controlled Trials Comparing Different Methods for the Removal of Large Biliary Stones

Study	Country	Period	Follow-up period	Groups	Participants, n	Sex, male/ female	Age mean/ median, y (SD/range)	Stone size (mm; mean)	Stones, n (mean number)	Prior interventions
Vlavianos et al, ¹⁸ 2003	United Kingdom	January 1995– July 1999	1 mo, 3 mo, 6 mo, 12 mo	Sphincteroplasty vs sphincterotomy	103 vs 99	25/78 vs 35/ 64	60.8 (56.8– 64.7) 61.9 (58.3– 65.4)	>10 mm: 37.9% vs 42.4%	≥3: 38.8% vs 25.3%	No, 100% index ERCP
Kim et al, ¹⁹ 2009	South Korea	June 2006– December 2008	2 d	S+EPLBD vs sphincterotomy	27 vs 28	10/15 vs 11/ 14	70.3 (8.7) vs 69.8 (9.2)	20.8 vs 21.3	2.2 vs 2.3	No, 100% index ERCP
Stefanidis et al, ²⁰ 2011	Greece	January 2005– June 2009	1 mo	S+EPLBD vs mechanical lithotripsy	45 vs 45	24/21 vs 22/ 23	69.4 (17.8) vs 68.2 (18.9)	14.9 vs 15.1	NR	No, 100% index ERCP
Oh and Kim, ²¹ 2012	South Korea	September 2010–August 2011	1 d	Sphincteroplasty vs sphincterotomy	40 vs 43	20/20 vs 23/ 30	72.3 (9.5) vs 68.7 (12.9)	13.2 vs 13.1	>1: 50% vs 35%	No, 100% index ERCP
Fu et al, ²² 2013	China	March 2011– May 2012	1 mo	Sphincteroplasty vs sphincterotomy	103 vs 103	52/51 vs 45/ 58	61.8 (17.4) vs 60.5 (14.7)	8.4 vs 7.7	2.2 vs 1.9	No, 100% index ERCP
Hwang et al, ²³ 2013	South Korea	Since May 2009	1 d	Sphincteroplasty vs S+EPLBD	62 vs 69	23/39 vs 33/ 36	70.4 (10.9) vs 68.2 (10.5)	15.7 vs 16.5	2.3 vs 2.8	No, 100% index ERCP
Bo et al, ²⁴ 2013	China	January 2008– January 2012	2 d	S+EPLBD vs sphincterotomy	63 vs 69	32/31 vs 36/ 33	67.3 (23.4) vs 68.4 (22.8)	20.6 vs 20.3	2.2 vs 2.3	No, 100% index ERCP
Teoh et al, ²⁵ 2013	China	September 2005– September 2011	1 mo	S+EPLBD vs sphincterotomy	73 vs 78	32/41 vs 40/ 38	71.6 (14.8) vs 72.9 (13.4)	12.5 vs 13.3	>3: 39.7% vs 32.1%	No, 100% index ERCP
Li et al, ²⁶ 2013	China	May 2008–April 2011	24 h, 12 min	S+EPLBD vs sphincterotomy	232 vs 230	96/136 vs 87/ 143	61.8 (16.7) vs 60.6 (16.6)	13.2 vs 12.7	≥3: 30.3% vs 25.6%	No, 100% index ERCP
Guo et al, ²⁷ 2015	China	July 2011– December 2013	24 h, 1 min	Sphincterotomy vs sphincteroplasty vs S+EPLBD	85 vs 85 vs 85	43/42 vs 45/ 40 vs 46/ 39	59 (16) vs 62 (17) vs 63 (16)	10 vs 10 vs 10	>3: 27.6% vs 24.7%	No, 100% index ERCP
Cheon et al, ²⁸ 2016	South Korea	May 2013–June 2015	24 h	Sphincteroplasty vs S+EPLBD	42 vs 44	21/21 vs 24/ 20	71.0 (12.4) vs 71.7 (10.1)	14.4 vs 14.0	2.6 vs 2.6	No, 100% index ERCP

Table 1. Continued

Study	Country	Period	Follow-up period	Groups	Participants, n	Sex, male/female	Age mean/median, y (SD/range)	Stone size (mm; mean)	Stones, n (mean number)	Prior interventions
Karsenti et al, ²⁹ 2017	France	September 2010–March 2015	At least 24 h	S+EPLBD vs sphincterotomy	77 vs 73	26/51 vs 31/42	76.7 (11.9) vs 81 (11.6)	16.5 vs 16.2	2.8 vs 3.6	No, 100% index ERCP
Omar et al, ³⁰ 2017	Egypt	August 2014–March 2016	At least 24 h	Sphincteroplasty vs sphincterotomy	61 vs 63	26/35 vs 25/38	47.8 (14.5 vs 44.8 (13.9)	13.9 vs 13.1	2.3 vs 2.1	No, 100% index ERCP
Franzini et al, ³¹ 2017	Brazil	April 2014–June 2016	1 wk	SOC vs S+EPLBD	50 vs 50	13/37 vs 13/37	52.1 (17.6) vs 59.7 (16.9)	>20 mm: 43.8% vs 44%	≥3: 35.4% vs 24.0%	Yes, 100% had failed extraction with standard techniques
Angsuwat-charakon et al, ³² 2018	Thailand	November 2017–November 2018	1 wk, 1 mo, 6 mo	SOC vs mechanical lithotripsy	16 vs 16	7/9 vs 5/11	62.7 (18.5) vs 63.1 (20.1)	19.5 vs 17.6	2 vs 2	Yes, 100% had failed extraction with sphincterotomy or sphincteroplasty
Buxbaum et al, ³³ 2018	United States	January 2013–March 2016	At least 24 h	SOC vs mechanical lithotripsy	42 vs 18	13/29 vs 6/12	51.6 (13.3) vs 42.6 (14.5)	18 vs 19	NR	Yes, 73% had previous ERCP
Park et al, ³⁴ 2018	South Korea	November 2010–October 2013	At least 24 h	Sphincteroplasty vs S+EPLBD	100 vs 100	55/45 vs 48/52	74 (56–91) vs 73 (49–91)	15.2 vs 14.6	2 vs 2	No, 100% index ERCP
Kogure et al, ³⁵ 2020	Japan	February 2013–August 2015	1 wk, 1 mo	Sphincteroplasty vs sphincterotomy	86 vs 85	38/48 vs 41/44	79.1 (8.1) vs 80.9 (8.2)	15.2 vs 14.3	≥4: 29.1% vs 34.1%	No, 100% index ERCP
Bang et al, ³⁶ 2020	United States	June 2016–August 2018	5 d, 1 mo, 6 mo	S+EPLBD vs SOC	33 vs 33	8/25 vs 12/21	63.9 (18.0) vs 72.8 (16.4)	15.3 vs 17.2	3.1 vs 3.7	Yes, 100% had failed extraction with standard techniques

ERCP, endoscopic retrograde cholangiopancreatography; NR, not reported; S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation; SOC, single-operator cholangioscopy (+electrohydraulic or laser lithotripsy).

the patients underwent a previous ERCP, and in 3 studies^{31,32,36} patients were recruited after having failed prior stone extraction using techniques other than those assessed in the study.

Quality Assessment of Included Studies

Quality assessment was performed in the context of the outcomes of interest. All studies were at high risk of performance and detection bias because of their design per se precluding the endoscopist blinding. Moreover, 3 studies were judged to be at higher risk of bias regarding both the random sequence generation and incomplete outcome reporting (attrition bias).^{19,20,28} The overall and study-level quality assessments are summarized in [Supplementary Figure 2](#), respectively.

Primary Outcome: Success Rate of Stone Removal

Pairwise meta-analysis. Based on 6 RCTs^{18,21,22,27,30,35} (710 patients), balloon sphincteroplasty was not significantly superior to sphincterotomy in terms of the success rate for CBD stone removal (RR, 1.08; 95% CI, 0.98–1.20) ($P = .12$) ([Supplementary Figure 3](#)). Likewise, no difference between S+EPLBD and sphincterotomy was observed based on 6 RCTs^{19,24–27,29} (RR, 1.09; 95% CI, 1.00–1.19) ([Supplementary Figure 3](#)), with evidence of heterogeneity ($I^2 = 73\%$). None of the other methods was compared directly with sphincterotomy. Regarding head-to-head comparisons between adjunctive interventions, only SOC resulted in statistically significantly higher rates of complete stone removal compared with mechanical lithotripsy^{32,33} (RR, 1.59; 95% CI, 1.14–2.20; $I^2 = 0\%$; $P = .006$), whereas the rest of the direct comparisons did not detect any statistically significant difference ([Supplementary Figure 3](#)).

Network meta-analysis. With network meta-analysis, we calculated the mixed-effect estimate as a weighted average of both pairwise (where available) and indirect treatment effects, and the overall results were largely similar with overlapping CIs, although differences were observed in effect size and statistical significance in some cases ([Table 2](#)). All treatments except mechanical lithotripsy significantly outperformed sphincterotomy in terms of stone removal rate, with RRs ranging from 1.03 to 1.29 ([Figure 2A](#)). The respective number needed to treat (NNT) was 15, 14, and 3 for balloon sphincteroplasty, S+EPLBD, and SOC vs sphincterotomy, respectively. When looking at the comparison of different adjunctive interventions, only SOC was significantly superior to the other methods (RR, 1.24; 95% CI, 1.07–1.45; NNT, 4) vs balloon sphincteroplasty (RR, 1.23; 95% CI, 1.06–1.42; NNT, 9) vs S+EPLBD (RR, 1.34; 95% CI, 1.14–1.58; NNT, 3) vs mechanical lithotripsy.

As a consequence, SOC-assisted lithotripsy ranked highest in increasing the success rate of stone removal

(SUCRA score, 0.99) followed by S+EPLBD (SUCRA score, 0.68) ([Table 3](#)). Our sensitivity analysis showed that the superiority of SOC over the aforementioned treatments remained significant in patients with larger stones (>15 mm), whereas only S+EPLBD was significantly superior to sphincterotomy in this specific subset of patients (RR, 1.14; 95% CI, 1.03–1.42) ([Supplementary Table 3](#)). Treatment ranking was confirmed with SOC (SUCRA score, 0.97) and S+EPLBD (SUCRA score, 0.71) ranking as the best treatment options in this setting ([Supplementary Table 4](#)). Similarly, when only studies evaluating index ERCPs were taken into account, S+EPLBD was superior to sphincterotomy (RR, 1.05; 95% CI, 0.01–1.08) ([Supplementary Table 5](#)). Considering that among studies recruiting only index ERCPs, and not prior failures, SOC was not offered as a treatment option, the treatment ranking confirmed that S+EPLBD was the most effective and safest modality (SUCRA score, 0.82) ([Supplementary Table 6](#)).

Quality of evidence. There was no indirectness or publication bias for any of the comparisons. However, the evidence was rated down for risk of bias in the literature, owing to the unblinded nature of the included trials and imprecision. Moreover, inconsistency owing to moderate-high heterogeneity was found in some comparisons. Therefore, based on both pairwise and indirect estimates, there was very low quality of evidence supporting the use of EPLBD or S+EPLBD over sphincterotomy, whereas all of the other comparisons were informed by low quality of evidence ([Table 2](#)).

Secondary Outcome: Adverse Event Rate

Overall, post-ERCP adverse event definitions were homogenous across included studies because established criteria were used in 14 of them. Among them, 11 studies^{19,23–30,33,34} used the 1991 international consensus criteria³⁷ and 3 studies^{32,35,36} used the lexicon proposed by the American Society of Gastroenterology in 2010.³⁸ Two studies^{20,21} used definitions provided in previously published literature, 2 studies^{22,31} used custom author definitions, and in only 1 study¹⁸ no specific AE definitions were provided. Finally, AEs were reported independently of their severity.

Pairwise meta-analysis. Based on 6 RCTs^{18,21,22,27,30,35} (956 patients), no difference was observed between balloon sphincteroplasty and sphincterotomy (RR, 0.83; 95% CI, 0.50–1.38; $I^2 = 31\%$) ([Supplementary Figure 4](#)). Similarly, no significant difference was observed in any of the other comparisons except for S+EPLBD that was significantly safer than mechanical lithotripsy (RR, 0.22; 95% CI, 0.05–0.97) ([Supplementary Figure 4](#)). No heterogeneity was observed in any of the aforementioned comparisons.

Network meta-analysis and quality of evidence. On network meta-analysis, none of the tested interventions were found to be significantly different in terms of adverse events compared with sphincterotomy or other treatments ([Table 2](#)), with only S+EPLBD showing a nonsignificant trend toward lower adverse event rates,

Table 2. GRADE Summary of Findings Reporting the Comparative Efficacy of Different Methods for Removal of Large Biliary Stones and the Comparative Rates of Adverse Events

	Success rate of stone removal		Adverse event rate	
	Risk ratio (95% CI)	Quality of evidence	Risk ratio (95% CI)	Quality of evidence
All treatments vs sphincterotomy				
Sphincteroplasty	1.03 (1.01–1.08)	Very low owing to imprecision, inconsistency, and risk of bias in the literature Risk difference: 0.07 (0.01–0.15)	0.80 (0.55–1.15)	Low owing to imprecision and risk of bias in the literature Risk difference: -0.02 (-0.07 to 0.03)
S+EPLBD	1.05 (1.01–1.08)	Very low owing to imprecision, inconsistency, and risk of bias in the literature Risk difference: 0.08 (0.01–0.15)	0.71 (0.50–1.02)	Low owing to imprecision and risk of bias in the literature Risk difference: -0.02 (-0.05 to 0.01)
Mechanical lithotripsy	1.03 (0.86–1.06)	Low owing to imprecision and risk of bias in the literature	1.77 (0.53–5.91)	Low owing to imprecision and risk of bias in the literature
SOC	1.29 (1.11–1.50)	Low owing to imprecision and risk of bias in the literature	0.79 (0.25–2.44)	Low owing to imprecision and risk of bias in the literature
Vs sphincteroplasty				
S+EPLBD	1.01 (0.97–1.05)	Low owing to imprecision and risk of bias in the literature	0.89 (0.58–1.36)	Low owing to imprecision and risk of bias in the literature
Mechanical lithotripsy	0.98 (0.83–1.03)	Low owing to imprecision and risk of bias in the literature	2.21 (0.65–7.51)	Low owing to imprecision and risk of bias in the literature
SOC	1.24 (1.07–1.45)	Low owing to imprecision and risk of bias in the literature	0.98 (0.31–3.11)	Low owing to imprecision and risk of bias in the literature
Vs S+EPLBD				
Mechanical lithotripsy	0.93 (0.83–1.01)	Low owing to imprecision and risk of bias in the literature	2.47 (0.78–7.78)	Low owing to imprecision and risk of bias in the literature
SOC	1.23 (1.06–1.42)	Low owing to imprecision and risk of bias in the literature	0.89 (0.37–3.20)	Low owing to imprecision and risk of bias in the literature
Vs mechanical lithotripsy				
SOC	1.34 (1.14–1.58)	Low owing to imprecision and risk of bias in the literature	0.44 (0.14–1.32)	Low owing to imprecision and risk of bias in the literature

NOTE. The quality of the evidence was rated based on GRADE methodology. Randomized controlled trials of direct comparison were rated down for the presence of any of the following factors: risk of bias in the literature, inconsistency, indirectness, imprecision, and publication bias. The quality of indirect estimates initially was derived from the lowest quality of first-order loops for direct estimates contributing to the indirect estimates. The quality of the network meta-analysis was derived from the quality of the combination of direct and indirect estimates and transitivity of trials. Risk ratios reaching the significance threshold are shown in bold.

CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation; SOC, single-operator cholangioscopy (+electrohydraulic or laser lithotripsy).

compared with sphincterotomy (RR, 0.71; 95% CI, 0.50–1.02) (Figure 2B and Table 2). Again, SOC ranked highest (SUCRA score, 0.76) followed by S+EPLBD (SUCRA score, 0.75) (Table 3). Moreover, as

reported in Table 3, mechanical lithotripsy showed the poorest value (SUCRA score, 0.10). The quality of evidence was judged mainly as low owing to risk of bias in the literature and imprecision.

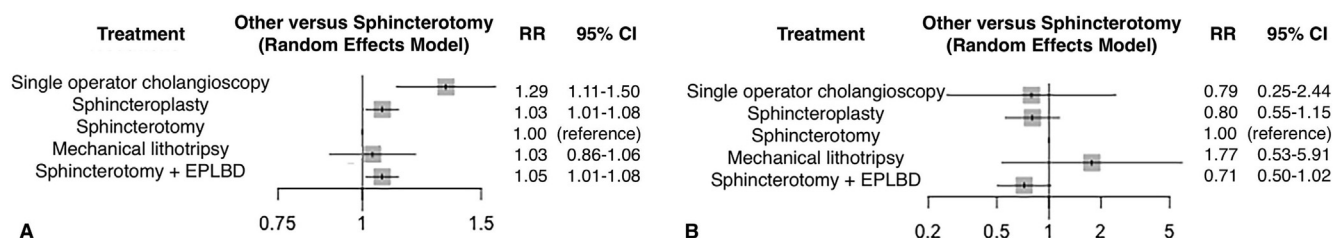


Figure 2. Forest plots reporting estimates derived from network meta-analysis assessing (A) success rate of stone removal, and (B) adverse event rate. Endoscopic sphincterotomy was used as reference. EPLBD, endoscopic papillary large balloon dilation; RR, relative risk.

Table 3. SUCRA Score Ranking for Success Rate of Stone Removal and Adverse Event Rate

Success rate of stone removal		Adverse event rate	
SOC	0.99	SOC	0.76
S+EPLBD	0.68	S+EPLBD	0.75
Sphincteroplasty	0.50	Sphincteroplasty	0.47
Mechanical lithotripsy	0.26	Sphincterotomy	0.40
Sphincterotomy	0.06	Mechanical lithotripsy	0.10

SOC, single operator cholangioscopy (+electrohydraulic or laser lithotripsy); S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation; SUCRA, surface under the cumulative ranking.

Other adverse events. [Supplementary Table 7](#) presents in detail the main adverse events reported in the included RCTs. Overall, adverse events were distributed equally among the tested treatments with PEP and bleeding being the most common adverse events. Pooled rates of PEP were 4.2% (2.3%–6.2%) after sphincterotomy, 3% (1.7%–4.4%) after balloon sphincteroplasty, 3.2% (2%–4.3%) after S+EPLBD, 3.1% (0%–6.8%) after mechanical lithotripsy, and 3.1% (0%–6.4%) after SOC. Bleeding was observed in 2% of patients (0.7%–3.2%) after sphincterotomy, in 0.7% (0.1%–1.3%) after balloon sphincteroplasty, in 1.2% (0.5%–1.9%) after S+EPLBD, in 2.4% (0.9%–3.5%) after mechanical lithotripsy, and in 1.2% (0%–3.3%) after SOC. The pooled rates of cholangitis were 1.1% (0.4%–1.8%) after sphincterotomy, 0.9% (0.1%–1.7%) after balloon sphincteroplasty, 0.9% (0.3%–1.5%) after S+EPLBD, 3.8% (1.6%–5.3%) after mechanical lithotripsy, and 2.9% (0%–6%) after SOC. Finally, only a single fatal event was observed in 1 trial,¹⁸ in a patient treated with sphincterotomy.

Small Study Effects and Network Coherence

We did not find any evidence of small study effects based on funnel plot asymmetry (data not shown), although the number of studies included in each comparison was relatively limited. There were no significant differences between direct and indirect estimates in closed loops that allowed assessment of network coherence (P value for difference between groups in which both direct and indirect estimates were available: success rate of stone removal, $P = .41$ –.95; AE rate, $P = .15$ –.92; need for mechanical lithotripsy, $P = .32$ –.89).

Discussion

In the present study, through a network meta-analysis, and using GRADE criteria to appraise the quality of evidence, we made several key observations regarding the optimal approach to patients with large bile stones during ERCP. First, all treatments except mechanical lithotripsy significantly outperformed endoscopic sphincterotomy in

terms of stone removal rate. On the other hand, moderate-quality evidence suggests that only SOC fared better than all other adjunctive treatments. As a consequence, SOC ranked highest in increasing the success rate of stone removal (SUCRA score, 0.99) followed by S+EPLBD (SUCRA score, 0.68).

Second, the superiority of SOC over the other treatments remained significant in patients with larger stones (>15 mm), and was shown to be the only valuable therapeutic option that resulted in a consistent improvement over the other modalities, again supported by moderate-quality evidence. The only alternative that was proven to be superior to endoscopic sphincterotomy in this setting was S+EPLBD, which again ranked as the second option even in the case of larger stones. This was a pivotal observation because SOC, despite its recent widespread implementation, is still not available in every setting and requires additional training with a learning curve to achieve expertise. Moreover, SOC, despite its efficacy, might prolong examination time, as has been shown recently³¹; this could lead to an increased requirement for patient sedation, which is not always desired or possible in every case. Finally, the cost of the procedure is another factor that should be taken into account. In a recent study comparing SOC with EPLBD-based techniques,³⁴ although total costs did not differ significantly (with SOC still being more expensive), SOC, however, was significantly more expensive in terms of procedural supplies (US \$7221 vs US \$3349; $P = .004$). This is a factor that cannot be underestimated because supplies are more or less stable in most countries, whereas total costs often are calculated differently in different health care systems. Taking this into account, the existence of an effective, widely available, and relatively cheap alternative, namely sphincterotomy, followed by endoscopic papillary large balloon dilation, for tackling larger stones, may offer endoscopists additional options, especially during index ERCPs. As shown in our sensitivity analysis including only studies with index ERCPs and no prior extraction failures, in which SOC was not offered as a treatment option, S+EPLBD remained the most efficacious and safe treatment modality compared with sphincteroplasty, mechanical lithotripsy, or simple endoscopic sphincterotomy.

Third, low-quality evidence suggested that no difference among the tested interventions was observed in terms of adverse event rates, in either direct or in indirect comparisons, with only mechanical lithotripsy resulting in the poorest value (SUCRA score, 0.10) in the ranking concerning this specific outcome. However, the imprecision of the estimates observed in the mechanical lithotripsy trials suggests that the evidence supporting the aforementioned finding is of very low quality, thus calling for particular caution when interpreting these results. Among the reported adverse events, PEP and bleeding were the most common adverse events, while only a single fatal event was observed in 1 trial in a patient treated with endoscopic sphincterotomy who

died of cardiorespiratory failure after randomization to endoscopic sphincterotomy; the latter having actually not been performed because the procedure was abandoned, but the death was considered on an intention-to-treat basis because it took place after the patient had been randomized.¹⁸ Based on our key observations, we propose an algorithm (Figure 3) for the management of large and/or difficult stones, in which sphincterotomy followed by endoscopic papillary large balloon dilation should be applied as the first method to extract large CBD stones. SOC with laser or electrohydraulic lithotripsy should be the step-up approach in case of failure or when a tapered distal bile duct does not allow large balloon dilation.

This network meta-analysis aimed to comparatively evaluate different techniques for removal of large CBD stones. Previous studies in this field consisted of pairwise meta-analyses comparing single pairs of interventions, while a previous network meta-analysis that was published before the introduction of SOC into clinical practice did not specifically assess large stones, but any kind of choledocholithiasis.⁸ To address the issue of heterogeneity among included studies, we performed a

predefined sensitivity analysis restricted to larger stones (>15 mm), which also confirmed SOC as the optimal treatment.

Another point of strength of our study was the fact that, apart from including only data from RCTs, we performed an objective critical appraisal of the overall quality of evidence using the standardized GRADE methodology. The primary reason that kept the evidence from being of higher quality was owing to the unblinded design of the included RCTs, a bias commonly found in endoscopic studies, in which blinding of the operator usually is not feasible. However, we believe that this critical appraisal could guide future recommendations to clinicians and inform forthcoming guidelines. Moreover, if both direct and indirect evidence was available, we observed no difference in effect estimates, supporting the transitivity assumption in our network meta-analysis.

There were certain limitations related to both the network analysis as well as individual studies that merit further discussion. First, the paucity of direct head-to-head trials and the moderate heterogeneity observed for certain comparisons resulted in low- to moderate-quality evidence for comparative efficacy of the different methods. Second, network meta-analyses may be subject to misinterpretation owing to conceptual heterogeneity, related to considerable differences in participants, interventions, co-interventions/background treatment, and outcome assessment, which may limit the comparability of trials. We tried to minimize this conceptual heterogeneity by strictly including studies in patients with CBD stones larger than 10 mm and assessing homogeneous outcomes. On the other hand, and as previously mentioned, a stone also can be characterized as difficult not only based on its size, but also by its shape (eg, barrel-shape) or by its difficulty in being removed, because of the shape of the bile duct (eg, in patients with a tapered CBD, which can be an obstacle to the stone's extraction, even when the stone does not have an excessive size per se). Finally, intrahepatic location of the stones usually constitutes another "difficult stone" group. For the sake of this study, other aspects that could define "difficult" bile stones could not be considered because no study applied inclusion criteria other than the stone size. Furthermore, any attempt to include these types of difficult stones in our analysis would not only increase its inhomogeneity, but also was practically impossible because it contains a high percentage of subjectivity (eg, which stone shape is more difficult than another, how tapered is the CBD, and so forth). Therefore, these parameters were excluded from our definition of "difficult" stones, which was based on an undisputedly objective parameter, namely size. In other words, because a "difficult" stone is in many aspects subjective, stone size (>10 mm) easily can serve as its surrogate. In addition, another limitation especially impacting adverse event rates was the heterogeneity of application of PEP preventive measures and the different use of adjunctive

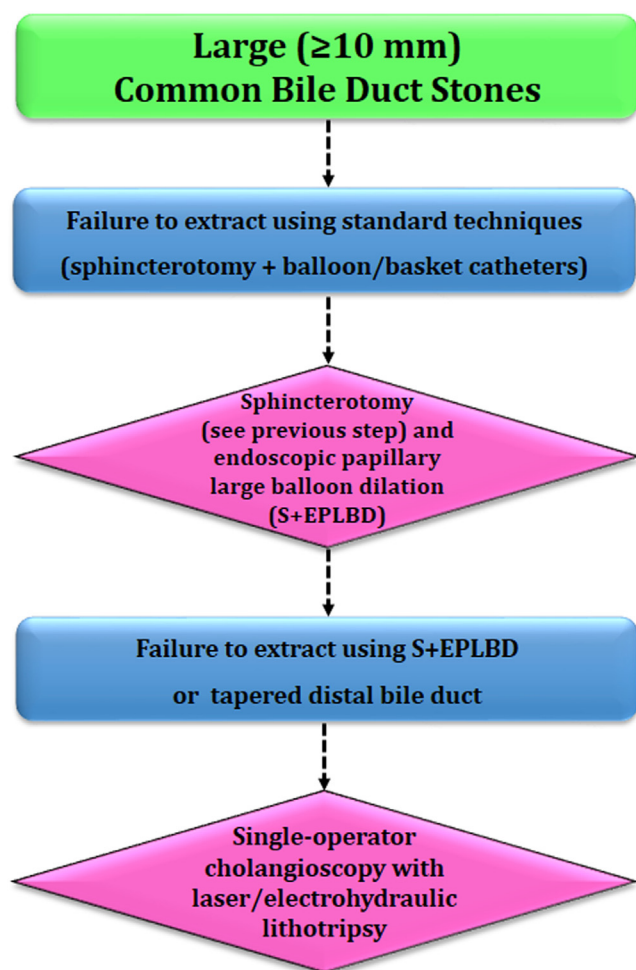


Figure 3. Proposed algorithm for the treatment of stones 10 mm or larger. S+EPLBD, sphincterotomy plus endoscopic papillary large balloon dilatation.

mechanical lithotripsy among the included RCTs, which is something expected and virtually unavoidable. Regarding limitations of individual studies, we acknowledge that some of them had a small sample size and others were hampered by some technical details as well as the need for mechanical lithotripsy, which were not reported or had inconsistent results in a significant part of the included trials. Moreover, no direct comparison could be made between SOC using laser and electrohydraulic lithotripsy since there are no available head-to-head RCTs. Nevertheless, a recent meta-analysis of cohort studies showed that laser lithotripsy was associated with a higher complete ductal clearance rate, higher stone fragmentation rate, and lower complication rate compared with electrohydraulic lithotripsy.³⁹ Although one might argue that it is preferable to use laser lithotripsy, further studies are warranted. Finally, when considering all the possible endoscopic techniques used for difficult stone management, we had to ignore the use of extracorporeal shock wave lithotripsy in combination with ERCP techniques because no RCT was available. This option, however, may be part of the armamentarium when available locally.

In conclusion, this network meta-analysis assessed the methods applied in the management of large biliary stones. Although robust GRADE methodology showed only a low to moderate level of evidence, we observed that SOC was more effective than other methods, in particular in patients with larger stones, whereas S+EPLBD could represent a less expensive and more widely available alternative.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://doi.org/10.1016/j.cgh.2021.10.013>.

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Reprint requests

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Paraskevas Gkolfakis (Conceptualization: Lead; Data curation: Lead; Methodology: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)

Daryl Ramai (Data curation: Supporting; Formal analysis: Supporting; Writing – review & editing: Supporting)

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Ioannis S. Papanikolaou (Data curation: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting)

Marianna Arvanitakis (Formal analysis: Supporting; Writing – review & editing: Supporting)

Daniel Blero (Data curation: Equal)

Arnaud Lemmers (Data curation: Supporting; Writing – review & editing: Supporting)

Pierre Eisendrath (Data curation: Supporting; Writing – review & editing: Supporting)

Lorenzo Fuccio (Writing – review & editing: Supporting)

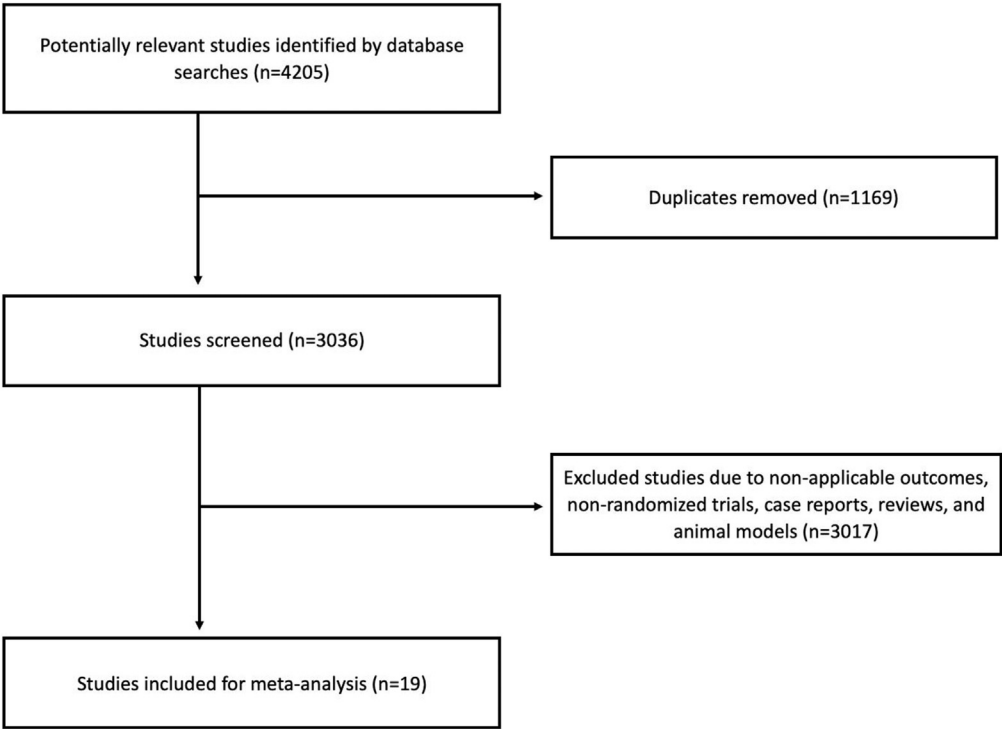
Konstantinos Triantafyllou (Formal analysis: Supporting; Writing – review & editing: Supporting)

Armando Gabbriellini (Writing – review & editing: Supporting)

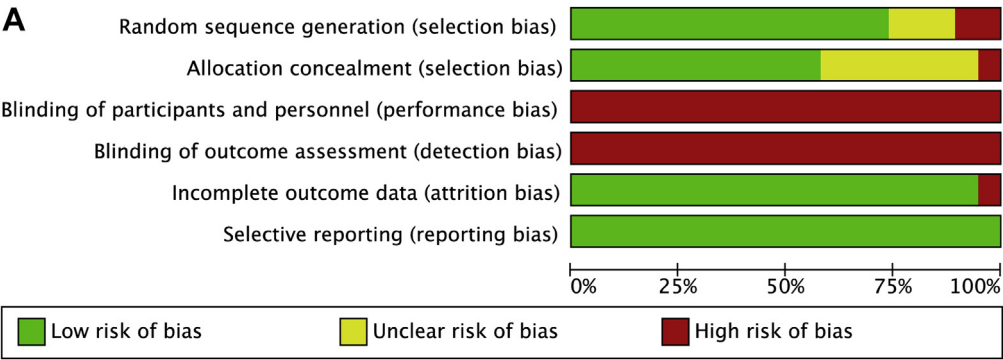
Jacques Devière (Data curation: Supporting; Formal analysis: Supporting; Supervision: Lead; Writing – review & editing: Supporting)

Conflicts of interest

The authors disclose no conflicts.



Supplementary Figure 1. Study flowchart.

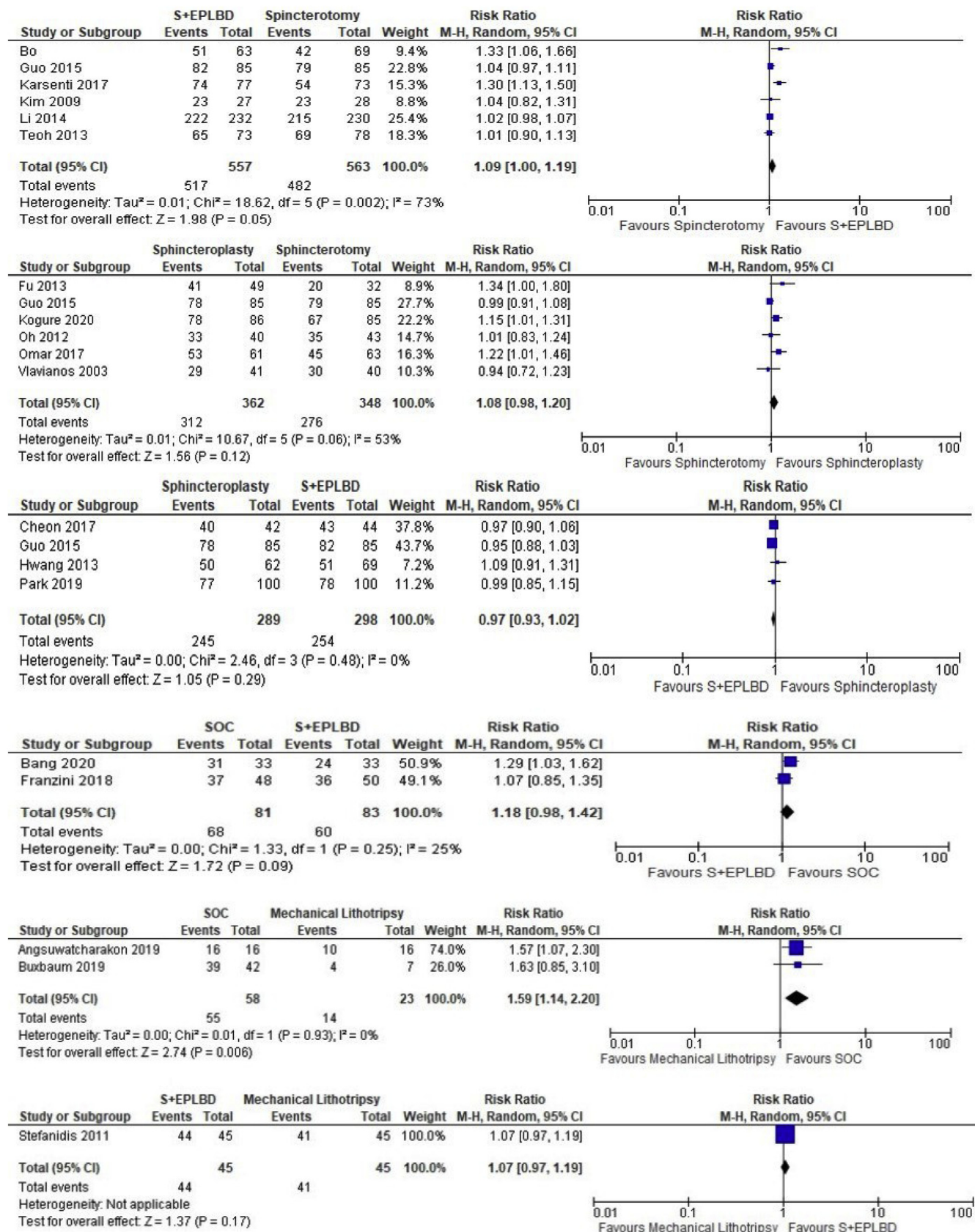


Supplementary Figure 2. (A) Overall quality assessment of included trials. (B) Study-level assessment of quality of included trials.

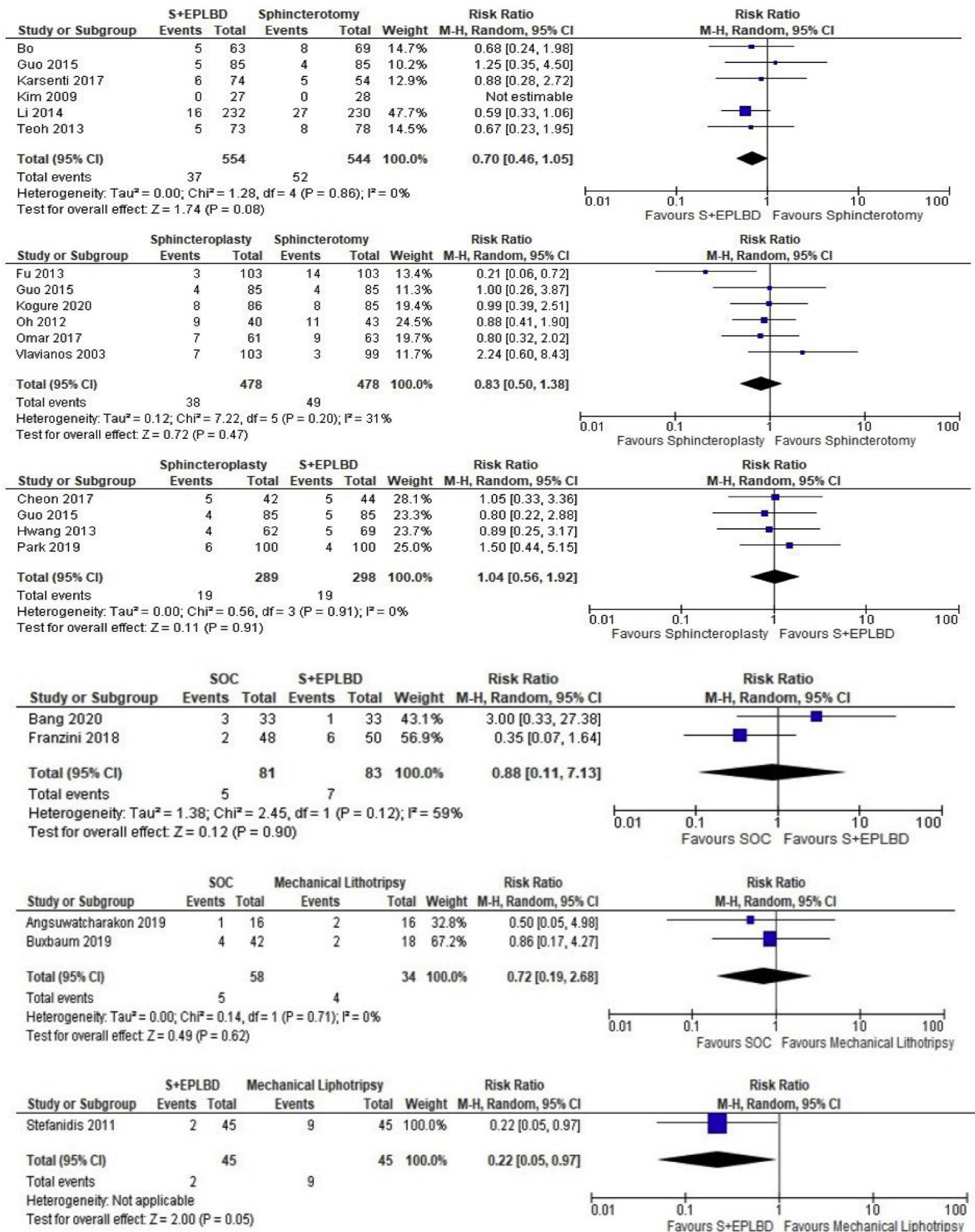
B

	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)
Angsuwatcharakon 2018	+	+	-	-	+	+
Bang 2020	+	+	-	-	+	+
Bo 2013	+	+	-	-	+	+
Buxbaum 2018	+	+	-	-	+	+
Cheon 2016	+	-	-	-	+	+
Franzini 2017	+	?	-	-	+	+
Fu 2013	?	+	-	-	+	+
Guo 2015	+	?	-	-	+	+
Hwang 2013	?	?	-	-	+	+
Karsenti 2017	+	+	-	-	+	+
Kim 2009	-	?	-	-	+	+
Kogure 2020	+	?	-	-	+	+
Li 2013	+	+	-	-	+	+
Oh 2012	+	?	-	-	+	+
Omar 2017	+	?	-	-	+	+
Park 2018	?	+	-	-	+	+
Stefanidis 2011	-	+	-	-	-	+
Teoh 2013	+	+	-	-	+	+
Vlavianos 2003	+	+	-	-	+	+

Supplementary Figure 2. Continued.



Supplementary Figure 3. Direct meta-analysis of different endoscopic techniques evaluating the success rate of stone removal. M-H, Mantel-Haenszel; SOC, single-operator cholangioscopy (+electrohydraulic or laser lithotripsy); S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation.



Supplementary Figure 4. Direct meta-analysis of different endoscopic techniques evaluating the adverse event rate. M-H, Mantel-Haenszel; SOC, single-operator cholangioscopy (+electrohydraulic or laser lithotripsy); S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation.

Supplementary Table 1. Search Strategy

PUBMED

"Electrohydraulic lithotripsy"[Text Word] OR "endoscopic sphincterotomy"[Text Word] OR (Large AND papillary AND balloon AND dilation) OR "Laser lithotripsy"[Text Word] OR "Mechanical lithotripsy"[Text Word] OR "Papillary balloon dilation"[Text Word] OR (Large AND diameter AND balloon AND dilation AND lithotripsy) OR "large-diameter balloon"[Text Word] OR "Dormia basket"[Text Word] OR (biliary AND orifice AND balloon AND dilation) OR "biliary endoscopic sphincterotomy"[Text Word] OR endoscopic papillary large balloon dilation OR "Endoscopic papillary large balloon dilatation"[Text Word] OR EPLBD OR (Digital AND cholangioscopy AND-guided AND laser) OR "cholangioscopy-guided laser lithotripsy"[Text Word] or "papillary balloon dilation"[Text Word] or sphincterotomy[tw] OR spyglass[Text Word]

"sphincterotomy, endoscopic"[MeSH Terms] OR "lithotripsy, laser"[MeSH Terms] OR "lithotripsy"[MeSH Terms] OR "sphincterotomy, endoscopic"[MeSH Terms] OR Sphincterotomy[mesh]

AND

Large OR impact* OR difficult* OR "barrel shaped" OR "Barrel shape" OR complex OR "> 15 mm" OR ">13 mm" OR multiple OR unsuspected OR retained OR failed OR intract* OR complicat*

Large[Text Word] OR impact*[Text Word] OR difficult*[Text Word] OR "barrel shaped"[Text Word] OR "Barrel shape"[Text Word] OR complex [Text Word] OR "> 15 mm"[Text Word] OR ">13 mm"[Text Word] OR multiple[Text Word] OR unsuspected[Text Word] OR retained[Text Word] OR failed[Text Word] OR intract*[Text Word] OR complicat*[Text Word]

"Bile duct"[Text Word] OR choledochal[Text Word] AND choledocholithiasis[Text Word] OR biliary[Text Word] OR bile[mesh] or biliary tract [mesh] or bile ducts[mesh] or common bile duct[mesh]

AND

Calculi[Text Word] OR stone[Text Word] OR stones[Text Word] or calculi[mesh] OR Calculi[mesh]

EMBASE

Results

2,407

#7

#5 NOT #6 AND [english]/lim

1,998

#6

#1 AND #2 AND #3 AND #4 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [oral]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim)

4,985

#5

#1 AND #2 AND #3 AND #4

98,064

#4

calculi:ti,ab,kw OR stone:ti,ab,kw OR stones:ti,ab,kw

262,167

#3

('bile duct':ti,ab,kw OR choledochal:ti,ab,kw) AND choledocholithiasis:ti,ab,kw OR biliary:ti,ab,kw OR bile:ti,ab,kw OR 'biliary tract':ti,ab,kw OR 'bile ducts':ti,ab,kw OR 'common bile duct':ti,ab,kw OR 'bile duct'/exp

9,642,824

#2

large:ti,ab,kw OR impact*:ti,ab,kw OR difficult*:ti,ab,kw OR 'barrel shaped':ti,ab,kw OR 'barrel shape':ti,ab,kw OR complex:ti,ab,kw OR '15 mm':ti,ab,kw OR (15:ti,ab,kw AND mm:ti,ab,kw) OR '13 mm':ti,ab,kw OR (13:ti,ab,kw AND mm:ti,ab,kw) OR complic*:ti,ab,kw OR fail*:ti,ab,kw OR multiple:ti,ab,kw OR unsuspect*:ti,ab,kw OR retain*:ti,ab,kw OR intract*:ti,ab,kw OR complicat*:ti,ab,kw

39,332

#1

Supplementary Table 1. Continued

'electrohydraulic lithotripsy':ti,ab,kw OR 'endoscopic sphincterotomy':ti,ab,kw OR ((large NEAR/3 papillary NEAR/3 balloon NEAR/3 dilation):ti,ab,kw) OR 'laser lithotripsy':ti,ab,kw OR 'mechanical lithotripsy':ti,ab,kw OR 'papillary balloon dilation':ti,ab,kw OR 'dormia basket':ti,ab,kw OR 'stone retrieval basket':ti,ab,kw OR ((biliary NEAR/3 orifice NEAR/4 balloon NEAR/3 dilation):ti,ab,kw) OR 'biliary endoscopic sphincterotomy':ti,ab,kw OR 'endoscopic papillary large balloon dilation':ti,ab,kw OR epld:ti,ab,kw OR 'cholangioscopy-guided laser lithotripsy':ti,ab,kw OR ((papillary NEAR/4 balloon NEAR/4 dilation):ti,ab,kw) OR ((papillary NEAR/4 balloon NEAR/4 dilatation):ti,ab,kw) OR sphincterotomy:ti,ab,kw OR spyglass:ti,ab,kw OR cholangioscopy:ti,ab,kw OR ((laser NEAR/2 lithotripsy):ti,ab,kw) OR 'lithotripsy':ti,ab,kw OR 'biliary tract endoscopy'/exp OR 'electrohydraulic lithotripsy'/exp OR 'endoscopic sphincterotomy'/exp OR 'stone retrieval basket'/exp OR 'lithotripsy'/exp OR 'laser lithotripsy'/exp OR spyscope:ti,ab,kw

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Refined by: [excluding] DOCUMENT TYPES: (MEETING ABSTRACT OR LETTER OR NOTE OR PROCEEDINGS PAPER OR ORIAL MATERIAL) AND LANGUAGES: (ENGLISH)

(Large OR impact* OR difficult* OR "barrel shaped" OR "Barrel shape" OR complex OR "> 15 mm" OR ">13 mm" OR multiple OR unsuspected OR retained OR failed OR intract* OR complicat*)

("Bile duct" OR choledochal AND choledocholithiasis OR biliary OR bile OR biliary tract OR bile ducts OR common bile duct or common bile ducts)

(Calculi OR stone OR stones OR calculi OR Calculi)

("large-diameter balloon" OR "Dormia basket" OR (Large AND diameter AND balloon AND dilation AND lithotripsy) OR "Laser lithotripsy" OR "Mechanical lithotripsy" OR "Papillary balloon dilation" OR (Large AND papillary AND balloon AND dilatation) OR (Large AND papillary AND balloon AND dilation) OR "sphincterotomy, endoscopic" OR "lithotripsy, laser" OR "lithotripsy" OR Sphincterotomy OR "endoscopic sphincterotomy" OR "Electrohydraulic lithotripsy" OR "endoscopic sphincterotomy") ("cholangioscopy guided laser lithotripsy" OR "papillary balloon dilation" OR sphincterotomy OR spyglass OR (Digital AND cholangioscopy AND guided AND laser) OR (Digital AND cholangioscopy AND guided AND laser) or TS="papillary balloon dilation"

Cochrane = 0

Supplementary Table 2. GRADE Categories of Quality of Evidence

GRADE quality of evidence	Meaning	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	We are moderately confident in the estimate of the effect; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an impact on our confidence in the estimate of effect and may change the estimate
Low	Our confidence in the estimate of the effect is limited; the true effect may be substantially different from the estimate of the effect	Further research is very unlikely to have an impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	We have very little confidence in the estimate of the effect; the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

Supplementary Table 3. Results of Network Meta-Analysis Based on Trials Evaluating the Success Rate of Stone Removal for Stones ≥ 15 mm

	Success rate of stone removal	
	Risk ratio (95% CI)	Quality of evidence
All treatments vs sphincterotomy		
Sphincteroplasty	0.98 (0.92–1.05)	Low owing to imprecision and risk of bias in the literature
S+EPLBD	1.14 (1.03–1.42)	Low owing to imprecision and risk of bias in the literature
Mechanical lithotripsy	1.02 (0.85–1.06)	Low owing to imprecision and risk of bias in the literature
SOC	2.21 (1.22–2.69)	Low owing to imprecision and risk of bias in the literature
Vs sphincteroplasty		
S+EPLBD	1.05 (0.99–1.12)	Low owing to imprecision and risk of bias in the literature
Mechanical lithotripsy	1.08 (0.86–2.25)	Low owing to imprecision and risk of bias in the literature
SOC	1.33 (1.04–1.51)	Low owing to imprecision and risk of bias in the literature
Vs S+EPLBD		
Mechanical lithotripsy	1.02 (0.83–1.21)	Low owing to imprecision and risk of bias in the literature
SOC	1.82 (1.08–2.42)	Low owing to imprecision and risk of bias in the literature
Vs mechanical lithotripsy		
SOC	1.27 (1.03–1.56)	Low owing to imprecision and risk of bias in the literature

S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation; SOC, single operator cholangioscopy (+electrohydraulic or laser lithotripsy).

Supplementary Table 4. SUCRA Score Ranking of Different Modalities Regarding the Success Rate of Removal of Stones ≥ 15 mm

Success rate of stone removal	
SOC	0.97
S+EPLBD	0.71
Mechanical lithotripsy	0.37
Sphincteroplasty	0.35
Sphincterotomy	0.12

S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation; SOC, single-operator cholangioscopy (+electrohydraulic or laser lithotripsy); SUCRA, surface under the cumulative ranking.

Supplementary Table 5. Results of Network Meta-Analysis Based on Trials Evaluating the Success Rate of Stone Removal in Index ERCPs

	Success rate of stone removal	
	Risk ratio (95% CI)	Quality of evidence
All treatments vs sphincterotomy		
Sphincteroplasty	1.03 (0.99–1.08)	Low owing to imprecision and risk of bias in the literature
S+EPLBD	1.05 (1.01–1.08)	Low owing to imprecision and risk of bias in the literature
Mechanical lithotripsy	1.02 (0.88–1.08)	Low owing to imprecision and risk of bias in the literature
Vs sphincteroplasty		
S+EPLBD	1.01 (0.97–1.05)	Low owing to imprecision and risk of bias in the literature
Mechanical lithotripsy	0.94 (0.84–1.05)	Low owing to imprecision and risk of bias in the literature
Vs S+EPLBD		
Mechanical lithotripsy	0.93 (0.84–1.03)	Low owing to imprecision and risk of bias in the literature

ERCP, endoscopic retrograde cholangiopancreatography; S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation.

Supplementary Table 6. SUCRA Score Ranking of Different Modalities Regarding the Success Rate of Removal of Stones in Index ERCPs

Success rate of stone removal	
S+EPLBD	0.82
Sphincteroplasty	0.69
Mechanical lithotripsy	0.25
Sphincterotomy	0.10

ERCP, endoscopic retrograde cholangiopancreatography; S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation; SUCRA, surface under the cumulative ranking.

Supplementary Table 7. Detailed List of the Adverse Events Reported in the Included Trials

Study	Groups	Overall early complications	Post-ERCP pancreatitis	Bleeding	Cholangitis	Death
VLavianos et al, ¹⁸ 2003	Sphincteroplasty vs sphincterotomy	7/103 vs 3/99	5/103 vs 1/99	0/103 vs 0/99	0/103 vs 0/99	0/103 vs 1/99
Kim et al, ¹⁹ 2009	S+EPLBD vs sphincterotomy	0/27 vs 0/28	0/27 vs 0/28	0/27 vs 0/28	0/27 vs 0/28	0/27 vs 0/28
Stefanidis et al, ²⁰ 2011	S+EPLBD vs mechanical lithotripsy	2/45 vs 9/45	1/45 vs 1/45	1/45 vs 1/45	0/45 vs 6/45	0/45 vs 0/45
Oh and Kim, ²¹ 2012	Sphincteroplasty vs sphincterotomy	9/40 vs 11/43	2/40 vs 3/43	4/40 vs 7/43	2/40 vs 1/43	0/40 vs 0/43
Fu et al, ²² 2013	Sphincteroplasty vs sphincterotomy	3/103 vs 14/103	3/88 vs 11/88	0/103 vs 3/103	NR	0/103 vs 0/103
Hwang et al, ²³ 2013	Sphincteroplasty vs S+EPLBD	4/62 vs 5/69	4/62 vs 3/69	0/62 vs 0/69	0/62 vs 0/69	0/62 vs 0/69
Bo et al, ²⁴ 2013	S+EPLBD vs sphincterotomy	5/63 vs 8/69	4/63 vs 6/69	0/63 vs 0/69	1/63 vs 1/69	0/63 vs 0/69
Teoh et al, ²⁵ 2013	S+EPLBD vs sphincterotomy	5/73 vs 8/78	2/73 vs 3/78	1/73 vs 0/78	1/73 vs 2/78	0/73 vs 0/78
Li et al, ²⁶ 2013	S+EPLBD vs sphincterotomy	16/232 vs 27/230	12/232 vs 15/230	4/232 vs 12/230	2/232 vs 2/230	0/232 vs 0/230
Guo et al, ²⁷ 2015	Sphincterotomy vs sphincteroplasty vs S+EPLBD	4/85 vs 4/85 vs 5/85	2/85 vs 2/85 vs 2/85	1/85 vs 1/85 vs 1/85	1/85 vs 1/85 vs 2/85	0/85 vs 0/85 vs 0/85
Cheon et al, ²⁸ 2016	Sphincteroplasty vs S+EPLBD	5/42 vs 5/44	3/42 vs 5/44	1/42 vs 1/44	1/42 vs 0/44	0/42 vs 0/44
Karsenti et al, ²⁹ 2017	S+EPLBD vs sphincterotomy	6/74 vs 5/54	1/74 vs 0/54	3/74 vs 2/54	0/74 vs 0/54	0/74 vs 0/54
Omar et al, ³⁰ 2017	Sphincteroplasty vs sphincterotomy	7/61 vs 9/63	3/61 vs 4/63	1/61 vs 4/63	2/61 vs 1/63	0/61 vs 0/63
Franzini et al, ³¹ 2017	SOC vs S+EPLBD	2/48 vs 6/50	1/48 vs 2/50	0/48 vs 2/50	1/48 vs 0/50	0/48 vs 0/50
Angsuwatcharakon et al, ³² 2018	SOC vs mechanical lithotripsy	1/16 vs 2/16	1/16 vs 1/16	1/16 vs 0/16	0/16 vs 0/16	0/16 vs 0/16
Buxbaum et al, ³³ 2018	SOC vs mechanical lithotripsy	4/42 vs 2/18	2/42 vs 1/18	0/42 vs 0/18	2/42 vs 1/18	0/42 vs 0/18
Park et al, ³⁴ 2018	Sphincteroplasty vs S+EPLBD	6/100 vs 4/100	1/100 vs 3/100	0/100 vs 0/100	0/100 vs 0/100	0/100 vs 0/100
Kogure et al, ³⁵ 2020	Sphincteroplasty vs sphincterotomy	8/86 vs 8/85	4/86 vs 5/85	0/86 vs 1/85	3/86 vs 2/85	0/86 vs 0/85
Bang et al, ³⁶ 2020	S+EPLBD vs SOC	1/33 vs 3/33	1/33 vs 1/33	0/33 vs 0/33	0/33 vs 0/33	0/33 vs 0/33

ERCP, endoscopic retrograde cholangiopancreatography; S+EPLBD, sphincterotomy followed by endoscopic papillary large balloon dilation; SOC, single-operator cholangioscopy (+electrohydraulic or laser lithotripsy).