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Endoscopic sphincterotomy vs papillary large balloon dilation vs combination modalities for large common bile duct stones: a network meta-analysis

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ABSTRACT

Background and study aims The optimal technique for removal of large common bile duct (CBD) stones (≥ 10 mm) during endoscopic retrograde cholangiopancreatography (ERCP) remains unclear. We aimed to perform a comparative analysis between different endoscopic techniques.

Methods Adhering to PRISMA guidelines, a stringent search of the following databases through January 12, 2021, were undertaken: PubMed/Medline, Embase, Web of Science, and Cochrane. Randomized controlled trials comparing the following endoscopic techniques were included: (1) Endoscopic sphincterotomy (EST); (2) Endoscopic papillary large balloon dilation (EPLBD); and (3) EST plus large balloon dilation (ESLBD). Stone clearance rate (SCR) on index ERCP was the primary outcome/endpoint. Need for mechanical lithotripsy (ML) and adverse events were also evaluated as secondary endpoint. Random effects model and frequentist approach were used for statistical analysis.

Results A total of 16 studies with 2545 patients (1009 in EST group, 588 in EPLBD group, and 948 patients in ESLBD group) were included. The SCR was significantly higher in ESLBD compared to EST risk ratio [RR]: 1.11, [confidence interval] CI: 1.00–1.24). Lower need for ML was noted for ESLBD (RR: 0.48, CI: 0.31–0.74) and EPLBD (RR: 0.58, CI: 0.34–0.98) compared to EST. All other outcomes including bleeding, perforation, post-ERCP pancreatitis, stone recurrence, cholecystitis, cholangitis, and mortality did not show significant difference between the three groups. Based on network ranking, ESLBD was superior in terms of SCR as well as lower need for ML and adverse events (AEs).

Conclusions Based on network meta-analysis, ESLBD seems to be superior with higher SCR and lower need for ML and AEs for large CBD stones.

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Introduction

Endoscopy is widely accepted as the first-line therapy for common bile duct (CBD) stone removal [1]. Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST), endoscopic papillary large balloon dilation (EPLBD), and/or combination of both i. e., EST plus large balloon dilation (ESLBD) has been utilized and evaluated in multiple longitudinal studies and randomized controlled trials (RCTs) for extraction of CBD stones [2]. Difficult stones are defined based on size, number, difficult shape, location of the stone, or anatomy of the patient [2]. European Society of Gastrointestinal Endoscopy (ESGE) guidelines from 2019 recommend ESLBD for difficult stones. This is an umbrella recommendation considering all factors including the large stones however no specific criteria or definition for large stone is given. Therefore, more data remain to be unveiled for optimal treatment technique for large stones (≥ 10 mm) [3].

A recent systematic review and network meta-analysis by Park et al. attempted to answer the question of best endoscopic technique to achieve stone clearance and concluded that ESLBD was superior compared to other techniques in terms of stone clearance rate on index ERCP (SCR). In addition, the authors also reported lower rates of post-ERCP pancreatitis (PEP) with EST and ESLBD, however, the result were not statistically significant [4]. The authors did not attempt to stratify analysis with regards to size of the stone.

Given the lack of evidence regarding efficacy of these techniques for CBD stone (≥ 10 mm), we attempt a systematic review and network meta-analysis of RCTs comparing the three techniques (EST, EPLBD and ESLBD) during ERCP to generate both direct and indirect evidence.

Methods

Search strategy

We followed the guidelines and framework laid in "Preferred Reporting items for Systematic Review and Meta-Analysis (PRISMA)" to conduct our study [5]. The following databases were systematically searched from inception through January 12, 2021: MEDLINE (PubMed platform, U.S. National Library of Medicine), Embase (Embase.com, Elsevier), Web of Science (Clarviate) and Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley). The initial search strategy was formulated by the investigators (Z.K. and M.A.) and further refined and conducted by an experienced librarian (W.L.-S.). Controlled vocabularies and medical subject terms were used for the concepts of "Common bile duct stone," "Endoscopic sphincterotomy," "balloon dilation," and "Endoscopic treatment or management," along with search hedges for RCTs to develop a search strategy for Embase. This was then translated into syntax and subject vocabulary of other databases for a comprehensive search. The citations were exported to Endnote X9 (Clarivate, Philadelphia, Pennsylvania, United States) and duplicates were identified and removed using software assistance with visual inspection. No restriction in terms of language was applied while screening for studies. A sample search strategy is highlighted in **Supplementary Table 1**.

Inclusion/exclusion criteria

Studies were considered on the basis of following parameters: (1) Patients: Adult patients (18 years or older) with large CBD stone ≥ 10 mm (either based on study inclusion criteria or actual data on mean stone diameter given); (2) Interventions: EPLBD and ESLBD; (3) Control: EST; (4) Primary outcomes: Stone clearance rate on index ERCP (SCR), overall stone removal (OSR), need for mechanical lithotripsy (ML), post-ERCP pancreatitis (PEP); and (5) Secondary outcomes: Adverse events (AEs), bleeding, stone recurrence, incidence of cholangitis, incidence of cholecystitis, overall mortality, and incidence of perforation. Only RCTs were considered eligible for inclusion, while other study designs i. e., cohort, cross-sectional, case-control, reviews, guidelines, case series, and case reports were excluded from our analysis to generate the highest level of evidence. We excluded abstracts as bias assessment is difficult due to lack of detailed methodology. If more than one study was available from a single center with overlapping study periods, data from the most recent updated study was considered eligible for inclusion to avoid duplicate data.

Primary and secondary endpoints

a) SCR: successful stone clearance on first/index ERCP.
b) OSR: successful stone removal in the respective intervention group irrespective of number of sessions needed.
c) ML: Use of mechanical lithotripsy as adjunct modality to break large stones for extraction.
d) AE: Any AEs related to the procedure. Overall AEs as well as specific events including bleeding, perforation, PEP, cholecystitis, cholangitis, and mortality were compared.

Screening and data abstraction

The screening was performed by two independent reviewers (Z.K. and M.A.). Initially screening was performed based on article title and abstracts. This was followed by full text screening of pertinent articles. Data abstraction was performed by two independent reviewers using Microsoft Excel (Microsoft, Redmond, Washington, United States) (Z.K. and M.A.). Discrepancies and conflicts were resolved through mutual discussion. Data regarding demographics (age, gender), stone size inclusion criteria, patient factors (diameter of stones, CBD diameter), and outcomes (SCR, OSR, ML, AE, PEP, bleeding, stone recurrence, perforation, mortality, cholangitis, and cholecystitis) were abstracted and tabulated using Microsoft Excel.

Data synthesis and statistical analysis

We performed pairwise meta-analysis (for direct evidence) and network meta-analysis (for direct + indirect evidence) using DerSimonian-Laird approach as a priori to pool and compare outcomes given the presumed heterogeneity in study population. We used Open Meta Analyst (CEBM, University of Oxford, Oxford, United Kingdom), and 'R' (Package: Netmeta, Bell labs, Murray Hill, New Jersey, United States) to conduct pairwise direct and network meta-analysis, respectively. Studies were

assigned weights by the inverse of its variance using within-studies variance as well as between-studies variance (tau-squared). For each binary outcome, forest plot, risk ratios (RR), 95 % confidence interval (CI), and *P* values were generated. The Cochrane Q test (with *P* value) and I^2 statistic (> 50 % considered substantial) was used to assess the heterogeneity and inconsistency within and between study designs [6]. Prediction interval (PI) using tau^2 was calculated and presented along with relevant CI.

We used the frequentist approach to rank the interventions in network meta-analysis. For each outcome, a *P* score was generated [7]. A higher *P* score (close to 1.00) corresponded to superior outcomes i. e., successful stone removal (SCR or OSR) and/or lower adverse outcomes (for e. g., lower rate of PEP). The validity of network meta-analysis was performed using the "netsplit" function to split the direct and indirect evidence and to test local inconsistency and *P* value was obtained (< 0.05 considered significant for inconsistent evidence between direct and indirect estimates). We used the "Grading of Recommendations Assessment, Development and Evaluation (GRADE)" approach to assess the certainty of evidence (High, Moderate, Low, Very Low) [8].

Bias assessment

The bias assessment for included RCTs was evaluated using the Cochrane risk of bias tool [9]. Publication bias was assessed qualitatively using the funnel plot and quantitatively using the Egger's regression analysis and rank correlation method. $P < 0.05$ was considered statistically significant for publication bias.

Results

A total of 16 studies were finalized for the systematic review and network meta-analysis [10–25]. A total of 2545 patients (1009, 588, and 948 patients in EST, EPLBD, and ESLBD group, respectively) were included (▶ **Table 1**). The study selection is shown in PRISMA diagram (▶ **Fig. 1**).

Study details

All studies were published between 2007 and 2020. Seven studies directly compared EST to ESLBD, four studies directly compared EST to EPLBD, three studies compared EPLBD to ESLBD, and two studies compared all three interventions simultaneously. The mean age of the patient ranged between 44.8 to 80.9 years and the proportion of male patients was 46.4 %, 47.8 %, and 48.9 % in the EST, EPLBD, and ESLBD groups, respectively. The individual outcome for each study is summarized in **Supplementary Table 2**.

Direct meta-analysis

EPLBD vs EST

The SCR and OSR was compared in 5 (RR: 0.98, CI: 0.96–1.01, PI: 0.71–1.37, *P* = 0.24, I^2 = 67.3 %) and six studies (RR: 0.99, CI: 0.87–1.12, PI: 0.87–1.12, *P* = 0.83, I^2 = 0 %) respectively and was not significantly different. A lower need for ML was noted for EPLBD compared to EST (5 studies, RR: 0.64, CI: 0.44–0.93, PI: 0.38–1.07, *P* = 0.02, I^2 = 6.0 %) (**Supplementary Fig. 1a, b, c**).

No significant difference was noted in overall AE (6 studies, RR: 0.95, CI: 0.62–1.45, PI: 0.62–1.45, *P* = 0.82, I^2 = 0 %), PEP (6 studies, RR: 1.04, CI: 0.58–1.87, PI: 0.58–1.87, *P* = 0.89, I^2 = 0%), bleeding (6 studies, RR: 0.46, CI: 0.15–1.47, PI: 0.15–1.47, *P* = 0.19, I^2 = 0 %), perforation (4 studies, RR: 1.47, CI: 0.23–9.22, PI: 0.23–9.22, *P* = 0.68, I^2 = 0 %), cholangitis (5 studies, RR: 1.36, CI: 0.48–3.87, PI: 0.48–3.87, *P* = 0.57, I^2 = 0 %), stone recurrence (2 studies, RR: 0.62, CI: 0.12–3.15, PI: 0.12–3.15, *P* = 0.57, I^2 = 0 %), and mortality (3 studies, RR: 0.99, CI: 0.10–9.41, PI: 0.10–9.41, *P* = 0.99, I^2 = 0 %) (**Supplementary Fig. 1d, e, f, g, h, i, j, k**).

ESLBD vs EST

Higher SCR was noted for ESLBD; however, the results did not achieve statistical significance (9 studies, RR: 1.08, CI: 0.99–1.17, PI: 0.84–1.38, *P* = 0.07, I^2 = 72.5 %). The OSR was not significantly different between the two groups (9 studies, RR: 1.01, CI: 0.99–1.03, PI: 0.99–1.03, *P* = 0.51, I^2 = 0 %). A significantly lower need for ML was observed for ESLBD compared to EST (9 studies, RR: 0.46, CI: 0.27–0.78, PI: 0.10–2.04, *P* = 0.004, I^2 = 69.6 %) (**Supplementary Fig. 2a, b, c**).

A lower rate of overall AEs was noted for ESLBD compared to EST; however, the result was not statistically significant (9 studies, RR: 0.71, CI: 0.48–1.04, PI: 0.40–1.24, *P* = 0.08, I^2 = 8.5 %). No significant difference was observed for bleeding (9 studies, RR: 0.71, CI: 0.36–1.41, PI: 0.36–1.41 *P* = 0.33, I^2 = 0 %), perforation (5 studies, RR: 0.56, CI: 0.13–2.39, PI: 0.13–2.39 *P* = 0.43, I^2 = 0 %), PEP (8 studies, RR: 0.85, CI: 0.51–1.40, PI: 0.51–1.40, *P* = 0.52, I^2 = 0 %), cholangitis (6 studies, RR: 0.69, CI: 0.23–2.10, PI: 0.23–2.10, *P* = 0.51, I^2 = 0 %), cholecystitis (4 studies, RR: 1.02, CI: 0.23–4.44, PI: 0.23–4.44, *P* = 0.98, I^2 = 0), stone recurrence (2 studies, RR: 0.71, CI: 0.28–1.84, PI: 0.28–1.84, *P* = 0.48, I^2 = 0 %), and mortality (2 studies, RR: 1.03, CI: 0.07–16.38, PI: 0.07–16.38, p = 0.98, I^2 = 0 %) (**Supplementary Fig. 2d, e, f, g, h, i, j, k**).

ESLBD vs EPLBD

The SCR was compared in five studies and a higher success rate was noted for ESLBD, however, this was not statistically significant (RR: 1.04, CI: 0.99–1.08, PI: 0.99–1.08, *P* = 0.12, I^2 = 0 %). The OSR was compared in five studies and no significant difference was observed (RR: 1.01, CI: 0.97–1.04, PI: 0.97–1.04, p = 0.76, I^2 = 0 %). The need for ML was not different between the two groups (5 studies, RR: 1.03, CI: 0.63–1.68, PI: 0.53–2.01, p = 0.90, I^2 = 8.1 %) (**Supplementary Fig. 3a, b, c**).

No significant difference was observed for overall AEs (5 studies, RR: 1.07, CI: 0.56–2.05, PI: 0.56–2.05, *P* = 0.84, I^2 = 0%), bleeding (5 studies, RR: 0.96, CI: 0.22–4.18, PI: 0.22–4.18, *P* = 0.96, I^2 = 0 %), perforation (3 studies, RR: 1.51, CI: 0.19–12.17, PI: 0.19–12.17, p = 0.70, I^2 = 0 %), PEP (5 studies, RR: 1.03, CI: 0.46–2.27, PI: 0.46–2.27, *P* = 0.95, I^2 = 0 %), and cholangitis (3 studies, RR: 1.34, CI: 0.26–6.84, PI: 0.26–6.84, *P* = 0.73, I^2 = 0 %) (**Supplementary Fig. 3d, e, f, g, h**). Not enough data were available to compare outcomes in terms of cholecystitis, mortality and CBD stone recurrence.

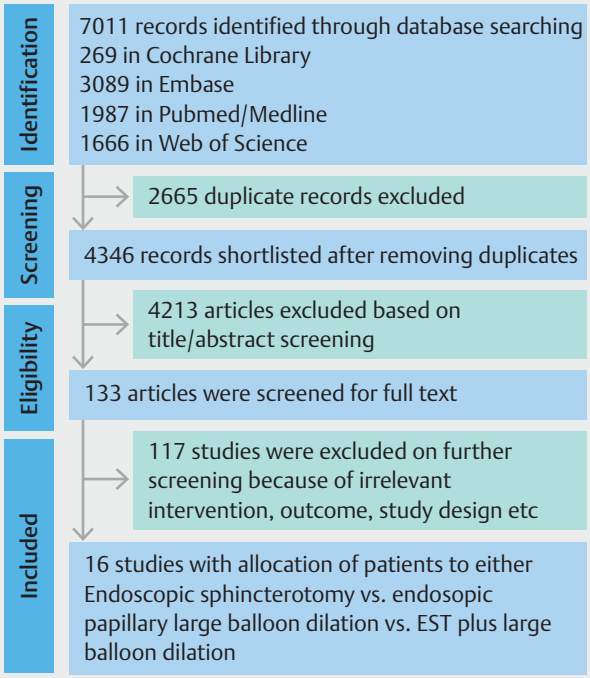
▶ **Table 1** Study details and demographics of included patients.

Study, year	Techniques compared	Study Period	Total no. patients, n	Age	Male gender, (%)	Inclusion criteria of CBD stone	Mean diameter of CBD stone, mm (SD)	Mean diameter of CBD, mm (SD)
Heo, 2007	EST vs ESLBD	2004–2005	EST: 100 ESLBD: 100	EST: 62.8 (15.7) ESLBD: 64.4 (12.8)	EST: 50.0 % ESLBD: 48.0 %	≤ 40 mm	EST: 15.0 (0.7) ESLBD: 16.0 (0.7)	NR
Kim, 2009	EST vs ESLBD	2006–2008	EST: 28 ESLBD: 27	EST: 69.8 (9.2) ESLBD: 70.3 (8.7)	EST: 39.3 % ESLBD: 37.0 %	15–50 mm	EST: 21.3 (5.2) ESLBD: 20.8 (4.1)	EST: 20.5 (5.7) ESLBD: 21.4 (6.3)
Stefanidis, 2011	EST vs ESLBD	2005–2009	EST: 45 ESLBD: 45	EST: 68.2 (18.9) ESLBD: 69.4 (17.8)	EST: 48.9 % ESLBD: 53.3 %	12–20 mm	NR	EST: 16. (4.2) ESLBD: 16.8 (3.7)
Oh, 2012	EST vs EPLBD	2010–2011	EST: 43 EPLBD: 40	EST: 68.7 (12.9) EPLBD: 72.3 (9.5)	EST: 53.5 % EPLBD: 50.0 %	> 10 mm	EST: 13.1 (3.9) EPLBD: 13.2 (3.6)	EST: 18.2 (4.6) EPLBD: 18.0 (4.3)
Hwang, 2013	EPLBD vs ESLBD	2009	EPLBD: 62 ESLBD: 69	EPLBD: 70.4 (10.9) ESLBD: 68.2 (10.5)	EPLBD: 37.1 % ESLBD: 47.8 %	≥ 12 mm	EPLBD: 15.7 (3.3) ESLBD: 16.5 (4.2)	EPLBD: 20.5 (4.4) ESLBD: 21.4 (4.6)
Minakari, 2013	EST vs EPLBD	2008–2011	EPLBD: 80 EST: 80	NR	EST: 52.5 % EPLBD: 48.9 %	10–20 mm	NR	NR
Bo, 2013	EST vs ESLBD	2008–2012	EST: 69 ESLBD: 63	EST: 68.4 (22.8) ESLBD: 67.3 (23.4)	EST: 52.2 % ESLBD: 50.8 %	15–50 mm	EST: 20.3 (5.3) ESLBD: 20.6 (5.4)	EST: 21.5 (6.5) ESLBD: 22.4 (7.3)
Teoh, 2013	EST vs ESLBD	2005–2011	EST: 78 ESLBD: 73	EST: 73.0 (13.4) ESLBD: 71.6 (14.8)	EST: 51.3 % ESLBD: 43.8 %	≥ 13 mm	EST: 17.9 (10.1) ESLBD: 16.3 (8.7)	EST: 23.4 (10.7) ESLBD: 18.3 (4.9)
Li, 2014	EST vs ESLBD	2008–2011	EST: 230 ESLBD: 232	EST: 60.6 (16.6) ESLBD: 61.8 (16.7)	EST: 37.8 % ESLBD: 41.4 %	≤ 30 mm	NR	EST: 12.7 (3.5) ESLBD: 13.2 (3.7)
Guo, 2015	EST vs EPLBD vs ESLBD	2011–2013	EST: 85 EPLBD: 85 ESLBD: 85	EST: 59 (16) EPLBD: 62 (17) ESLBD: 63 (16)	EST: 50.6 % EPLBD: 52.9 % ESLBD: 54.1 %	≥ 10 mm	EST: 17.5 (8.7) EPLBD: 15 (5.8) ESLBD: 15 (5.8)	EST: 18.8 (8.4) EPLBD: 16.3 (5.5) ESLBD: 16.3 (5.5)
Chu, 2017	EST vs EPLBD vs ESLBD	2009–2011	ESLBD: 33 EST: 32 EPLBD: 30	ESLBD: 64.8 (5.5) EST: 65.6 (7.4) EPLBD: 64.7 (6.5)	ESLBD: 45.5 % EST: 56.3 % EPLBD: 43.3 %	≥ 10 mm	NR	ESLBD: 18.1 (4.2) EST: 17.9 (5.5) EPLBD: 18.4 (5.8)
Karsenti, 2017	EST vs ESLBD	2010–2015	EST: 73 ESLBD: 77	EST: 80.9 (11.6) ESLBD: 76.7 (11.9)	EST: 42.5 % ESLBD: 33.8 %	≥ 13 mm	EST: 16.2 (3.5) ESLBD: 16.5 (3.3)	EST: 16.9 (3.9) ESLBD: 16.8 (4.7)
Omar, 2017	EST vs EPLBD	2014–2016	EPLBD: 61 EST: 63	EPLBD: 47.8 (14.5) EST: 44.8 (13.9)	EPBLD: 42.6 % EST: 39.7 %	> 10 mm	EPBLD: 13.9 (2.4) EST: 13.1 (2.6)	EPBLD: 18.2 (4.6) EST: 17.1 (4.3)
Cheon, 2017	EPLBD vs ESLBD	2013–2015	EPLBD: 42 ESLBD: 44	EPLBD: 71.0 (12.4) ESLBD: 71.7 (10.1)	EPLBD: 50.0 % ESLBD: 54.5 %	12–34 mm	EPLBD: 14.4 (3.3) ESLBD: 14.0 (2.1)	EPLBD: 15.8 (3.6) ESLBD: 16.1 (3.2)

▶ **Table 1** Continued

Study, year	Techniques compared	Study Period	Total no. patients, n	Age	Male gender, (%)	Inclusion criteria of CBD stone	Mean diameter of CBD stone, mm (SD)	Mean diameter of CBD, mm (SD)
Park, 2018	EPLBD vs ESLBD	2010–2013	EPLBD: 100 ESLBD: 100	EPLBD: 73.8 (10.1) ESLBD: 71.5 (12.1)	EPLBD: 55.0 % ESLBD: 48.0 %	> 10 mm	EPLBD: 15.2 (0.6) ESLBD: 14.6 (0.5)	EPLBD: 19.1 (5.4) ESLBD: 22.8 (10.1)
Kogure, 2020	EST vs EPLBD	2013–2015	EST: 85 EPLBD: 86	EST: 80.9 (8.2) EPLBD: 79.1 (8.1)	EST: 48.2 % EPLBD: 44.2 %	≥ 10 mm	EST: 14.3 (4.8) EPLBD: 15.2 (4.6)	EST: 16.0 (4.0) EPLBD: 16.4 (3.6)

EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy; ESLBD, EST plus large balloon dilation; SD, standard deviation.



▶ **Fig. 1** PRISMA flow diagram.

Network meta-analysis

The SCR was significantly higher in ESLBD group compared to EST group (RR: 1.11, CI: 1.00–1.24, PI: 0.90–1.37). Lower need for ML was noted for both ESLBD (RR: 0.48, CI: 0.31–0.74, PI: 0.30–0.77) and EPLBD (RR: 0.58, CI: 0.34–0.98, PI: 0.25–1.01) group compared to EST group. Significant heterogeneity (I^2 = 51.1 %) was noted for need of ML. All other outcomes including overall AE, bleeding, perforation, PEP, stone recurrence, cholecystitis, cholangitis, and mortality did not show significant difference between the three groups i. e., EST, EPLBD, and ESLBD (▶ **Table 2**) (▶ **Fig. 2a, b, c, d, e, f, g, h, i, j, k**, **Supplementary Fig. 4**).

Ranking of interventions

Based on frequentist approach, ESLBD was noted to be superior compared to other interventions in terms of SCR, lower need for ML, overall AEs, perforation, PEP, and cholangitis. EPLBD was noted to be superior compared to other interventions for lower rates of bleeding. OSR was comparable for EPLBD and ESLBD and higher than EST (▶ **Fig. 3**).

Validity of meta-analysis

Risk of bias for individual studies using Cochrane risk of bias tools is summarized in **Supplementary Table 3**. All studies had high risk of bias due to impractical blinding of endoscopist to study intervention group as well as lack of blinding of study personnel to outcomes. The funnel plot for SCR demonstrated visible asymmetry (particularly when comparing EPLBD vs EST and ESLBD vs EST) while symmetrical plot was observed for OSR (▶ **Fig. 4a, b**). The Egger's regression (*P* value) was 0.06 and 0.98 and rank correlation test (*P* value) was 0.25 and 0.97 for SCR and OSR respectively.

Using the netsplit technique, the direct and indirect evidence for meta-analysis was compared and no significant difference was noted for all outcomes (supplementary material).

GRADE assessment

The overall quality of evidence was rated as high for OSR, AEs, perforation, bleeding, PEP, cholangitis, CBD stone recurrence and mortality. The quality of evidence for SCR between EPLBD vs EST and ESLBD vs EST as well as need for ML between ESLBD vs EST was rated as moderate due to substantial heterogeneity based on I^2 statistic (inconsistency). The quality of evidence was rated as moderate for cholecystitis as there were no direct studies comparing ESLBD and EPLBD.

Discussion

This systematic review and network meta-analysis of 16 RCTs with 2545 patients evaluated the effectiveness and safety of ESLBD, EPLBD, and EST for large CBD stone (i. e. ≥ 10 mm) removal. We illustrated that ESLBD has superiority in SCR compared to other techniques. In addition, both ESLBD and EPLBD showed lower need of ML compared to EST.

▶ **Table 2** Results from network meta-analysis.

Outcomes	No. pairwise comparison	EPLBD vs ESLBD, RR (95% CI)	ESLBD vs EST, RR (95% CI)	EPLBD vs EST, RR (95% CI)	Heterogeneity (within designs), I^2	Heterogeneity (within designs), Q (*P* value)	Inconsistency (between designs), Q (*P* value)	GRADE assessment
SCR	19	0.96 (0.83–1.10)	1.11 (1.00–1.24)[1]	1.06 (0.92–1.22)	0%	4.84 (0.93)	1.79 (0.62)	High
OSR	20	1.00 (0.88–1.13)	1.01 (0.92–1.12)	1.02 (0.90–1.15)	0%	0.45 (1.00)	0.08 (0.99)	High
ML	19	1.20 (0.70–2.05)	0.48 (0.31–0.74)[1]	0.58 (0.34–0.98)[1]	51.1%	25.80 (0.01)	4.86 (0.18)	Moderate
AE	20	1.15 (0.73–1.82)	0.75 (0.53–1.06)	0.86 (0.58–1.29)	0%	9.92 (0.70)	1.11 (0.77)	High
Bleeding	20	0.78 (0.27–2.28)	0.67 (0.34–1.30)	0.52 (0.19–1.43)	0%	7.21 (0.89)	0.38 (0.94)	High
Perforation	12	1.22 (0.25–5.81)	0.75 (0.21–2.75)	0.91 (0.20–4.08)	0%	2.20 (0.99)	0.73 (0.39)	High
PEP	19	1.09 (0.61–1.95)	0.89 (0.55–1.42)	0.96 (0.57–1.63)	0%	4.74 (0.97)	1.60 (0.66)	High
Cholangitis	14	1.52 (0.45–5.15)	0.80 (0.30–2.19)	1.23 (0.45–3.35)	0%	2.35 (0.94)	2.79 (0.42)	High
Cholecystitis	5	0.97 (0.01–64.21)	1.02 (0.23–4.47)	0.99 (0.02–49.81)	0%	0.01 (1.00)	NA	Moderate
Stone recurrence	5	0.92 (0.14–6.11)	0.71 (0.26–1.94)	0.66 (0.13–3.39)	0%	NA	1.28 (0.53)	Moderate
Mortality	7	0.98 (0.09–10.67)	1.02 (0.09–11.10)	1.00 (0.12–8.15)	0%	0 (0.99)	0 (1.00)	High

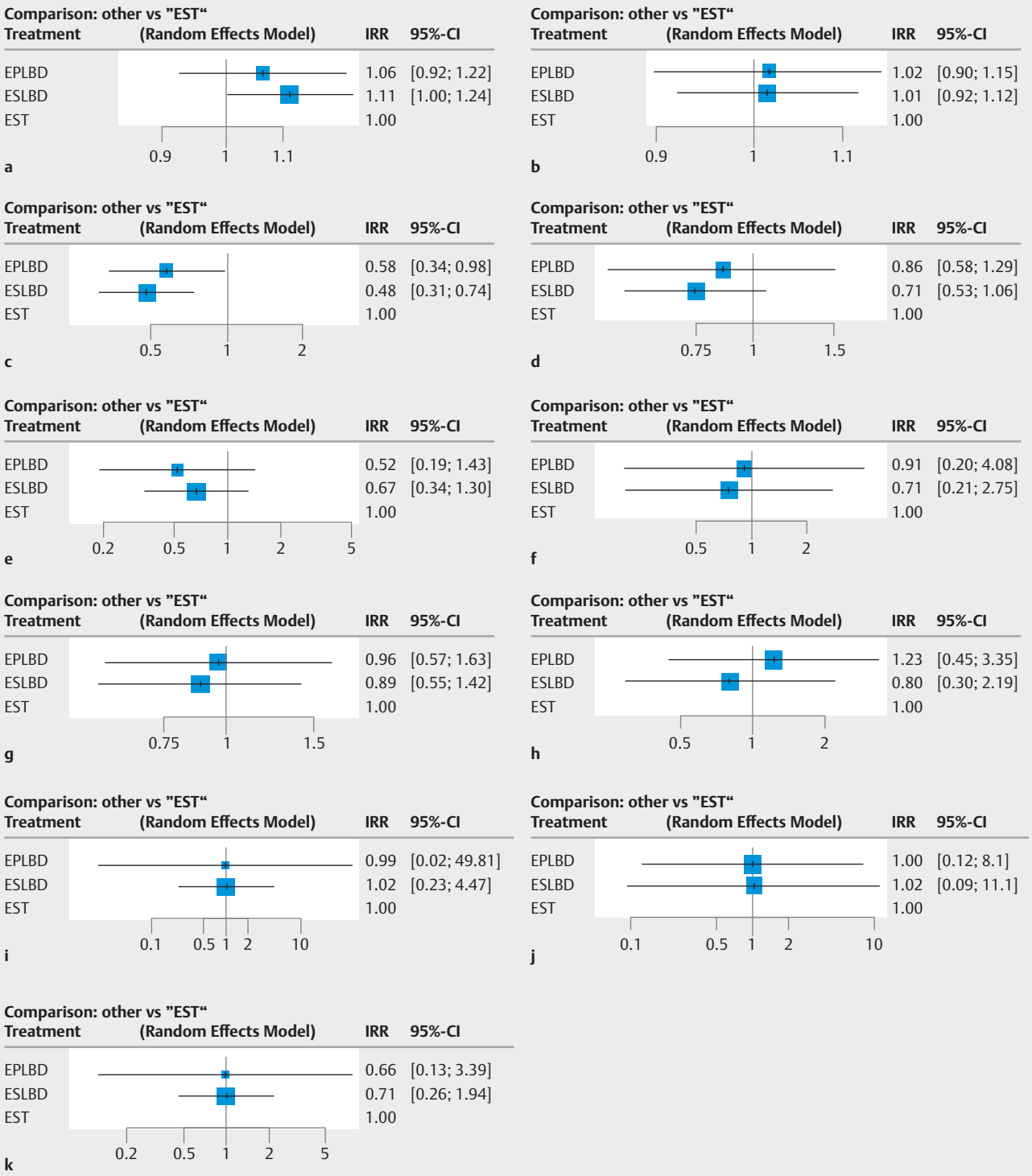
AE, adverse events; CI, confidence interval; EPLBD, endoscopic papillary large balloon dilation; ESLBD, endoscopic sphincterotomy plus large balloon dilation; EST, endoscopic sphincterotomy; ML, mechanical lithotripsy; OSR, overall stone removal; PEP, post-ERCP pancreatitis; RR, risk ratio; SCR, stone clearance on index ERCP.
[1] Denotes significant result.

EST was first introduced by Kawai et al in 1974 and immediately became the standard technique at the time during ERCP for stone removal [26]. The technique was limited in cases of tortuous CBD or presence of large and multiple stones sometimes necessitating repeat procedure or the use of ML. This was followed by the introduction of EPLBD by Staritz et al in 1982, where stone were extracted using balloon dilation without the need for EST [27]. This method was also somewhat limited due to resulting higher PEP rates [28]. Erosz et al. then introduced ESLBD, a combination of both techniques i. e. EST and EPLBD to reduce the AEs as well as increase the efficacy of the procedure [29]. There has been limited and contradictory data on the effectiveness and AEs of the three modalities; therefore, we decided to pool the data and performed a network meta-analysis.

Both EST and EPLBD have their own advantages. EST is able to make the outlet large enough for the stone to pass while EPLBD is able to clear long tortuous tracts using balloon dilation. Theoretically, by combining both techniques as ESLBD, the overall effectiveness i. e., SCR is anticipated to increase and need for adjuvant modality i. e., ML is expected to decrease [30, 31]. De Clemente Jr. et al. in their recent meta-analysis of 11 RCTs found a lower need for ML in ESLBD compared to EST [32]. Indeed, the net ranking in our analysis reflected the superiority of ESLBD in improving SCR and decreased need for ML.

In addition to higher effectiveness, ESLBD had lower overall AEs, perforation, PEP, and cholangitis compared to the other modalities. PEP is the most common complication after ERCP with incidence of 3% to 15% [33]. Previous studies have shown higher rates of PEP with EPLBD compared to EST (16.7% vs 6.7%) likely because of compartment syndrome from hemorrhage/edema and an uncut sphincter of Oddi [34, 35]. By combining EST to balloon dilation as ESLBD, this complication is lowered which was demonstrated in our analysis.

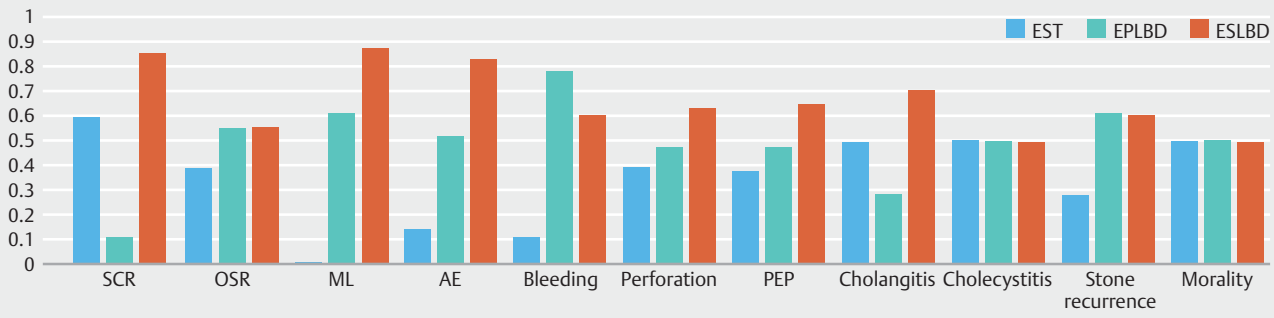
We compare our study to the network meta-analysis by Park et al. The authors in this comprehensive review compared the three techniques and demonstrated the superiority of ESLBD in improving SCR as well as decreasing the rates of ML, PEP, and other adverse outcomes [24]. The authors in this review included stones of all sizes. We only included studies with large stones i. e. ≥10 mm and found consistent results. In addition, newer studies were published that we included in our analysis.



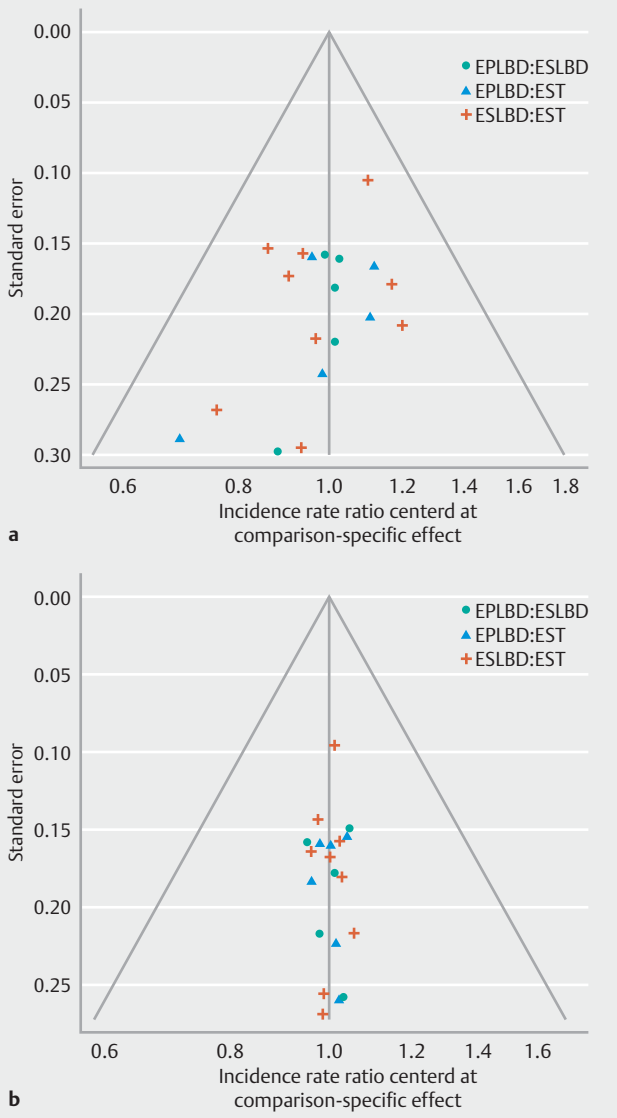
▶ **Fig. 2** Forest plot for network meta-analysis demonstrating **a** stone clearance rate on index ERCP, **b** overall stone removal, **c** need for mechanical lithotripsy, **d** overall adverse events, **e** bleeding, **f** perforation, **g** post-ERCP pancreatitis, **h** cholangitis, **i** cholecystitis, **j** mortality and **k** CBD stone recurrence. CI, confidence interval; EPLBD, endoscopic papillary large balloon dilation; EST, endoscopic sphincterotomy; ESLBD, EST plus large balloon dilation; IRR, incidence relative risk).

Our results further validate the previous network meta-analysis by Park et al. and support the use of ESLBD by endoscopists to clear large CBD stones.

Our study had some limitations. First, in these RCTs there was inability to blind due to nature of the procedure. Second, there was heterogeneity in technical details of procedures in-



▶ **Fig. 3** Ranking of interventions compared in network meta-analysis. (Note: For SCR and OSR, higher number reflects improved rates. For other outcomes, higher number reflects lower rates.) AE, adverse events; EPLBD, endoscopic papillary large balloon dilation; ESLBD, endoscopic sphincterotomy plus large balloon dilation; EST, endoscopic sphincterotomy; ML, mechanical lithotripsy; OSR, overall stone removal; PEP, post-ERCP pancreatitis; SCR, stone clearance rate on index ERCP.



▶ **Fig. 4** Funnel plot revealing **a** asymmetry for stone clearance on index ERCP session, **b** no visible asymmetry for overall stone removal. EPLBD, endoscopic papillary large balloon dilation; ESLBD, endoscopic sphincterotomy plus large balloon dilation; EST, endoscopic sphincterotomy.

cluding the extent of sphincterotomy incision or duration of balloon insertion. Third, we did not use abstracts, which could limit the data, although increasing the quality at the same time. Fourth, meta-analysis can identify statistical significance, which may not necessarily translate into clinical significance and hence readers should use our systematic review as a guide and not as absolute recommendation. Fifth, the type, shape, and location of the stone and biliary anatomy are other factors leading to difficulty, that are not considered in this analysis. Lastly, we did not conduct subgroup analysis in different geographical locations. For example, Park et al. found a higher rate of PEP in non-Asian population that was attributed to more sphincter of Oddi dysfunction in non-Asian cohorts [24]. Our study had some strengths. All the studies were RCTs, hence, avoiding confounders associated with observational studies. The overall quality of evidence using GRADE methodology was rated as high for factors associated with effectiveness including SCR, OSR, and ML, and AEs including perforation, bleeding, PEP, cholangitis, and mortality. Other major strengths were that through conducting a stringent search strategy, performing an exhaustive search, and performing both direct and network (direct and indirect) meta-analysis, we conducted a comprehensive meta-analysis on updated studies comparing all the three modalities of EST, EPLBD, and ESLBD.

Conclusions

In conclusion, our meta-analysis illustrated a higher effectiveness of ESLBD compared to EPLBD and EST in terms of lower ML and higher SCR for large CBD stones. In addition, ESLBD showed less AEs compared to other modalities including perforation, cholangitis, and PEP. The standard method, EST, has the lowest effectiveness and highest AEs.

Competing interests

N. Thosani is consultant for Boston Scientific Corp, Pentax America, Ambu. He has received royalty from UpToDate and is speaker for Abbvie. He has creatorship rights for ROSEAId inc.

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