Supplementary Online Content

Ricci C, Pagano N, Taffurelli G, et al. Comparison of efficacy and safety of 4 combinations of laparoscopic and intraoperative techniques for management of gallstone disease with biliary duct calculi: a systematic review and network meta-analysis. *JAMA Surg*. Published online May 30, 2018. doi:10.1001/jamasurg.2018.1167

eAppendix. Methods

eFigure 1. PRISMA Flow Diagram

eFigure 2. Quality Assessment of the Study Based on the Cochrane Collaboration Tool for Assessing Risk of Bias in Randomized Trials

eFigure 3. Network Geometry of All Outcomes

eFigure 4. Contribution Plots of All Outcomes

eFigure 5. Forest Plots of All Outcomes

eFigure 6. Cluster Rank Combined the Surface Under the Cumulative Ranking Curve (SUCRA) Values, Success Rate and Mortality Rate

eFigure 7. Funnel Plots of the Network Estimates of All Outcomes

eTable 1. Covariate Potential Source of Heterogeneity in the Studies Included

eTable 2. The Ranking of the Approaches Ranking for All Outcomes

eTable 3. Meta-regression of Confounding Covariates Influencing Heterogeneity

References.

eAppendix. Methods

Information sources and search strategy

A systematic literature search was conducted in order to identify all online published studies, comparing all types of endoscopic or surgical managements of gallstones associated with biliary duct calculi, using the Medline, Scopus and the ISI-Web of Science databases. The last search was carried out on September14[th], 2017.The bibliographies of the studies and related reviews were included for additional references. The following search terms were used in several logical combinations: "(LCBDE[All Fields] OR LC[All Fields] OR preoperative-ERCP[All Fields] OR (("postoperative period"[MeSH Terms] OR ("postoperative"[All Fields] AND "period"[All Fields]) OR "postoperative period"[All Fields] OR ("post"[All Fields] AND "operative"[All Fields]) OR "post operative"[All Fields]) AND ("cholangiopancreatography, endoscopic retrograde"[MeSH Terms] OR ("cholangiopancreatography"[All Fields] AND "endoscopic"[All Fields] AND "retrograde"[All Fields]) OR "endoscopic retrograde cholangiopancreatography"[All Fields] OR "ercp"[All Fields])) OR ("Rendezvous (Buffalo)"[Journal] OR "rendezvous"[All Fields]) OR (intraoperative[All Fields] AND ("cholangiopancreatography, endoscopic retrograde"[MeSH Terms] OR ("cholangiopancreatography"[All Fields] AND "endoscopic"[All Fields] AND "retrograde"[All Fields]) OR "endoscopic retrograde cholangiopancreatography"[All Fields] OR "ercp"[All Fields])) OR one-stage[All Fields] OR two-stage[All Fields] OR single-stage[All Fields]) AND (("gallstones"[MeSH Terms] OR "gallstones"[All Fields] OR "gallstone"[All Fields]) OR ("calculi"[MeSH Terms] OR "calculi"[All Fields] OR "stone"[All Fields]) OR ("calculi"[MeSH Terms] OR "calculi"[All Fields]) OR (CBD[All Fields] AND ("calculi"[MeSH Terms] OR "calculi"[All Fields] OR "stone"[All Fields]))) AND (("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("surgery"[Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "surgery"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields]) OR ("endoscopy"[MeSH Terms] OR "endoscopy"[All Fields] OR "endoscopic"[All Fields])) AND (("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields]) OR ("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomized"[All Fields]) OR (controlled[All Fields] AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields])) OR ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]) OR study[All Fields])". Thomson Reuters Endnote version X7® was used to remove the duplicate studies.

Eligibility criteria

The eligibility criteria were either the comparative design between any type of endoscopic or surgical procedure for the management of gallstones and biliary duct calculi. In order to build the network of comparative studies, the various approaches were clustered into 4 arms: LC + LCBDE, LC + PostERCP, PreERCP + LC and LC + IntraERCP. It should be noted that, in the LC + LCBDE arm, some studies included only laparoscopic common bile duct exploration by means of choledochotomy while others also included the trans-cystic common bile duct exploration. No further divisions are made in this group because both approaches was frequently used in the same study. No additional major technical differences were found to justify more than three clusters for the ERCP procedures.

Study selection

Two independent investigators (C.R. and R.C) carried out the study selection. Those articles which satisfied the eligibility criteria were evaluated in full text form in order to verify the presence of the inclusion criteria and the absence of the exclusion criteria. The inclusion criteria were : 1) comparison between at least two of the above-mentioned techniques; 2) randomized clinical design; 3) data reporting the success rate in all arms; 4) reporting at least one of the following outcomes in all arms: overall morbidity, overall mortality, acute pancreatitis, biliary leak, overall

bleeding, overall operative time, LOS or total cost. On the contrary, the following criteria were used to exclude studies: 1) letters to the editor, case reports, reviews, systematic reviews or meta-analyses, guidelines, prospective or retrospective non-randomized comparative studies and abstracts without a full text; 2) randomized studies including open cholecystectomies or laparotomic common bile duct exploration; 3) studies reporting unextractable data; 4) studies at risk for patient cohort duplication based on affiliation, author and year of publication and 5) language other than English. Therefore, if two studies were reported by the same institution (and/or authors), either the most recent study or the one of higher quality was included. Finally, a PRISMA flowchart was also formulated in order to demonstrate the transparency of the conclusions reached by the authors.

Data collection process and item

Two independent reviewers (C.A.P and G.T.) carried out the data extraction using standardized data forms. All the data from each of the studies included was entered into a dedicated spreadsheet (Excel 2007, Microsoft Corporation®). The following data were extracted in order to describe the characteristics of each study: first author, affiliation and country, year of publication, type of patients enrolled, age, male/female ratio, study design, sample size of each arm and the outcomes of interest. The qualitative assessment of the studies was carried out on the basis of the Cochrane Collaboration tool for assessing the risk of bias in randomized trials. Any disagreement between the reviewers was resolved by discussion or consultation with the last author (F.M.).

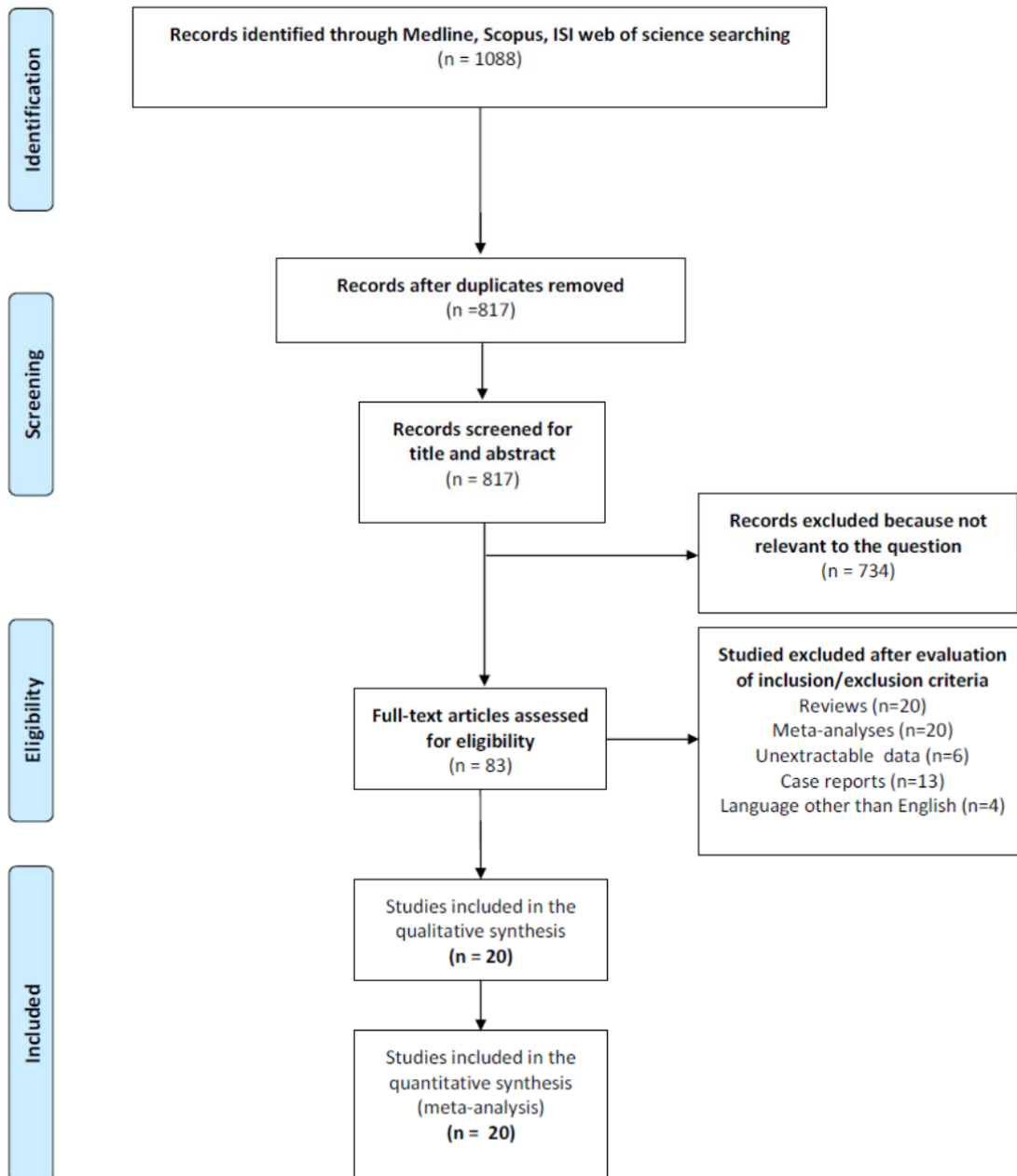**Outcomes of Interest and Definitions**

The success of the procedure was defined as the clearance of the common bile duct according to the "intention-to-treat" analysis. Namely, the success rate was defined by the ratio between the patients who completed the assigned procedure without protocol violations(numerator) and all randomized patients in each arm (denominator). For the ERCP arms, overall mortality, overall morbidity, overall bleeding, overall operative time, LOS and total cost were included in the cumulative data of both the endoscopic and the surgical procedures. Acute pancreatitis and biliary leak were defined according to the protocol of each randomized study.

Statistical analysis

Frequentist network meta-analysis was used to compare all the approaches available for treating gallstones and common biliary ductal calculi, generating a network for each outcome of interest [1]. The analysis was carried out according to the PRISMA extension statement incorporating Network Meta-Analyses of Health Care Interventions[2]. First, the meta-analytical results of all the pairwise ("head-to-head") comparisons in each network were calculated in order to obtain two main type of estimations: 1) indirect estimates, deriving from the analysis in network format and indicating the meta-analytical results of the "head-to-head" comparisons which had never appeared in the literature; 2) mixed estimates, indicating the meta-analytical results of all the "head-to-head" comparisons already available in the literature, but implemented by their analysis in network format [3]. All indirect and mixed estimates were reported as odds ratios (ORs) or mean differences (MDs) for dichotomous outcomes and continuous variables, respectively. The ORs and MDs were expressed with 95% confidence intervals (CIs). An OR with CIs crossing 1 or an MD with CIs crossing 0 indicated that the two competitive approaches for the removal of ductal calculi were equivalent. It should be noted that, the network estimates (indirect and mixed) were reported in the forest plot[4].Second, the network format permitted generating the "relative ranking probability" which represented the probability that each approach would be the best, the second, the third and the worst with a certain degree of uncertainty for each outcome of interest. Thus, using these values, the surface under the cumulative ranking (SUCRA) curves and mean ranks were obtained. In practice, the SUCRA value, expressed as a percentage, showed the probability, without uncertainty, that each approach would be the best option, based on the analyzed outcome represented [5]. Finally, the SUCRA values of the three outcomes of interest selected (two main indicators of safety, as well as overall morbidity and mortality, and one for efficacy as well as success rate) were used to calculate the safety/efficacy ratio [4]. Thus, in order to establish the best approach to the safety/efficacy ratio, two clustered ranking plots were created: overall morbidity/success rate and overall mortality/success rate. The robustness of the networks was assessed by evaluating the presence of inconsistency, heterogeneity and publication bias according to the PRISMA extension statement incorporating Network Meta-Analyses of Health Care Interventions[1]. The presence of inconsistency was evaluated using the "loop" approach [6]; when the ratio of two odds ratios (RoR) with CIs or the absolute difference between the direct and indirect estimations (IF) with CIs were close to 0 and 1 for dichotomous and continuous variables, respectively, inconsistency was absent. On

the other hand, the restricted maximum likelihood method was used to estimate heterogeneity. The extent of heterogeneity in each network was evaluated by comparing the magnitude of a common heterogeneity variance for the network (tau [τ]) with an empirical distribution of heterogeneity variances, considering the range of expected treatment estimates (ORs and MDs). A τ value less than 0.1 indicated a very low level of heterogeneity while a τ value from 0.1 to 0.5 indicated a reasonable level; a τ value from 0.5 to 1.0 was considered a fairly high level and a τ value greater than 1.0 represented very high heterogeneity [7] . When the τ value was > 0.5, a multivariate meta-regression analysis was carried out in order to identify the reason for the heterogeneity in the outcome under study. Thus, the effects of all the covariates were reported using a beta (β) coefficient and a P value. A two-sided P value <0.05 indicated a significant impact of the covariate on the values of OR/MD for the outcome considered. Publication/reporting bias was reported using an adjusted funnel plot. Each funnel plot was tested using the Begg's test in order to identify whether the asymmetry was attributable to the small sample size effect. A two-sided P value <0.05 indicated a significant small sample size effect [8].

Flow Diagram


```
┌──────────────┐
│ Identification│   ┌─────────────────────────────────────────────────────┐
└──────────────┘   │ Records identified through Medline, Scopus, ISI web of │
                   │ science searching (n = 1088)                           │
                   └─────────────────────────────────────────────────────┘
                                        │
                                        ▼
┌──────────────┐   ┌─────────────────────────────────┐
│  Screening   │   │ Records after duplicates removed │
└──────────────┘   │ (n =817)                         │
                   └─────────────────────────────────┘
                                        │
                                        ▼
                   ┌─────────────────────┐      ┌──────────────────────────────┐
                   │ Records screened for │─────▶│ Records excluded because not  │
                   │ title and abstract   │      │ relevant to the question      │
                   │ (n = 817)            │      │ (n = 734)                     │
                   └─────────────────────┘      └──────────────────────────────┘
                                        │
                                        ▼
┌──────────────┐   ┌─────────────────────┐      ┌──────────────────────────────┐
│ Eligibility  │   │ Full-text articles   │─────▶│ Studied excluded after        │
└──────────────┘   │ assessed for         │      │ evaluation of inclusion/      │
                   │ eligibility (n = 83) │      │ exclusion criteria            │
                   └─────────────────────┘      │ Reviews (n=20)                │
                                        │        │ Meta-analyses (n=20)          │
                                        ▼        │ Unextractable data (n=6)      │
                   ┌─────────────────────┐      │ Case reports (n=13)           │
                   │ Studies included in  │      │ Language other than English   │
                   │ the qualitative      │      │ (n=4)                         │
                   │ synthesis (n = 20)   │      └──────────────────────────────┘
                   └─────────────────────┘
                                        │
┌──────────────┐                        ▼
│  Included    │   ┌─────────────────────┐
└──────────────┘   │ Studies included in  │
                   │ the quantitative     │
                   │ synthesis            │
                   │ (meta-analysis)      │
                   │ (n = 20)             │
                   └─────────────────────┘
```

eFigure 1. PRISMA Flow Diagram.

eTable 1. Covariate potential source of heterogeneity in the studies included

First Author	Study Design		Year	Country (W or E)	Ductal Calculi	Age (MD, 95% CI)	Male (OR, 95% CI)	Trans-cystic approach in LCBDE arm	Risk of bias
Rhodes et al. [17]	LC + LCBDE vs. LC + PostERCP		1998	UK (W)	Proven	-6 (-12 to 1)	0.80 (0.31 to 2.03)	28/40 (0.7)	Low/Unclear
Cuschieri et al. [18]	LC + LCBDE vs. PreERCP + LC		1999	Europe and Australia (W)	Suspected	NE	NE	45/133 (0.4)	Low/Unclear
Sgourakis et al. [19]	LC + LCBDE vs. PreERCP + LC		2002	Greece (W)	Suspected	NE	NE	NE	High
Nathanson et al. [20]	LC + LCBDE vs. LC + PostERCP		2005	Australia (W)	Proven	-4 -(12 to 4)	1.05 (0.44 to 2.52)	0/57 (0)	Low/Unclear
Hong et al. [21]	LC + LCBDE vs. LC + IntraERCP		2006	China (E)	Proven	NE	NE	0/141 (0)	Low/Unclear
Lella et al. [22]	PreERCP + LC vs. LC +IntraERCP		2006	Italy (W)	Proven	NE	NE	NA	Low/Unclear
Morino et al. [23]	PreERCP + LC vs. LC +IntraERCP		2006	Italy (W)	Proven	6 (-1 to 12)	1.65 (0.75 to 3.88)	NA	Low/Unclear
Rabago et al. [24]	PreERCP + LC vs. LC +IntraERCP		2006	Spain (W)	Suspected	NE	NE	NA	Low/Unclear
Noble et al. [25]	LC + LCBDE vs. PreERCP + LC		2009	U.K. (W)	Proven	2 (1 to 3)*	1.54 (0.66 to 3.57)	5/44 (0.1)	Low/Unclear
Bansal et al. [26]	LC + LCBDE vs. PreERCP + LC		2010	India (E)	Proven	8 (-1 to 16)	0.73 (0.15 to 3.49)	0/15(0)	High
Rogers et al. [27]	LC + LCBDE vs. PreERCP + LC		2010	US (W)	Suspected	-5 (-6 to -4)*	1.01 (0.45 to 2.28)	57/57 (1)	Low/Unclear
ElGeide et al. [28]	PreERCP + LC vs. LC +IntraERCP		2011	Egypt (W)	Proven	-3 (-5 to -1)*	1.19 (0.64 to 2.23)	NA	Low/Unclear
ElGeide et al. (§) [29]	LC + LCBDE vs. LC + IntraERCP		2011	Egypt (W)	Proven	4 (2 to 6)*	0.87 (0.48 to 1.57)	57/115(0.5)	Low/Unclear

Ferulano et al. [30]	LC + LCBDE vs . PreERCP + LC		2011	Italy (W)	Suspected	NE	NE	NE	High
Tzovars et al. [31]	PreERCP + LC vs. LC +IntraERCP		2012	Greece (W)	Proven	3 (-3 to 4)	1.04 (0.47 to 2.29)	NA	Low/Unclear
Koc et al. [32]	LC + LCBDE vs. PreERCP + LC		2013	Turkey (W)	Proven	-3 (-10 to 4)	1.08 (0.49 to 2.37)	0/57(0)	Low/Unclear
Ding et al. [33]	LC + LCBDE vs . PreERCP + LC		2014	China (E)	Proven	0 (-2 to 2)	0.82 (0.48 to 1.39)	0/110(0)	Low/Unclear
Sahoo et al. [34]	PreERCP + LC vs. LC +IntraERCP		2014	India (E)	Proven	NE	NE	NA	Low/Unclear
Lv et al. [35]	LC + LCBDE vs. PreERCP + LC		2016	China (E)	Proven	-3 (-10 to 4)	1.65 (0.43 to 4.17)	NE	High
Poh et al. [36]	LC + LCBDE vs. LC + IntraERCP		2016	Australia (W)	Proven	-1 (-9 to 7)	1.17 (0.54 to 2.55)	29/52 (0.6)	Low/Unclear

Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography; W: Western; E: Eastern; MD: Mean Difference; 95% CI= 95% confidence interval; OR: Odds ratio; NE: not extractable, NA= not applicable

eFigure 2. Quality assessment of the study based on the Cochrane Collaboration tool for assessing risk of bias in randomized trials.
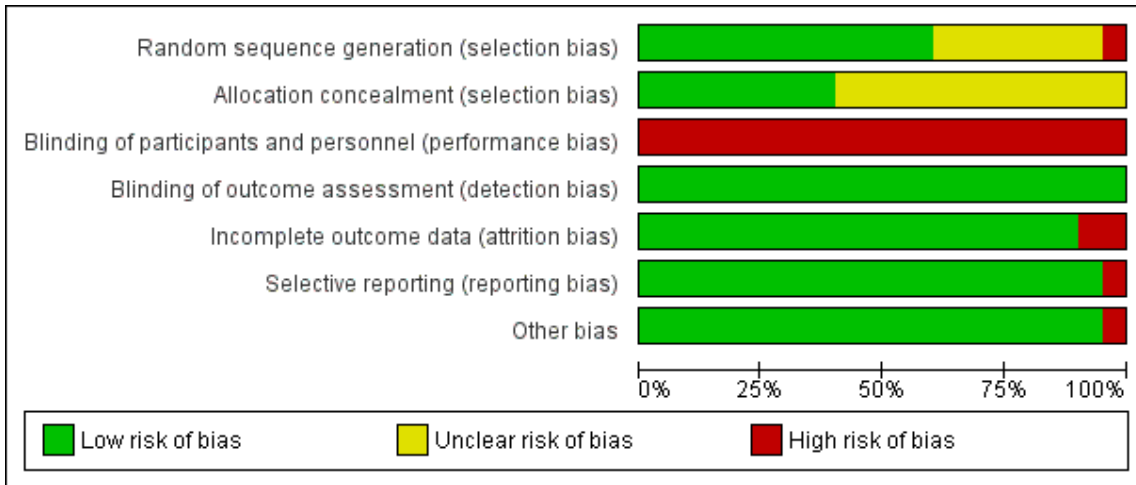
eFigure 3 (Panels A-I). Network geometry of all outcomes.
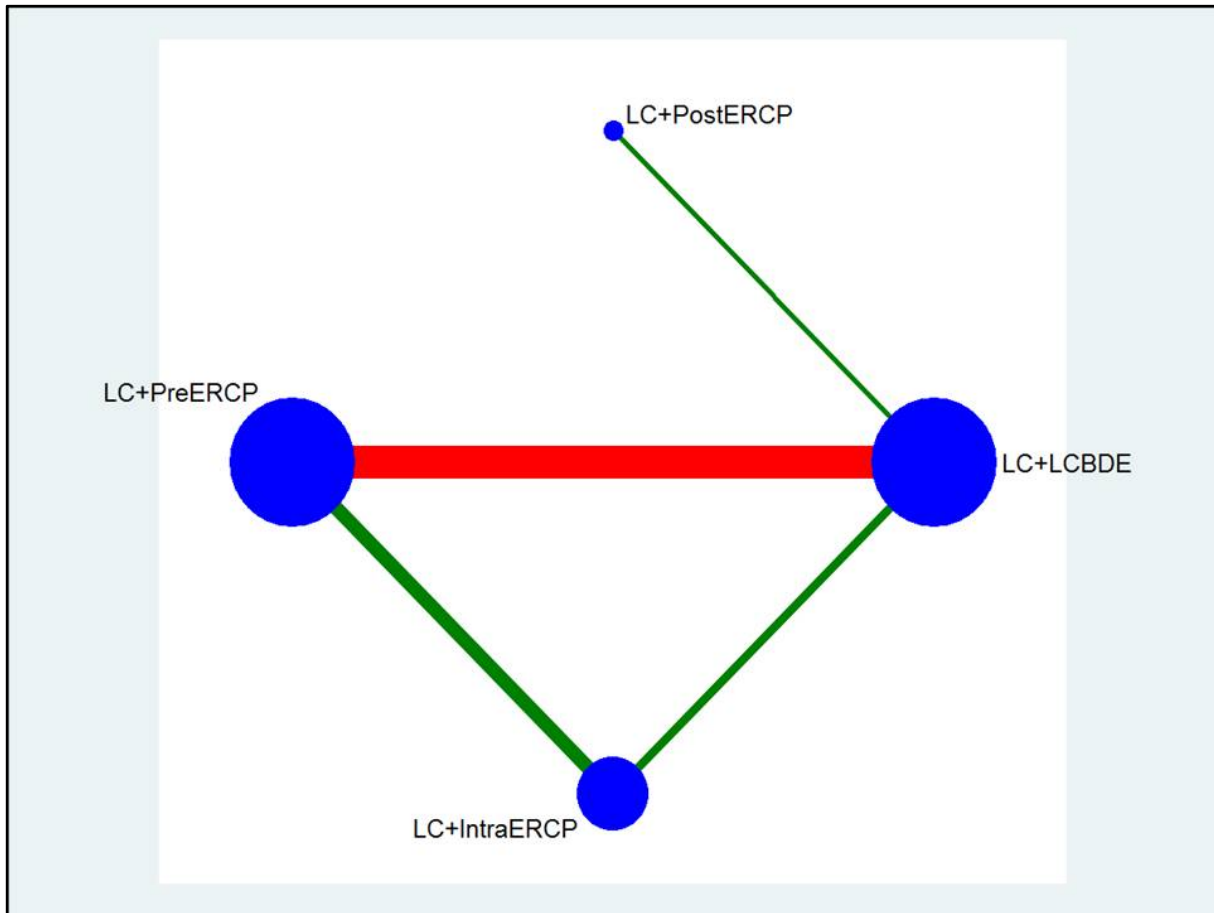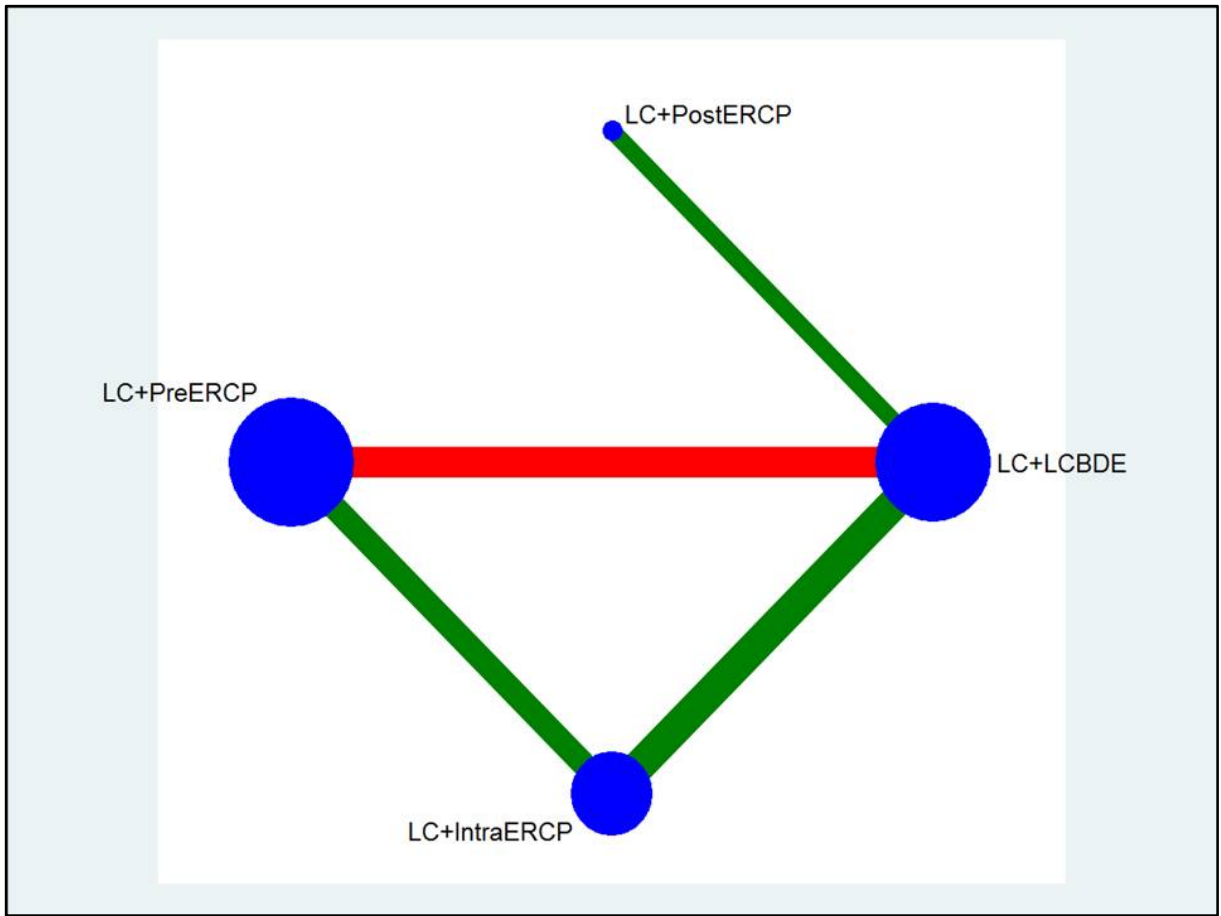
Panel A. Success rate

Legend: the blue nodes represent the interventions compared while the edges represent the direct comparisons available (comparisons evaluated in at least one study) between pairs of interventions. The node sizes are weighted based on the number of patients in each arm while the edges are weighted using inverse variance. The edge colors (green or red) are weighted based on the quality of the studies included. A green edge indicates the comparison with high quality studies while a red line indicates comparison with low quality studies. LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.
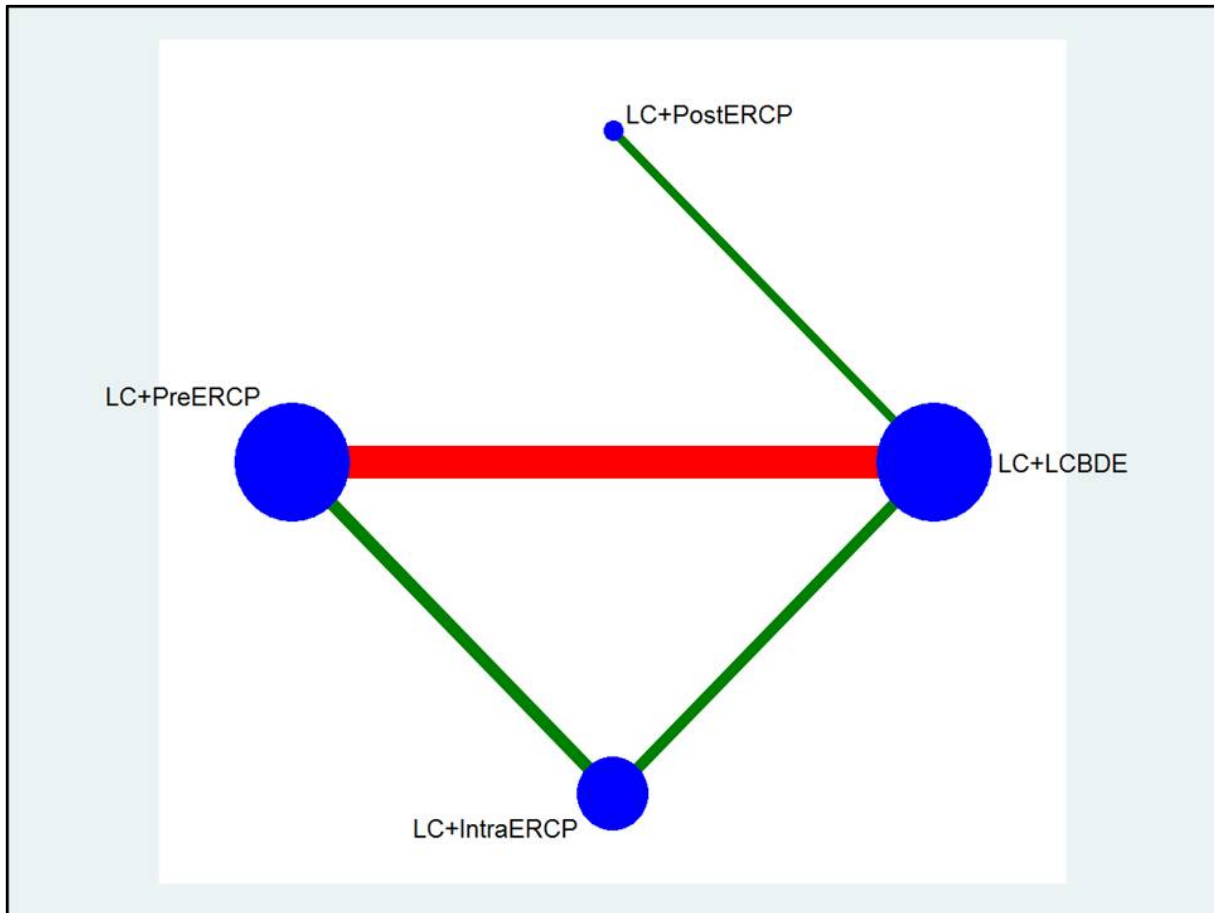
Panel B. Overall mortality rate

Legend: the blue nodes represent the interventions compared while the edges represent the direct comparisons available (comparisons evaluated in at least one study) between pairs of interventions. The node sizes are weighted based on the number of patients in each arm while the edges are weighted using inverse variance. The edge colors (green or red) are weighted based on the quality of the studies included. A green edge indicates the comparison with high quality studies while a red line indicates comparison with low quality studies. LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.
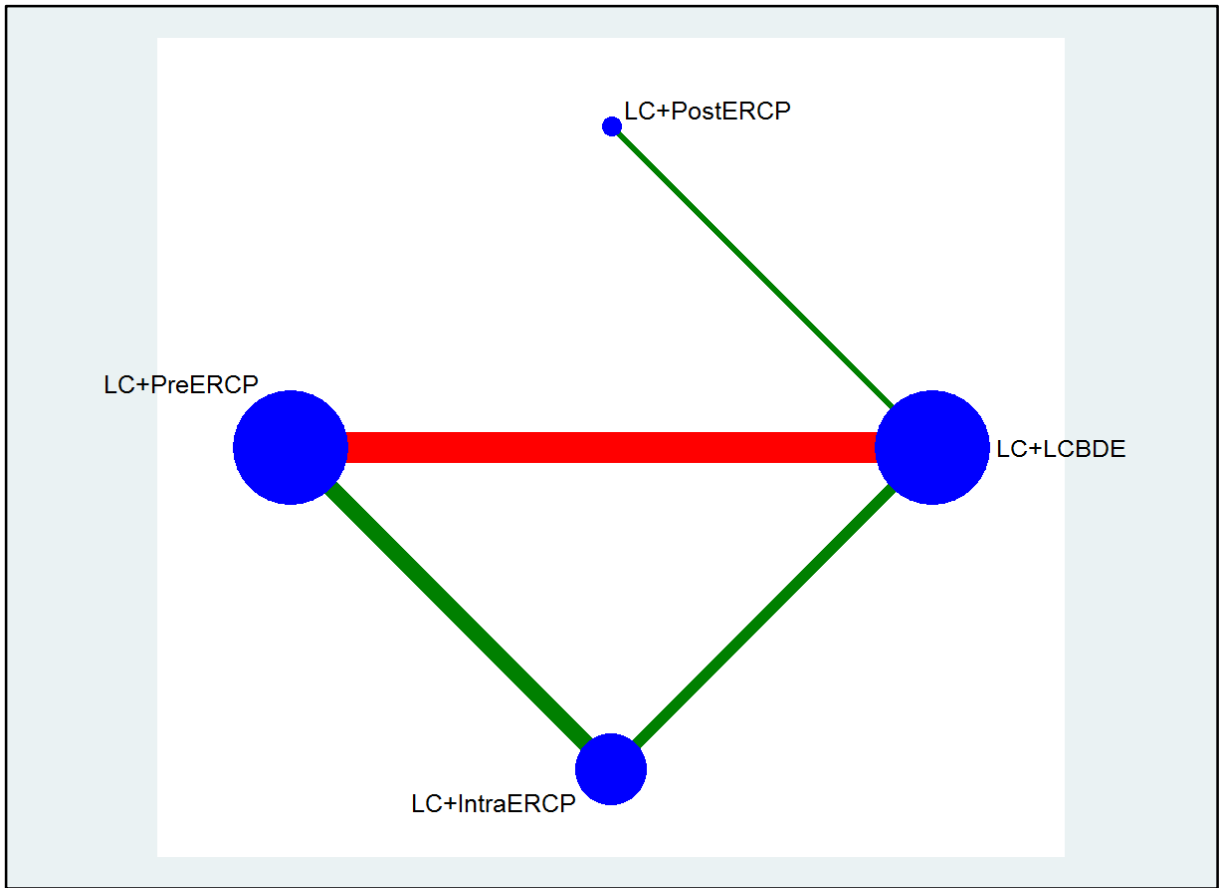
Panel C. Overall morbidity rate

Legend: the blue nodes represent the interventions compared while the edges represent the direct comparisons available (comparisons evaluated in at least one study) between pairs of interventions. The node sizes are weighted based on the number of patients in each arm while the edges are weighted using inverse variance. The edge colors (green or red) are weighted based on the quality of the studies included. A green edge indicates the comparison with high quality studies while a red line indicates comparison with low quality studies. LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.
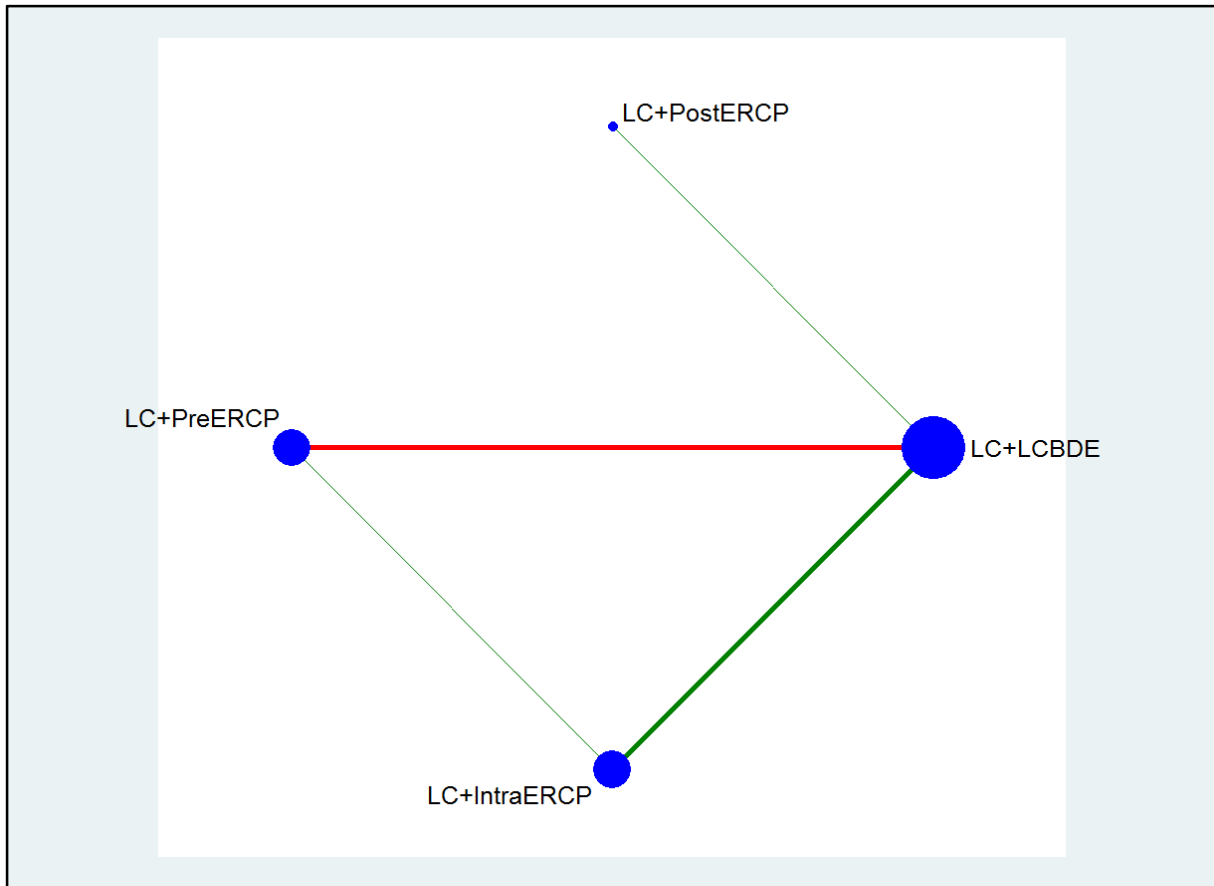
Panel D. Acute pancreatitis

Legend: the blue nodes represent the interventions compared while the edges represent the direct comparisons available (comparisons evaluated in at least one study) between pairs of interventions. The node sizes are weighted based on the number of patients in each arm while the edges are weighted using inverse variance. The edge colors (green or red) are weighted based on the quality of the studies included. A green edge indicates the comparison with high quality studies while a red line indicates comparison with low quality studies. LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

Panel E. Biliary leak

Legend: the blue nodes represent the interventions compared while the edges represent the direct comparisons available (comparisons evaluated in at least one study) between pairs of interventions. The node sizes are weighted based on the number of patients in each arm while the edges are weighted using inverse variance. The edge colors (green or red) are weighted based on the quality of the studies included. A green edge indicates the comparison with high quality studies while a red line indicates comparison with low quality studies. LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.
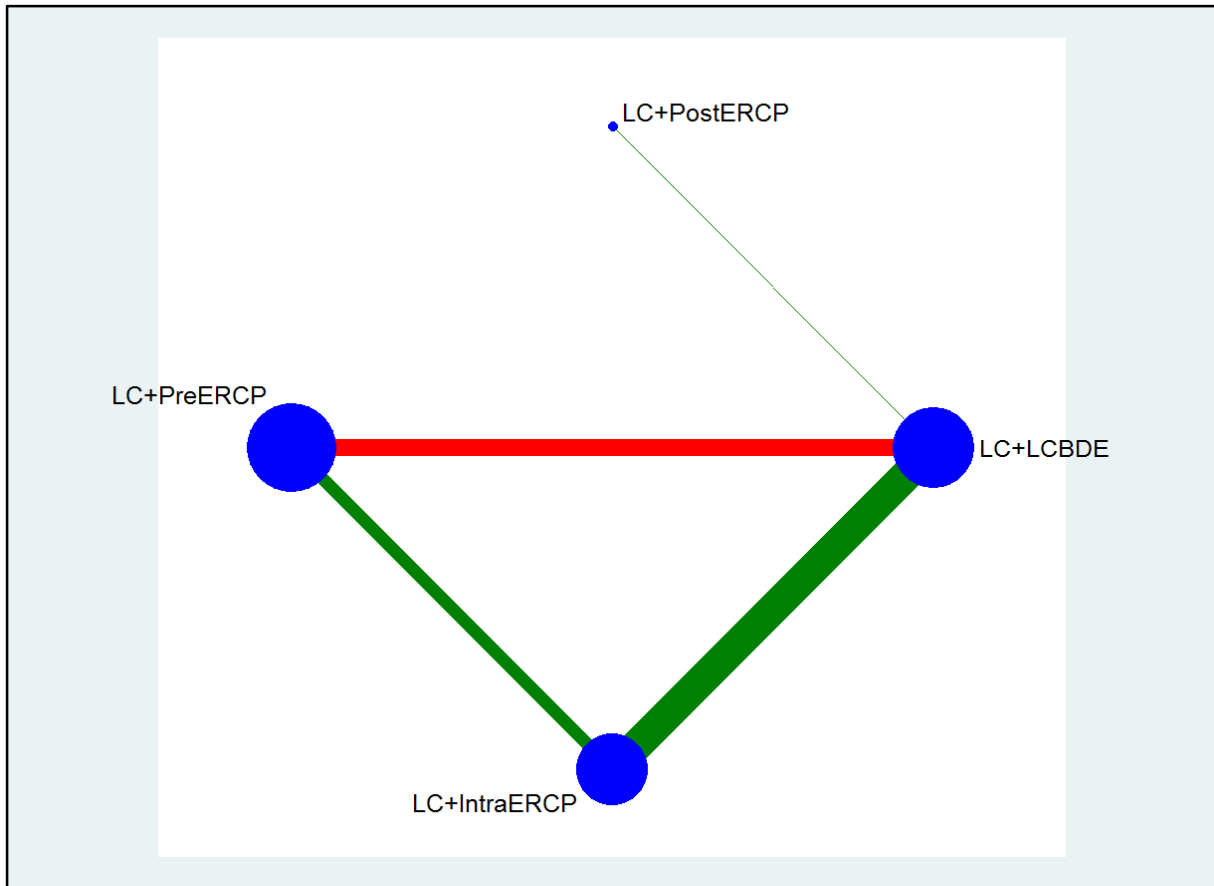
Panel F. Overall bleeding

Legend: the blue nodes represent the interventions compared while the edges represent the direct comparisons available (comparisons evaluated in at least one study) between pairs of interventions. The node sizes are weighted based on the number of patients in each arm while the edges are weighted using inverse variance. The edge colors (green or red) are weighted based on the quality of the studies included. A green edge indicates the comparison with high quality studies while a red line indicates comparison with low quality studies. LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

Panel G. Overall operative time

Legend: the blue nodes represent the interventions compared while the edges represent the direct comparisons available (comparisons evaluated in at least one study) between pairs of interventions. The node sizes are weighted based on the number of patients in each arm while the edges are weighted using inverse variance. The edge colors (green or red) are weighted based on the quality of the studies included. A green edge indicates the comparison with high quality studies while a red line indicates comparison with low quality studies. LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.
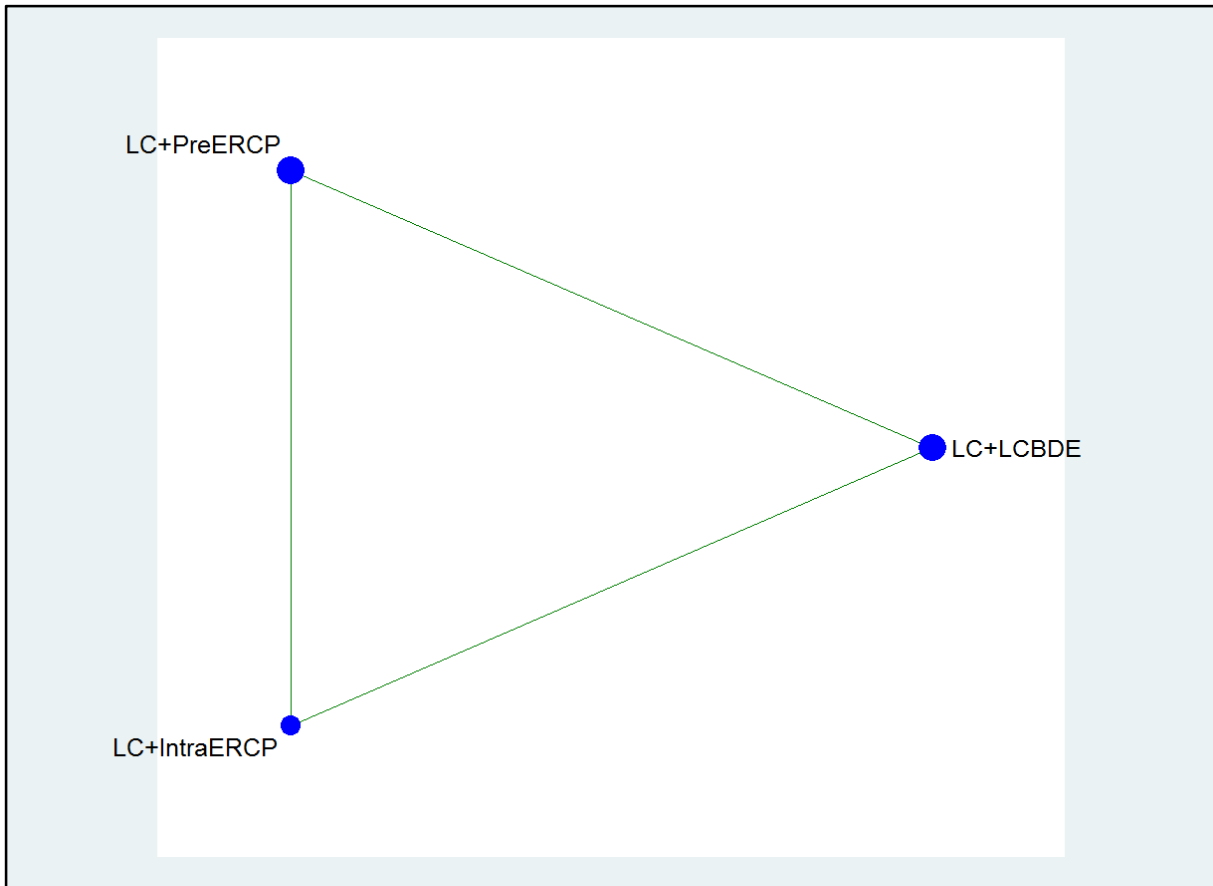
Panel H. Length of hospital stay

Legend: the blue nodes represent the interventions compared while the edges represent the direct comparisons available (comparisons evaluated in at least one study) between pairs of interventions. The node sizes are weighted based on the number of patients in each arm while the edges are weighted using inverse variance. The edge colors (green or red) are weighted based on the quality of the studies included. A green edge indicates the comparison with high quality studies while a red line indicates comparison with low quality studies. LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.
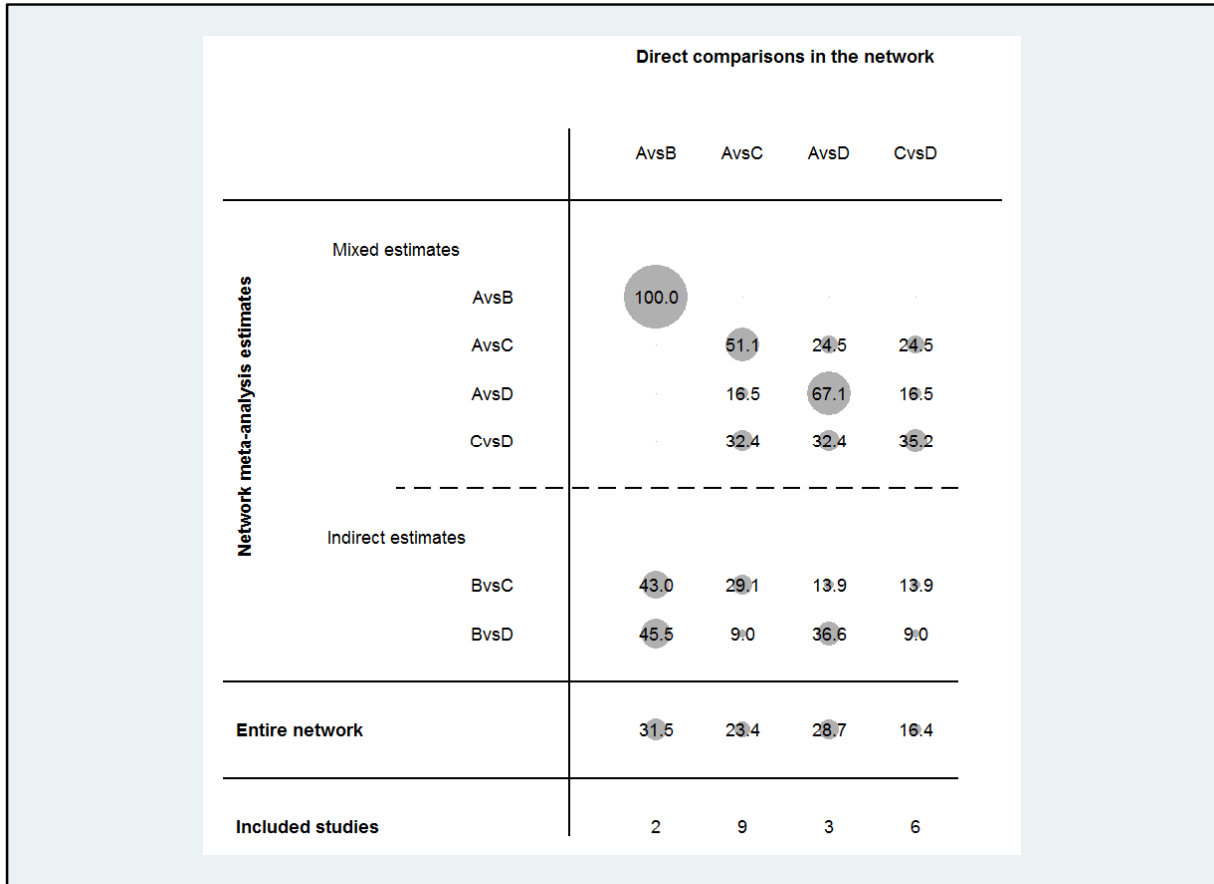
Panel I. Total cost

Legend: the blue nodes represent the interventions compared while the edges represent the direct comparisons available (comparisons evaluated in at least one study) between pairs of interventions. The node sizes are weighted based on the number of patients in each arm while the edges are weighted using inverse variance. The edge colors (green or red) are weighted based on the quality of the studies included. A green edge indicates the comparison with high quality studies while a red line indicates comparison with low quality studies. LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.
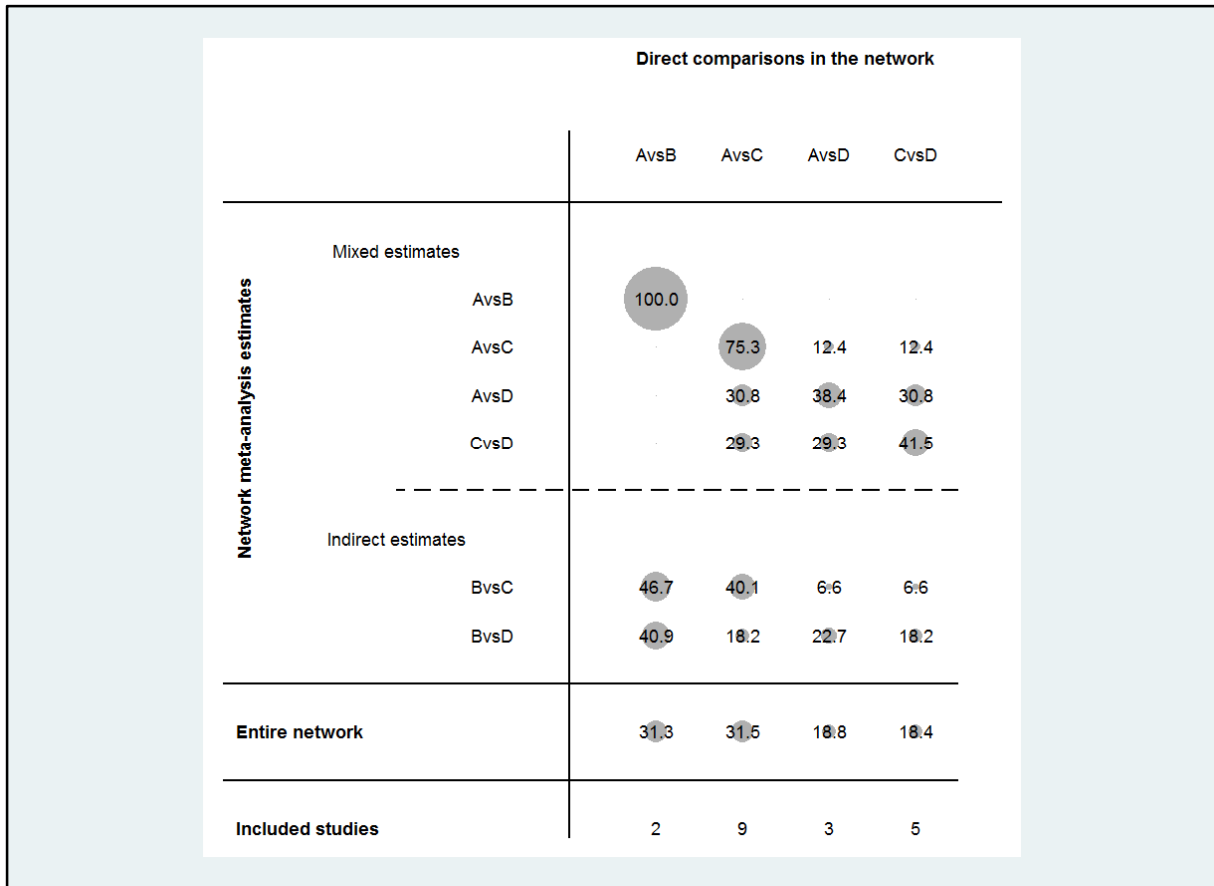
eFigure 4 (Panels A-I). Contribution plots of all outcomes.
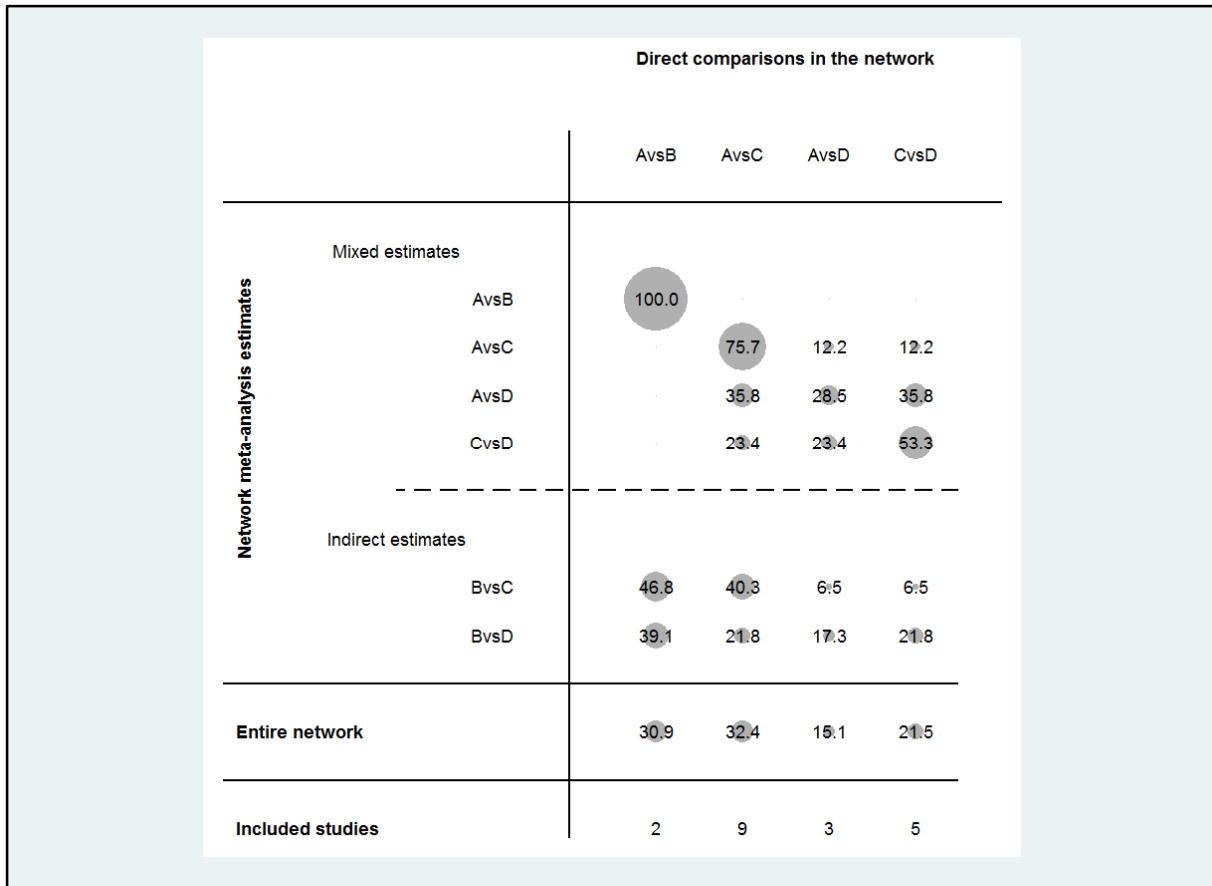
Panel A. Success rate

Legend: All available direct comparisons (comparisons evaluated in at least one study) are reported in the columns while the following are reported in the rows: 1) the mixed comparisons (namely the estimates already available in the literature but implemented by network) and 2) the indirect comparisons (namely the comparisons not available in the literature but generated by the network). The table should be read from left to right; each row contains the contribution of each direct comparison in the network (mixed and indirect) estimates and, thus, the cumulative sum of the contributions is 100 (in percentages). In the plots, the contribution of each direct comparison in building the entire network are also reported; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).

Panel B. Overall mortality rate

Direct comparisons in the network

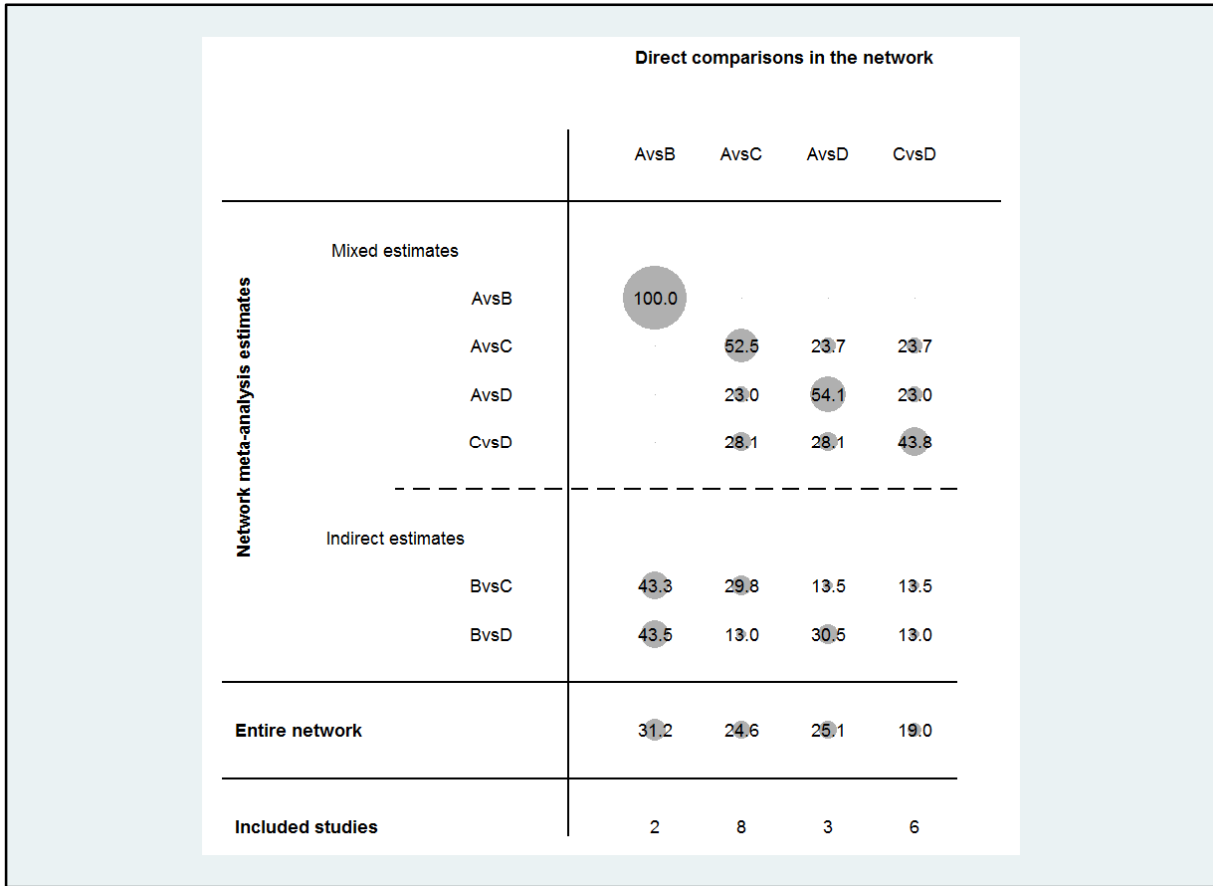| Network meta-analysis estimates	AvsB	AvsC	AvsD	CvsD
Mixed estimates				
AvsB	100.0			
AvsC		75.3	12.4	12.4
AvsD		30.8	38.4	30.8
CvsD		29.3	29.3	41.5
Indirect estimates				
BvsC	46.7	40.1	6.6	6.6
BvsD	40.9	18.2	22.7	18.2
Entire network	31.3	31.5	18.8	18.4
Included studies	2	9	3	5

Legend: All available direct comparisons (comparisons evaluated in at least one study) are reported in the columns while the following are reported in the rows: 1) the mixed comparisons (namely the estimates already available in the literature but implemented by network) and 2) the indirect comparisons (namely the comparisons not available in the literature but generated by the network). The table should be read from left to right; each row contains the contribution of each direct comparison in the network (mixed and indirect) estimates and, thus, the cumulative sum of the contributions is 100 (in percentages). In the plots, the contribution of each direct comparison in building the entire network are also reported; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).
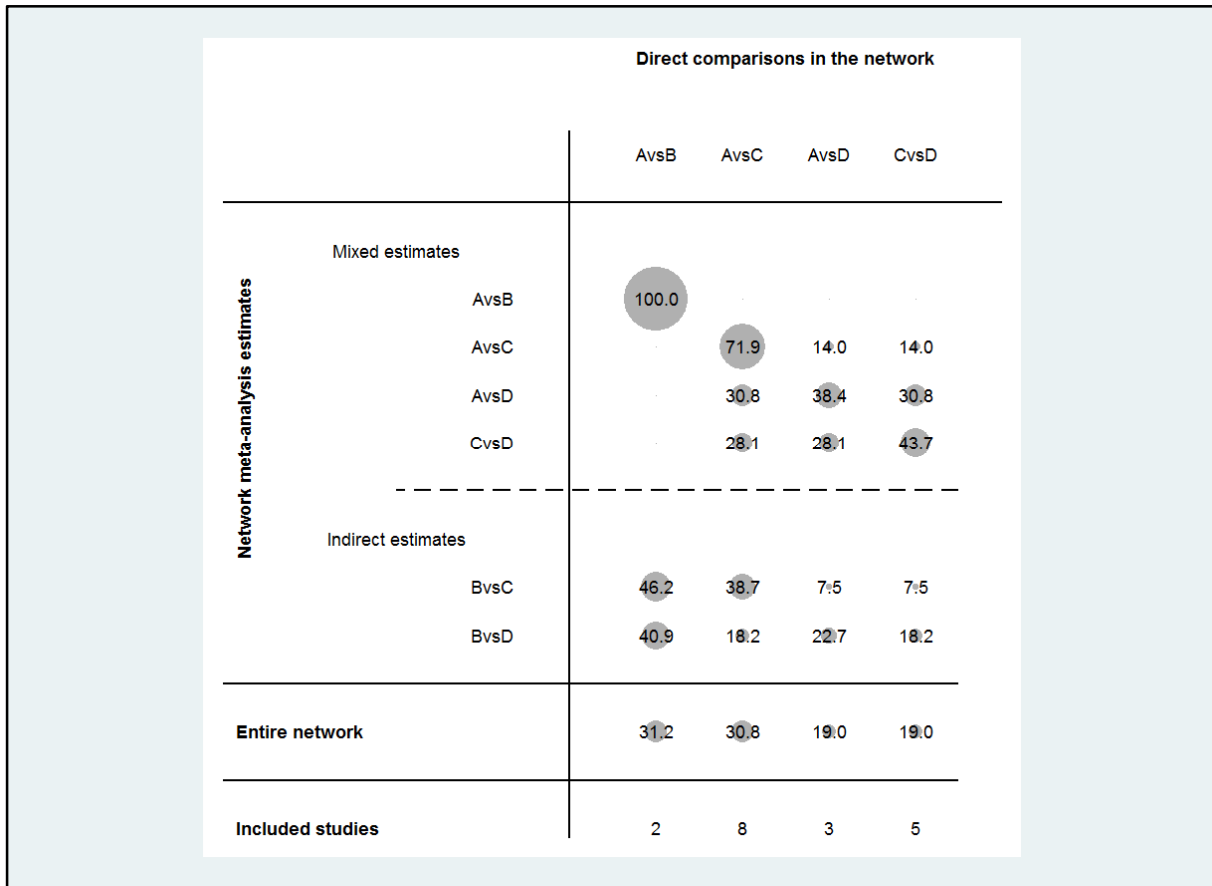
Panel C. Overall morbidity rate

Legend: All available direct comparisons (comparisons evaluated in at least one study) are reported in the columns while the following are reported in the rows: 1) the mixed comparisons (namely the estimates already available in the literature but implemented by network) and 2) the indirect comparisons (namely the comparisons not available in the literature but generated by the network). The table should be read from left to right; each row contains the contribution of each direct comparison in the network (mixed and indirect) estimates and, thus, the cumulative sum of the contributions is 100 (in percentages). In the plots, the contribution of each direct comparison in building the entire network are also reported; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).

Panel D. Acute pancreatitis

Direct comparisons in the network

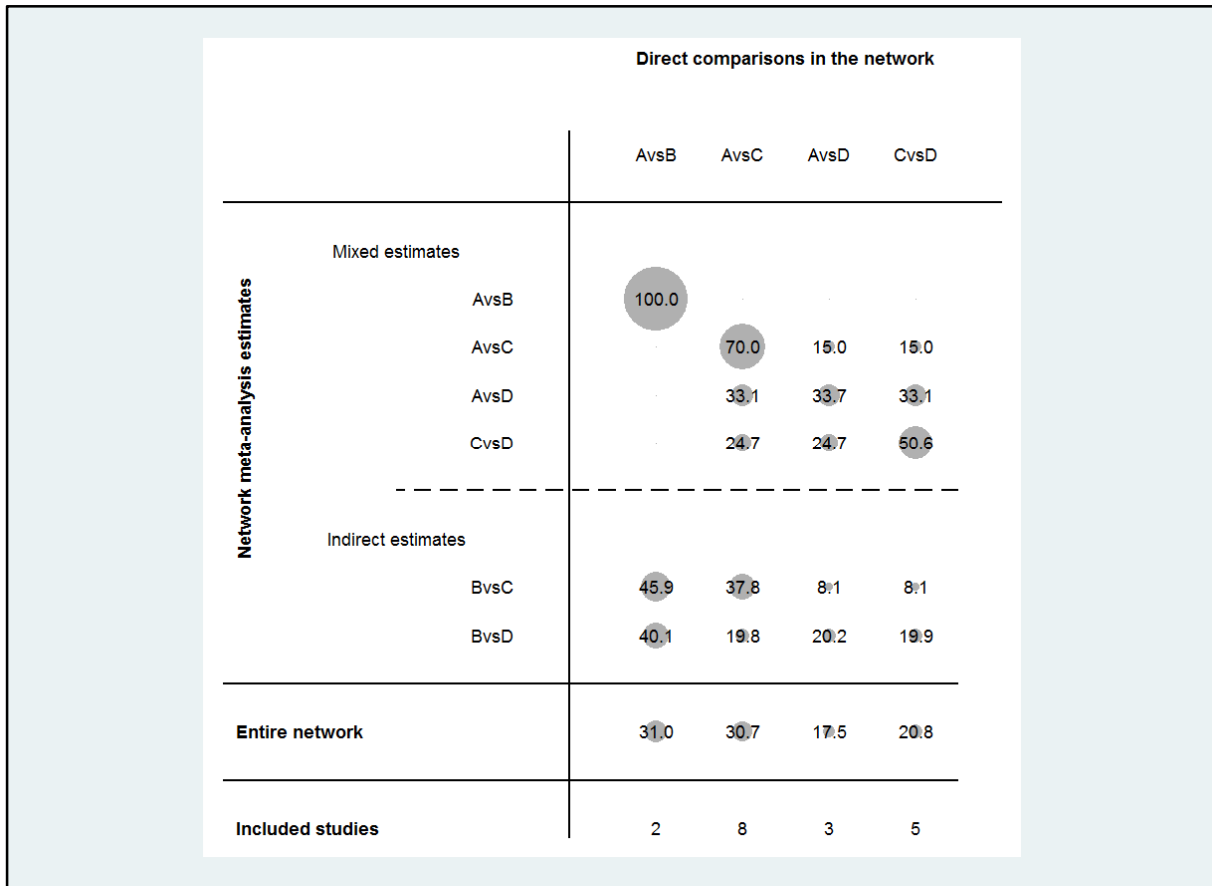| Network meta-analysis estimates		AvsB	AvsC	AvsD	CvsD
Mixed estimates					
	AvsB	100.0			
	AvsC		52.5	23.7	23.7
	AvsD		23.0	54.1	23.0
	CvsD		28.1	28.1	43.8
Indirect estimates					
	BvsC	43.3	29.8	13.5	13.5
	BvsD	43.5	13.0	30.5	13.0
Entire network		31.2	24.6	25.1	19.0
Included studies		2	8	3	6

Legend: All available direct comparisons (comparisons evaluated in at least one study) are reported in the columns while the following are reported in the rows: 1) the mixed comparisons (namely the estimates already available in the literature but implemented by network) and 2) the indirect comparisons (namely the comparisons not available in the literature but generated by the network). The table should be read from left to right; each row contains the contribution of each direct comparison in the network (mixed and indirect) estimates and, thus, the cumulative sum of the contributions is 100 (in percentages). In the plots, the contribution of each direct comparison in building the entire network are also reported; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).

Panel E. Biliary leak

Legend: All available direct comparisons (comparisons evaluated in at least one study) are reported in the columns while the following are reported in the rows: 1) the mixed comparisons (namely the estimates already available in the literature but implemented by network) and 2) the indirect comparisons (namely the comparisons not available in the literature but generated by the network). The table should be read from left to right; each row contains the contribution of each direct comparison in the network (mixed and indirect) estimates and, thus, the cumulative sum of the contributions is 100 (in percentages). In the plots, the contribution of each direct comparison in building the entire network are also reported; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).

Panel F. Overall bleeding

Direct comparisons in the network

Network meta-analysis estimates

	AvsB	AvsC	AvsD	CvsD
Mixed estimates				
AvsB	100.0			
AvsC		70.0	15.0	15.0
AvsD		33.1	33.7	33.1
CvsD		24.7	24.7	50.6
Indirect estimates				
BvsC	45.9	37.8	8.1	8.1
BvsD	40.1	19.8	20.2	19.9
Entire network	31.0	30.7	17.5	20.8
Included studies	2	8	3	5

Legend: All available direct comparisons (comparisons evaluated in at least one study) are reported in the columns while the following are reported in the rows: 1) the mixed comparisons (namely the estimates already available in the literature but implemented by network) and 2) the indirect comparisons (namely the comparisons not available in the literature but generated by the network). The table should be read from left to right; each row contains the contribution of each direct comparison in the network (mixed and indirect) estimates and, thus, the cumulative sum of the contributions is 100 (in percentages). In the plots, the contribution of each direct comparison in building the entire network are also reported; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).
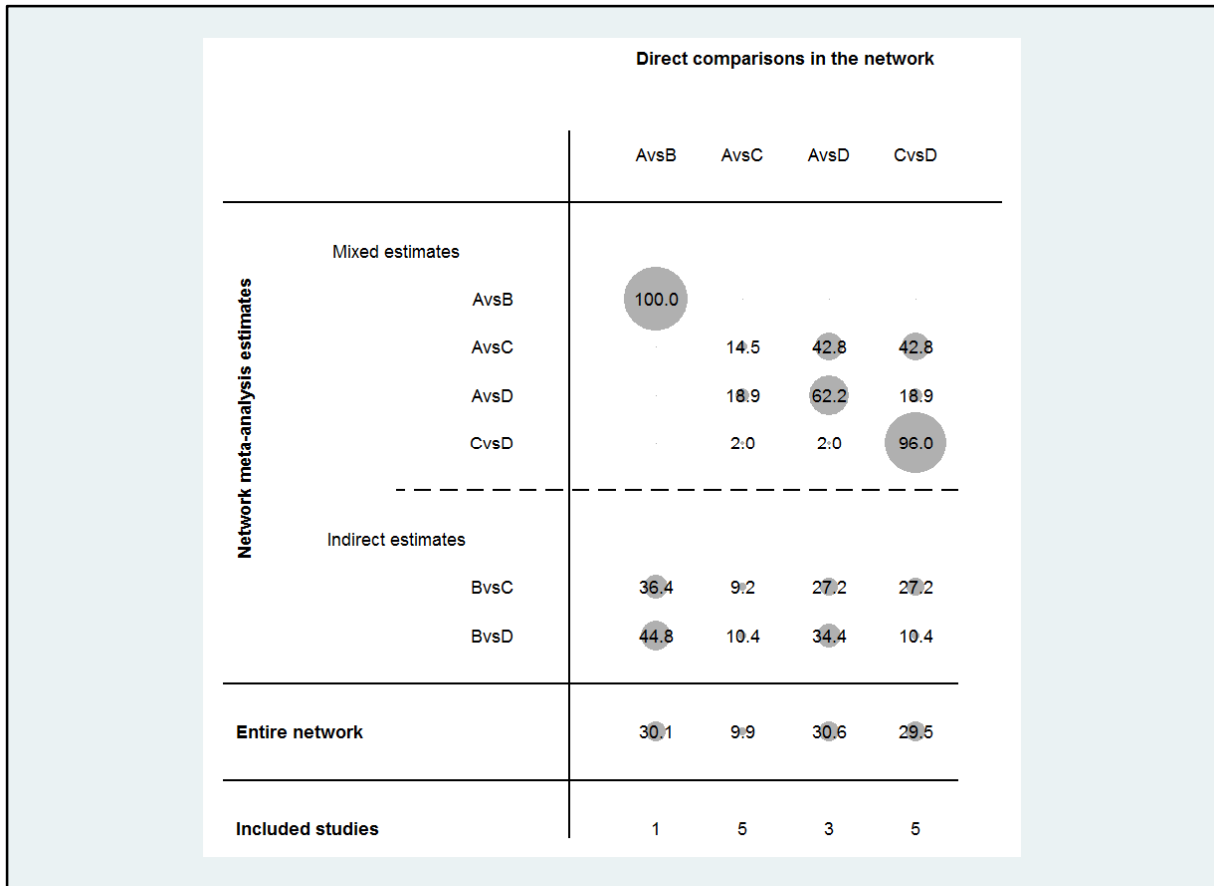
Panel G. Overall operative time

	Direct comparisons in the network			
	AvsB	AvsC	AvsD	CvsD
Mixed estimates				
AvsB	96.0	1.4	2.2	0.4
AvsC	0.1	30.2	34.8	34.9
AvsD	0.1	23.2	53.5	23.2
CvsD		13.9	13.9	72.1
Indirect estimates				
BvsC	39.2	18.3	20.9	21.6
BvsD	43.1	12.9	30.2	13.7
Entire network	29.8	17.3	26.9	26.0
Included studies	1	3	3	1

(Left axis label: Network meta-analysis estimates)

Legend: All available direct comparisons (comparisons evaluated in at least one study) are reported in the columns while the following are reported in the rows: 1) the mixed comparisons (namely the estimates already available in the literature but implemented by network) and 2) the indirect comparisons (namely the comparisons not available in the literature but generated by the network). The table should be read from left to right; each row contains the contribution of each direct comparison in the network (mixed and indirect) estimates and, thus, the cumulative sum of the contributions is 100 (in percentages). In the plots, the contribution of each direct comparison in building the entire network are also reported; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).

Panel H. Length of hospital stay

Direct comparisons in the network

Network meta-analysis estimates	AvsB	AvsC	AvsD	CvsD
Mixed estimates				
AvsB	100.0			
AvsC		14.5	42.8	42.8
AvsD		18.9	62.2	18.9
CvsD		2.0	2.0	96.0
Indirect estimates				
BvsC	36.4	9.2	27.2	27.2
BvsD	44.8	10.4	34.4	10.4
Entire network	30.1	9.9	30.6	29.5
Included studies	1	5	3	5

Legend: All available direct comparisons (comparisons evaluated in at least one study) are reported in the columns while the following are reported in the rows: 1) the mixed comparisons (namely the estimates already available in the literature but implemented by network) and 2) the indirect comparisons (namely the comparisons not available in the literature but generated by the network). The table should be read from left to right; each row contains the contribution of each direct comparison in the network (mixed and indirect) estimates and, thus, the cumulative sum of the contributions is 100 (in percentages). In the plots, the contribution of each direct comparison in building the entire network are also reported; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).
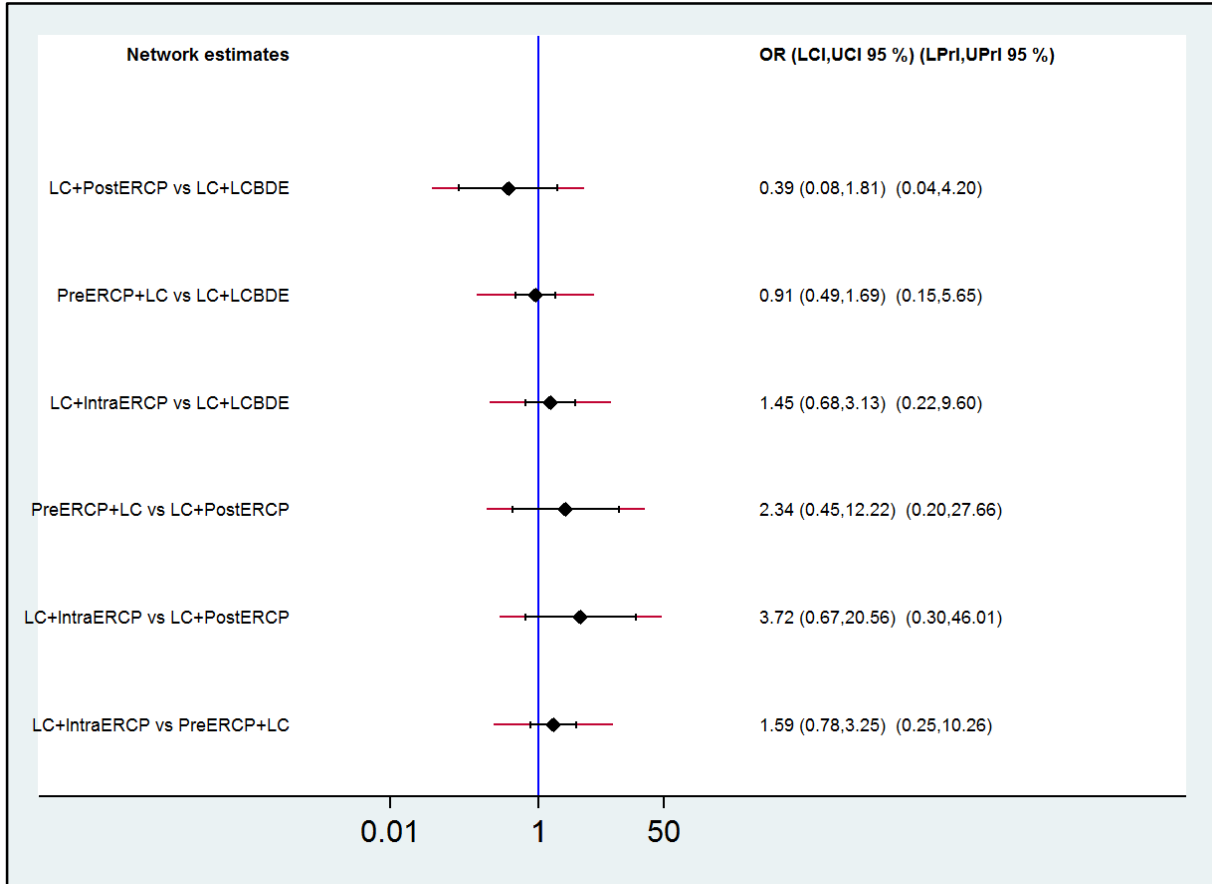
Panel I. Total cost

Legend: All available direct comparisons (comparisons evaluated in at least one study) are reported in the columns while the following are reported in the rows: 1) the mixed comparisons (namely the estimates already available in the literature but implemented by network) and 2) the indirect comparisons (namely the comparisons not available in the literature but generated by the network). The table should be read from left to right; each row contains the contribution of each direct comparison in the network (mixed and indirect) estimates and, thus, the cumulative sum of the contributions is 100 (in percentages). In the plots, the contribution of each direct comparison in building the entire network are also reported; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).
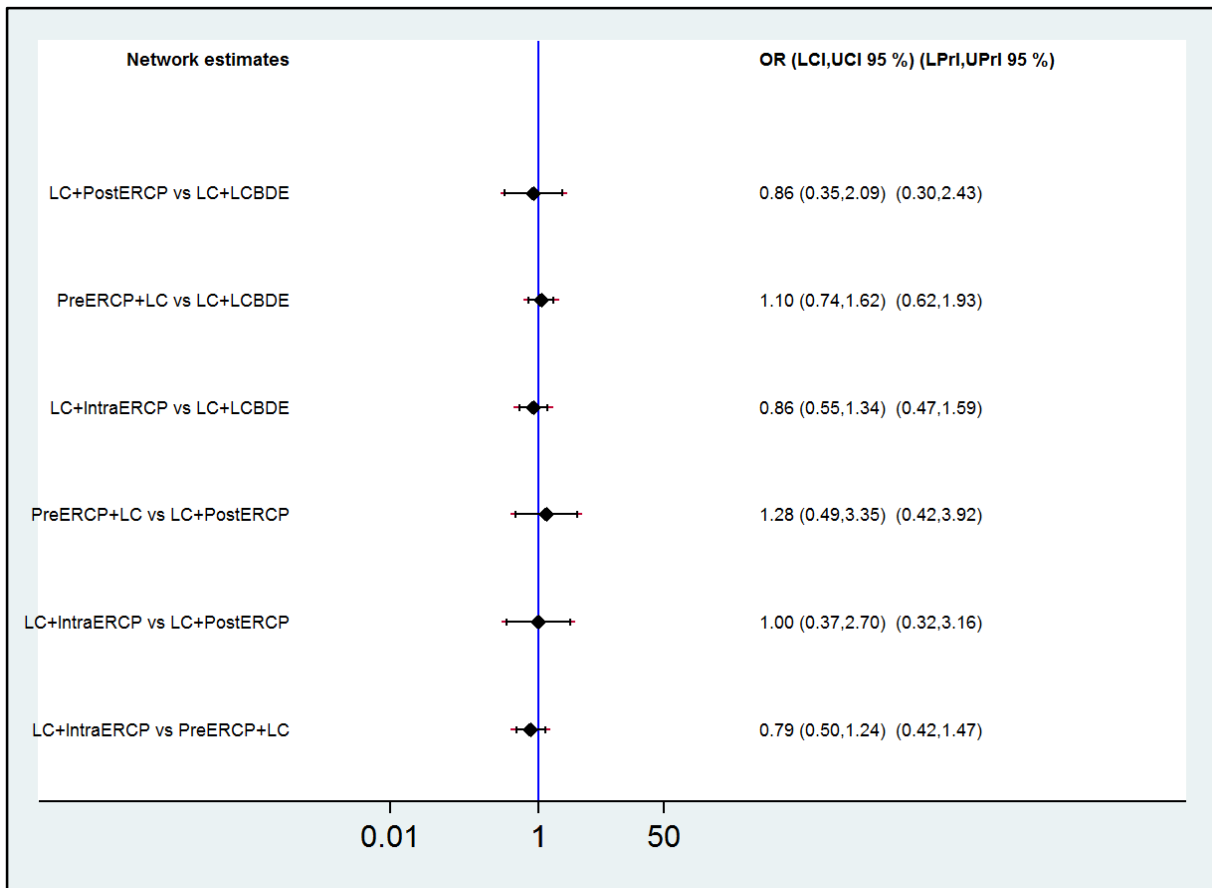
eFigure 5 (Panels A-I). Forest plots of all outcomes

Panel A. Success rate

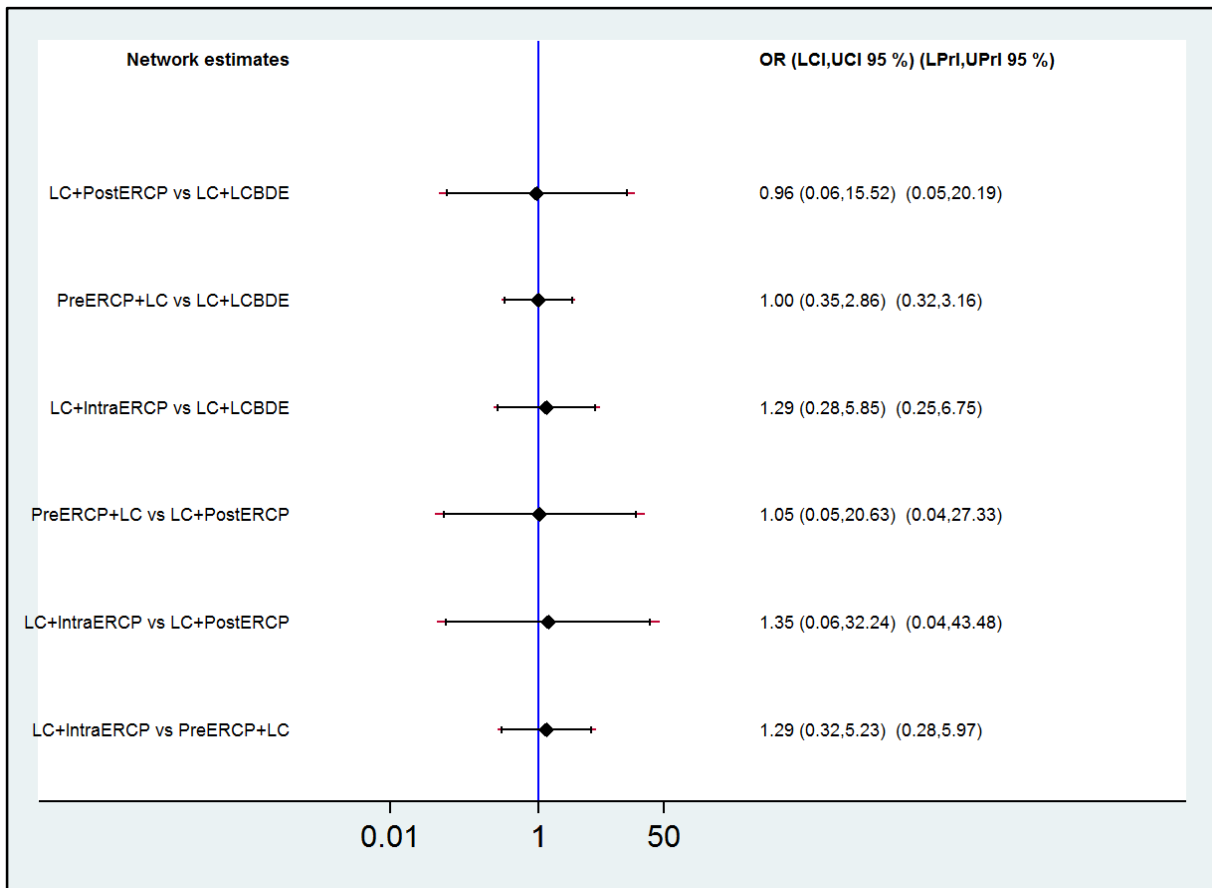| Network estimates		OR (LCI,UCI 95 %) (LPrI,UPrI 95 %)
LC+PostERCP vs LC+LCBDE		0.39 (0.08,1.81) (0.04,4.20)
PreERCP+LC vs LC+LCBDE		0.91 (0.49,1.69) (0.15,5.65)
LC+IntraERCP vs LC+LCBDE		1.45 (0.68,3.13) (0.22,9.60)
PreERCP+LC vs LC+PostERCP		2.34 (0.45,12.22) (0.20,27.66)
LC+IntraERCP vs LC+PostERCP		3.72 (0.67,20.56) (0.30,46.01)
LC+IntraERCP vs PreERCP+LC		1.59 (0.78,3.25) (0.25,10.26)

Legend: The results are reported as Odds ratios (ORs) and 95% confidence intervals (CIs). The blue line (line of null effect) is equal to 1. The solid black lines represent the CIs while the diamond summarizes the ORs. For each pairwise comparison, the forest plot should be read as following: if the diamond with the entire CI did not reach the blue line of null effect, there is a significant difference. If the entire CI is on the left of the null effect, the event is significantly higher in the "intervention arm" while, when the entire CI is on the right, the event is statistically more frequent in the "reference arm". When the entire CI crosses the line of null effect, the difference between the two procedures compared is not statistically significant. In addition, a red line reports the Predictive Interval (PrI), namely the interval within which the estimate of a future study is expected to be. Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

Panel B. Overall mortality rate

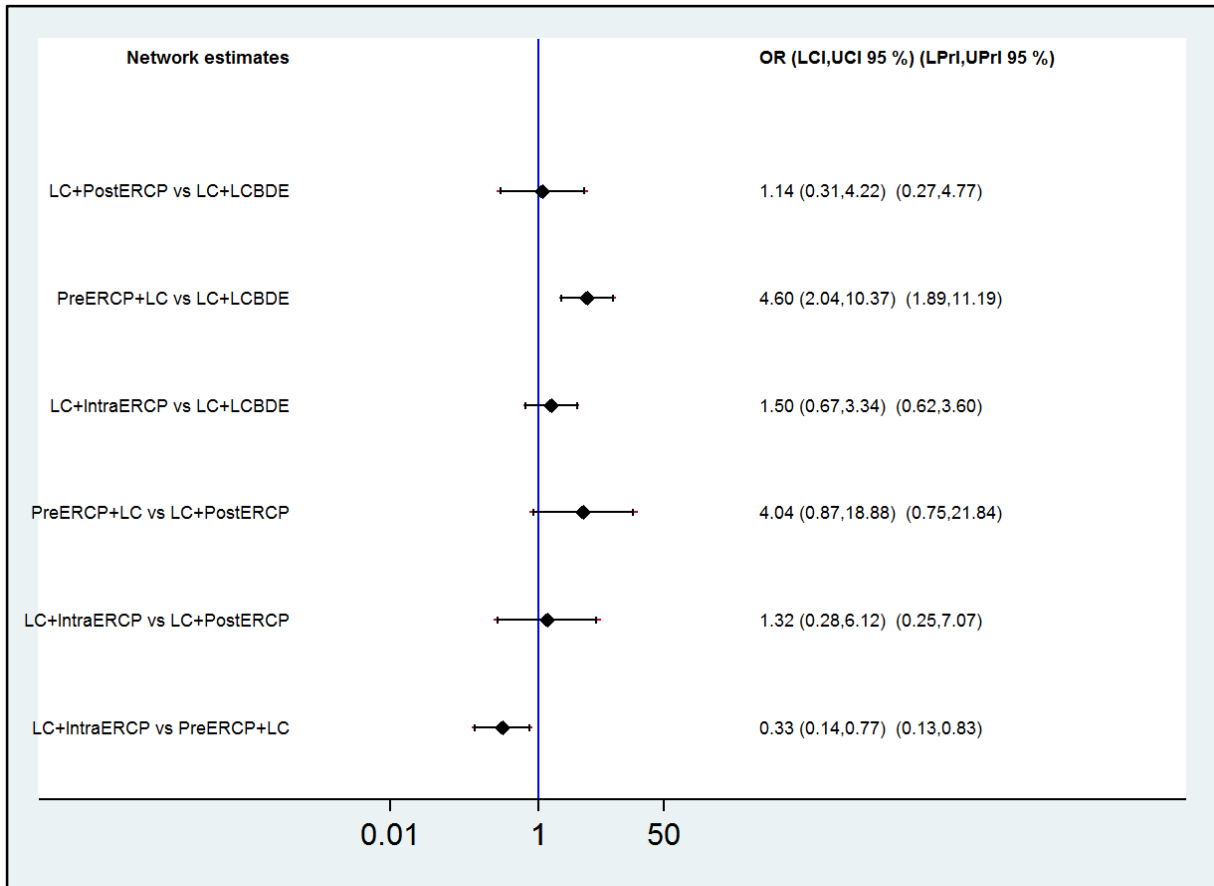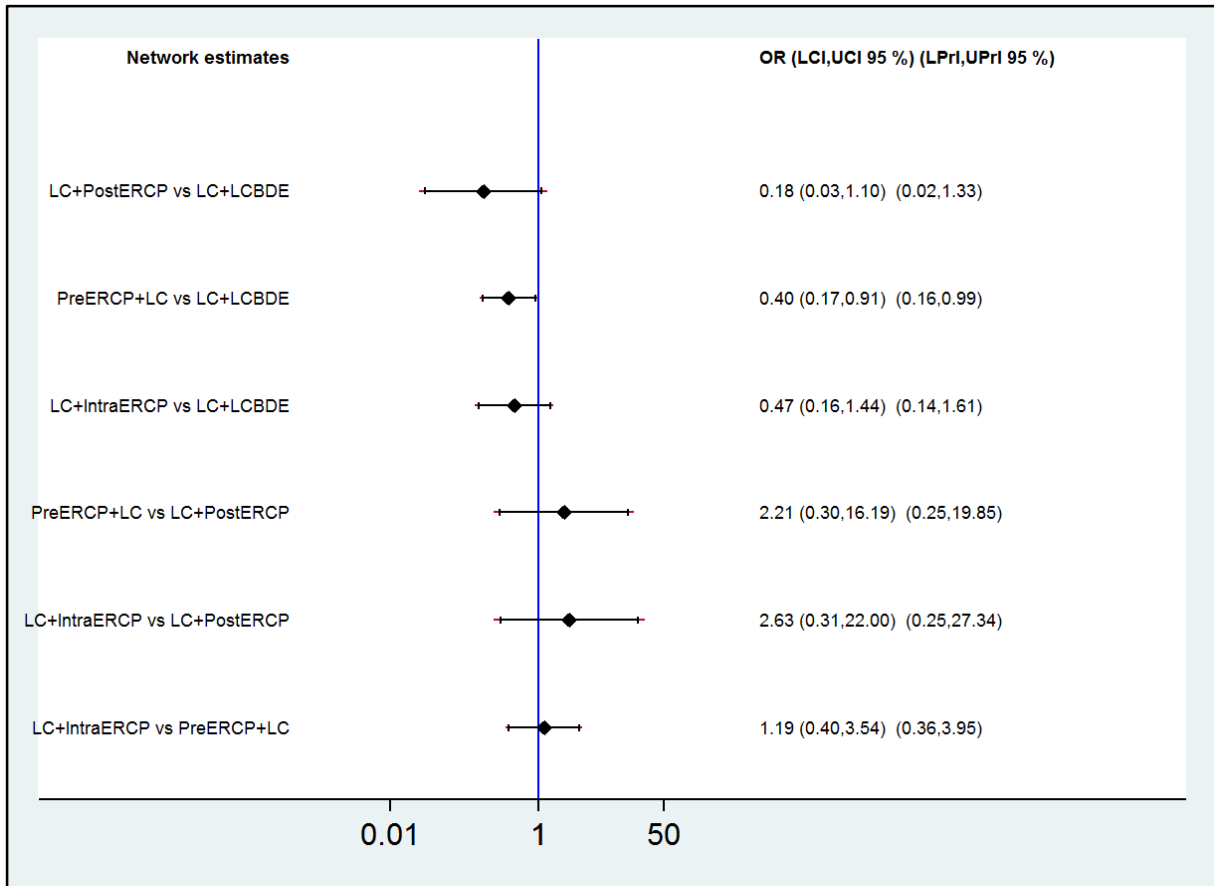| Network estimates	OR (LCI,UCI 95 %) (LPrI,UPrI 95 %)
LC+PostERCP vs LC+LCBDE	0.86 (0.35,2.09) (0.30,2.43)
PreERCP+LC vs LC+LCBDE	1.10 (0.74,1.62) (0.62,1.93)
LC+IntraERCP vs LC+LCBDE	0.86 (0.55,1.34) (0.47,1.59)
PreERCP+LC vs LC+PostERCP	1.28 (0.49,3.35) (0.42,3.92)
LC+IntraERCP vs LC+PostERCP	1.00 (0.37,2.70) (0.32,3.16)
LC+IntraERCP vs PreERCP+LC	0.79 (0.50,1.24) (0.42,1.47)

Legend: The results are reported as Odds ratios (ORs) and 95% confidence intervals (CIs). The blue line (line of null effect) is equal to 1. The solid black lines represent the CIs while the diamond summarizes the ORs. For each pairwise comparison, the forest plot should be read as following: if the diamond with the entire CI did not reach the blue line of null effect, there is a significant difference. If the entire CI is on the left of the null effect, the event rate is significantly higher in the "intervention arm" while, when the entire CI is on the right, the event is statistically more frequent in the "reference arm". When the entire CI crosses the line of null effect, the difference between the two procedures compared is not statistically significant. In addition, a red line reports the Predictive Interval (PrI), namely the interval within which the estimate of a future study is expected to be. Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

Panel C: Overall morbidity rate

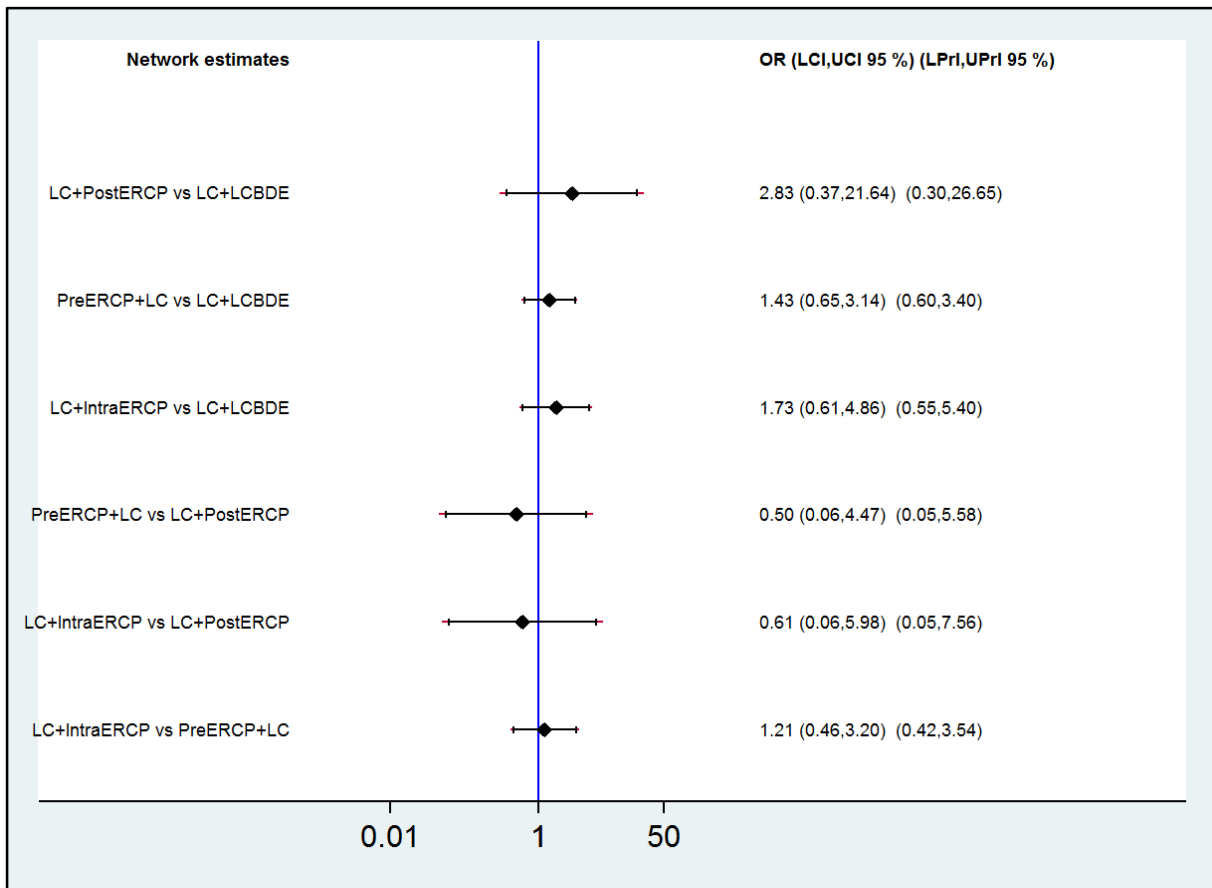| Network estimates		OR (LCI,UCI 95 %) (LPrI,UPrI 95 %)
LC+PostERCP vs LC+LCBDE		0.96 (0.06,15.52) (0.05,20.19)
PreERCP+LC vs LC+LCBDE		1.00 (0.35,2.86) (0.32,3.16)
LC+IntraERCP vs LC+LCBDE		1.29 (0.28,5.85) (0.25,6.75)
PreERCP+LC vs LC+PostERCP		1.05 (0.05,20.63) (0.04,27.33)
LC+IntraERCP vs LC+PostERCP		1.35 (0.06,32.24) (0.04,43.48)
LC+IntraERCP vs PreERCP+LC		1.29 (0.32,5.23) (0.28,5.97)

0.01   1   50

Legend: The results are reported as Odds ratios (ORs) and 95% confidence intervals (CIs). The blue line (line of null effect) is equal to 1. The solid black lines represent the CIs while the diamond summarizes the ORs. For each pairwise comparison, the forest plot should be read as following: if the diamond with the entire CI did not reach the blue line of null effect, there is a significant difference. If the entire CI is on the left of the null effect, the event rate is significantly higher in the "intervention arm" while, when the entire CI is on the right, the event is statistically more frequent in the "reference arm". When the entire CI crosses the line of null effect, the difference between the two procedures compared is not statistically significant. In addition, a red line reports the Predictive Interval (PrI), namely the interval within which the estimate of a future study is expected to be. Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

Panel D. Acute pancreatitis

Network estimates		OR (LCI,UCI 95 %) (LPrI,UPrI 95 %)
LC+PostERCP vs LC+LCBDE		1.14 (0.31,4.22) (0.27,4.77)
PreERCP+LC vs LC+LCBDE		4.60 (2.04,10.37) (1.89,11.19)
LC+IntraERCP vs LC+LCBDE		1.50 (0.67,3.34) (0.62,3.60)
PreERCP+LC vs LC+PostERCP		4.04 (0.87,18.88) (0.75,21.84)
LC+IntraERCP vs LC+PostERCP		1.32 (0.28,6.12) (0.25,7.07)
LC+IntraERCP vs PreERCP+LC		0.33 (0.14,0.77) (0.13,0.83)

0.01   1   50

Legend: The results are reported as Odds ratios (ORs) and 95% confidence intervals (CIs). The blue line (line of null effect) is equal to 1. The solid black lines represent the CIs while the diamond summarizes the ORs. For each pairwise comparison, the forest plot should be read as following: if the diamond with the entire CI did not reach the blue line of null effect, there is a significant difference. If the entire CI is on the left of the null effect, the event rate is significantly higher in the "intervention arm" while, when the entire CI is on the right, the event is statistically more frequent in the "reference arm". When the entire CI crosses the line of null effect, the difference between the two procedures compared is not statistically significant. In addition, a red line reports the Predictive Interval (PrI), namely the interval within which the estimate of a future study is expected to be. Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.
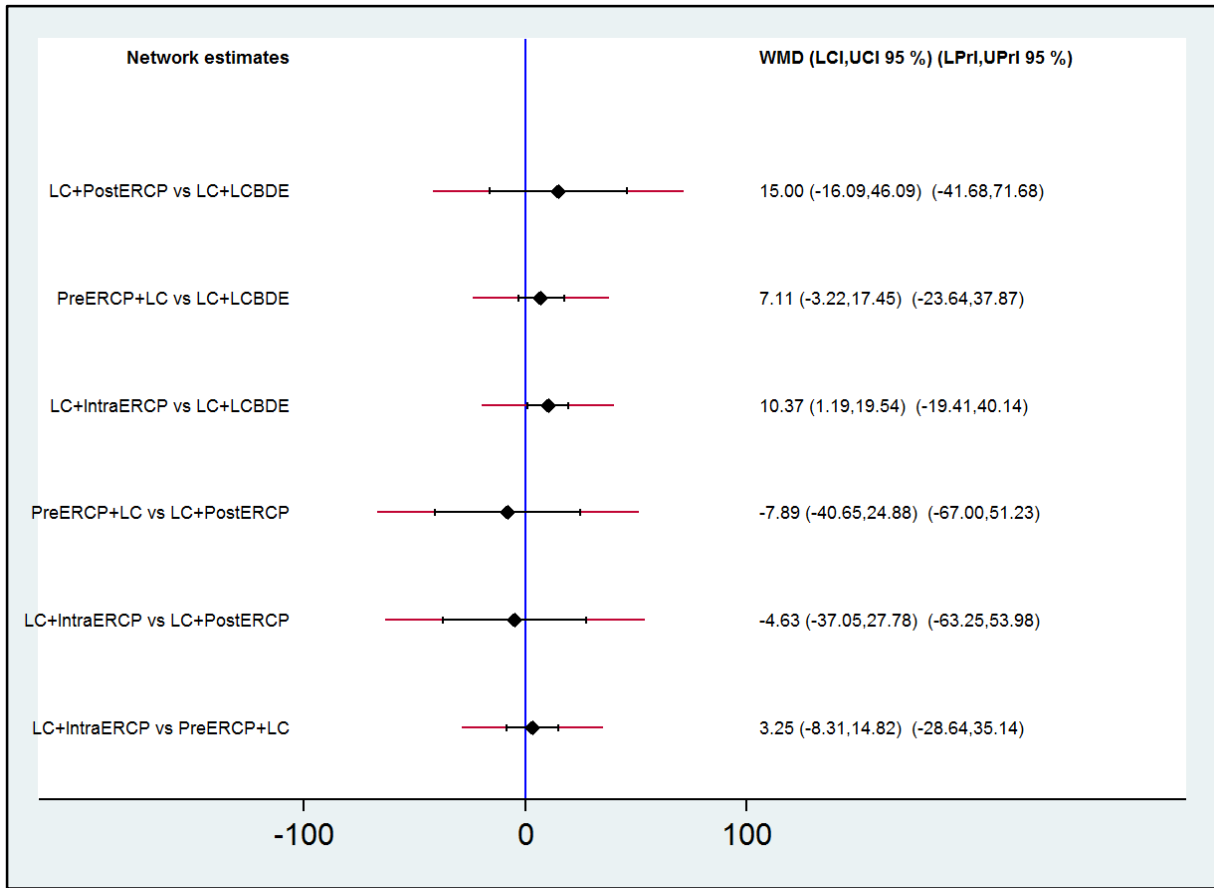
Panel E. Biliary leak

Network estimates · **OR (LCI,UCI 95 %) (LPrI,UPrI 95 %)**

Comparison	OR (LCI,UCI 95 %) (LPrI,UPrI 95 %)
LC+PostERCP vs LC+LCBDE	0.18 (0.03,1.10) (0.02,1.33)
PreERCP+LC vs LC+LCBDE	0.40 (0.17,0.91) (0.16,0.99)
LC+IntraERCP vs LC+LCBDE	0.47 (0.16,1.44) (0.14,1.61)
PreERCP+LC vs LC+PostERCP	2.21 (0.30,16.19) (0.25,19.85)
LC+IntraERCP vs LC+PostERCP	2.63 (0.31,22.00) (0.25,27.34)
LC+IntraERCP vs PreERCP+LC	1.19 (0.40,3.54) (0.36,3.95)

0.01   1   50

Legend: The results are reported as Odds ratios (ORs) and 95% confidence intervals (CIs). The blue line (line of null effect) is equal to 1. The solid black lines represent the CIs while the diamond summarizes the ORs**.** For each pairwise comparison, the forest plot should be read as following: if the diamond with the entire CI did not reach the blue line of null effect, there is a significant difference. If the entire CI is on the left of the null effect, the event rate is significantly higher in the "intervention arm" while, when the entire CI is on the right, the event is statistically more frequent in the "reference arm". When the entire CI crosses the line of null effect, the difference between the two procedures compared is not statistically significant. In addition, a red line reports the Predictive Interval (PrI), namely the interval within which the estimate of a future study is expected to be. Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.
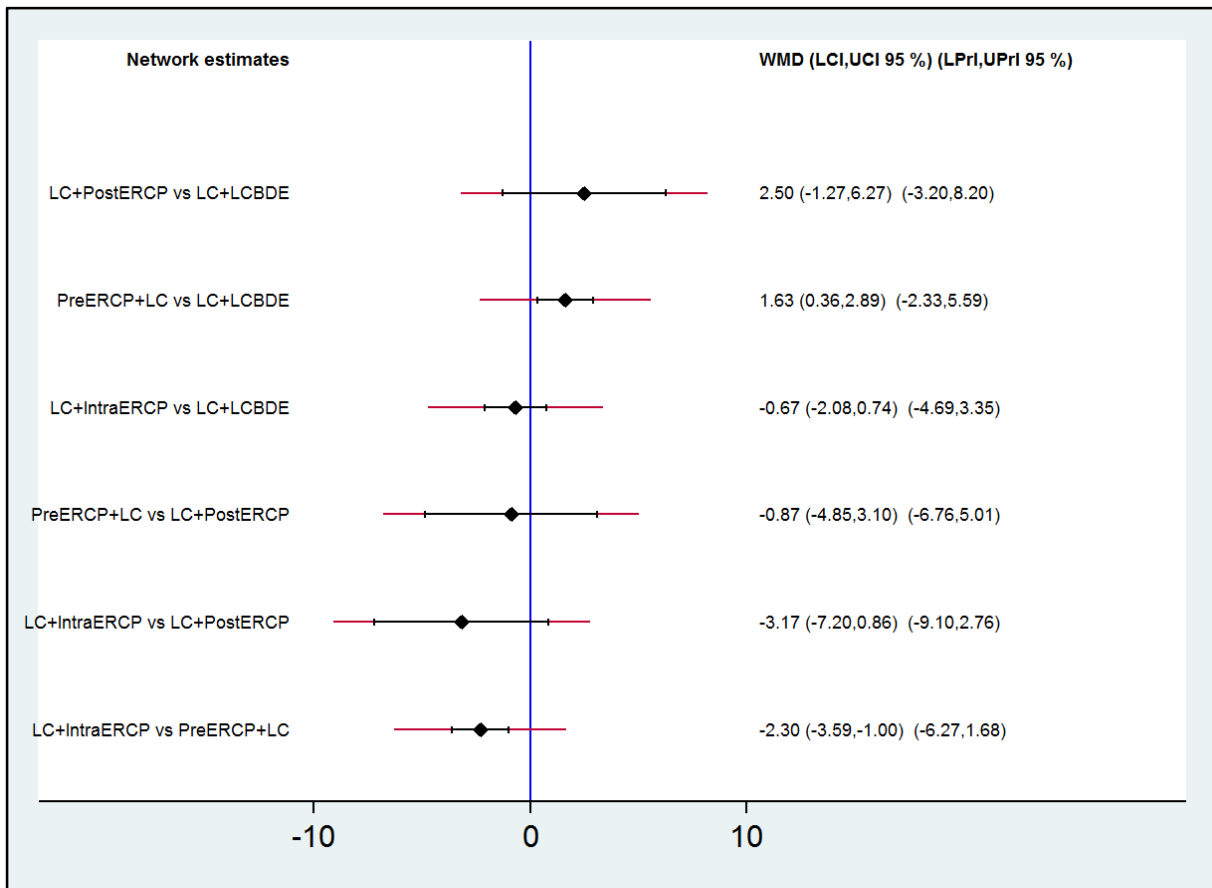
Panel F. Overall bleeding

Network estimates		OR (LCI,UCI 95 %) (LPrI,UPrI 95 %)
LC+PostERCP vs LC+LCBDE		2.83 (0.37,21.64) (0.30,26.65)
PreERCP+LC vs LC+LCBDE		1.43 (0.65,3.14) (0.60,3.40)
LC+IntraERCP vs LC+LCBDE		1.73 (0.61,4.86) (0.55,5.40)
PreERCP+LC vs LC+PostERCP		0.50 (0.06,4.47) (0.05,5.58)
LC+IntraERCP vs LC+PostERCP		0.61 (0.06,5.98) (0.05,7.56)
LC+IntraERCP vs PreERCP+LC		1.21 (0.46,3.20) (0.42,3.54)

0.01   1   50

Legend: The results are reported as Odds ratios (ORs) and 95% confidence intervals (CIs). The blue line (line of null effect) is equal to 1. The solid black lines represent the CIs while the diamond summarizes the ORs. For each pairwise comparison, the forest plot should be read as following: if the diamond with the entire CI did not reach the blue line of null effect, there is a significant difference. If the entire CI is on the left of the null effect, the event rate is significantly higher in the "intervention arm" while, when the entire CI is on the right, the event is statistically more frequent in the "reference arm". When the entire CI crosses the line of null effect, the difference between the two procedures compared is not statistically significant. In addition, a red line reports the Predictive Interval (PrI), namely the interval within which the estimate of a future study is expected to be. Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

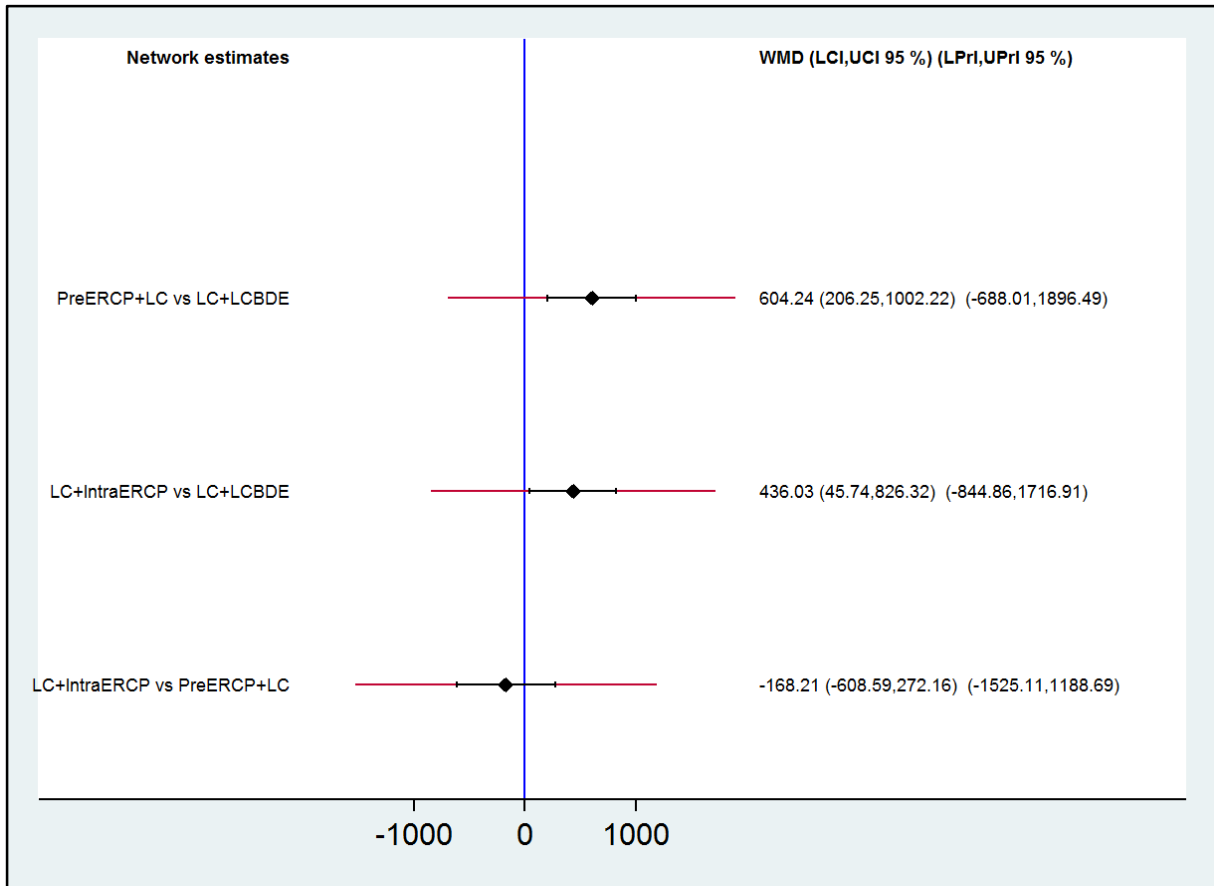**Panel G.** Overall operative time

Network estimates / **WMD (LCI,UCI 95 %) (LPrI,UPrI 95 %)**

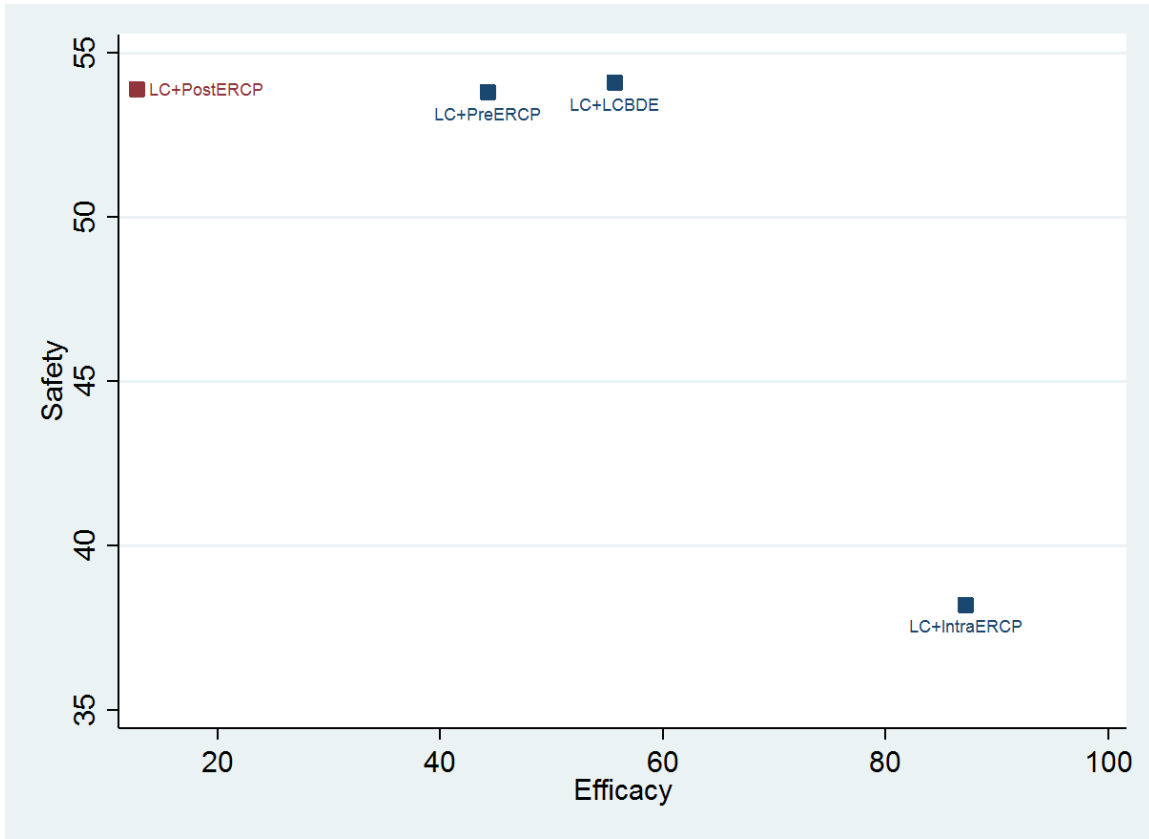| Network estimates	WMD (LCI,UCI 95 %) (LPrI,UPrI 95 %)
LC+PostERCP vs LC+LCBDE	15.00 (-16.09,46.09) (-41.68,71.68)
PreERCP+LC vs LC+LCBDE	7.11 (-3.22,17.45) (-23.64,37.87)
LC+IntraERCP vs LC+LCBDE	10.37 (1.19,19.54) (-19.41,40.14)
PreERCP+LC vs LC+PostERCP	-7.89 (-40.65,24.88) (-67.00,51.23)
LC+IntraERCP vs LC+PostERCP	-4.63 (-37.05,27.78) (-63.25,53.98)
LC+IntraERCP vs PreERCP+LC	3.25 (-8.31,14.82) (-28.64,35.14)

-100   0   100

Legend: The results are reported as Weighted Mean Difference (WMD) and 95% confidence intervals (CIs). The blue line (line of null effect) is equal to 0. The solid black lines represent the CIs while the diamond summarizes the ORs. For each pairwise comparison, the forest plot should be read as following: if the diamond with the entire CI did not reach the blue line of null effect, there is a significant difference. If the entire CI is on the left of the null effect, the value is significantly higher in the "intervention arm" while, when the entire CI is on the right, the value is statistically higher in the "reference arm". When the entire CI crosses the line of null effect, the difference between the two procedures compared is not statistically significant. In addition, a red line reports the Predictive Interval (PrI), namely the interval within which the estimate of a future study is expected to be. Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

Panel H. Length of hospital stay

Network estimates	WMD (LCI,UCI 95 %) (LPrI,UPrI 95 %)
LC+PostERCP vs LC+LCBDE	2.50 (-1.27,6.27) (-3.20,8.20)
PreERCP+LC vs LC+LCBDE	1.63 (0.36,2.89) (-2.33,5.59)
LC+IntraERCP vs LC+LCBDE	-0.67 (-2.08,0.74) (-4.69,3.35)
PreERCP+LC vs LC+PostERCP	-0.87 (-4.85,3.10) (-6.76,5.01)
LC+IntraERCP vs LC+PostERCP	-3.17 (-7.20,0.86) (-9.10,2.76)
LC+IntraERCP vs PreERCP+LC	-2.30 (-3.59,-1.00) (-6.27,1.68)

Legend: The results are reported as Weighted Mean Difference (WMD) and 95% confidence intervals (CIs). The blue line (line of null effect) is equal to 0. The solid black lines represent the CIs while the diamond summarizes the ORs**.** For each pairwise comparison, the forest plot should be read as following: if the diamond with the entire CI did not reach the blue line of null effect, there is a significant difference. If the entire CI is on the left of the null effect, the value is significantly higher in the "intervention arm" while, when the entire CI is on the right, the value is statistically higher in the "reference arm". When the entire CI crosses the line of null effect, the difference between the two procedures compared is not statistically significant. In addition, a red line reports the Predictive Interval (PrI), namely the interval within which the estimate of a future study is expected to be. Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

Panel I. Total costs

Legend: The results are reported as Weighted Mean Difference (WMD) and 95% confidence intervals (CIs). The blue line (line of null effect) is equal to 0. The solid black lines represent the CIs while the diamond summarizes the ORs. For each pairwise comparison, the forest plot should be read as following: if the diamond with the entire CI did not reach the blue line of null effect, there is a significant difference. If the entire CI is on the left of the null effect, the value is significantly higher in the "intervention arm" while, when the entire CI is on the right, the value is statistically higher in the "reference arm". When the entire CI crosses the line of null effect, the difference between the two procedures compared is not statistically significant. In addition, a red line reports the Predictive Interval (PrI), namely the interval within which the estimate of a future study is expected to be. Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

eTable 2. The ranking of the approaches ranking for all outcomes. The probability in percentages of the ranking of the approaches from best to worst is reported in the row

Outcomes of interest	Probability Ranking for each approach (%)															
	LC + LCBDE				LC + PostERCP				LC + PreERCP				LC + IntraERCP			
	Best	2nd	3rd	Worst	Best	2nd	3rd	Worst	Best	2nd	3rd	Worst	Best	2nd	3rd	Worst
Success rate	12.9	45.7	37.1	4.3	6.5	5.8	7.3	80.4	7.5	31.3	47.8	13.4	73.1	17.2	7.8	1.9
Overall morbidity	8.3	32.1	42.5	17.1	48.3	15.6	11.9	24.2	4.6	13.9	29.7	51.8	38.8	38.4	15.9	6.9
Overall mortality	18.4	37.7	31.7	12.2	43.4	10.4	10.7	35.5	21.5	31.9	33.1	13.5	16.7	20.0	24.5	38.8
Acute Pancreatitis	48.5	44.0	7.5	0	39.7	25.0	31.4	3.9	0	0.2	4.1	95.7	11.8	30.8	57.0	0.4
Biliary Leak	0	0.5	13.8	85.7	73.8	13.0	11.1	2.1	14.1	51.9	32.8	1.2	12.1	34.6	42.3	11.0
Overall bleeding	62.0	27.2	9.6	1.2	13.6	9.6	13.2	63.6	13.2	40.7	36.2	9.9	11.2	22.5	41.0	25.3
Overall operative time	72.2	25.2	2.1	0	18.4	10.9	11.6	59.1	8.2	44.1	36.0	11.7	0.7	19.8	50.3	29.2
LOS	14.1	75.7	10.2	0	5.2	7.0	22.1	65.7	0	0.5	65.2	34.3	80.7	16.8	2.5	0
Total costs ($)	97.9	2.0	0.1	NA	NA	NA	NA	NA	0.3	22.3	77.4	NA	1.8	75.7	22.5	NA

Legend: LC: Laparoscopic Cholecystectomy; LCBDE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: I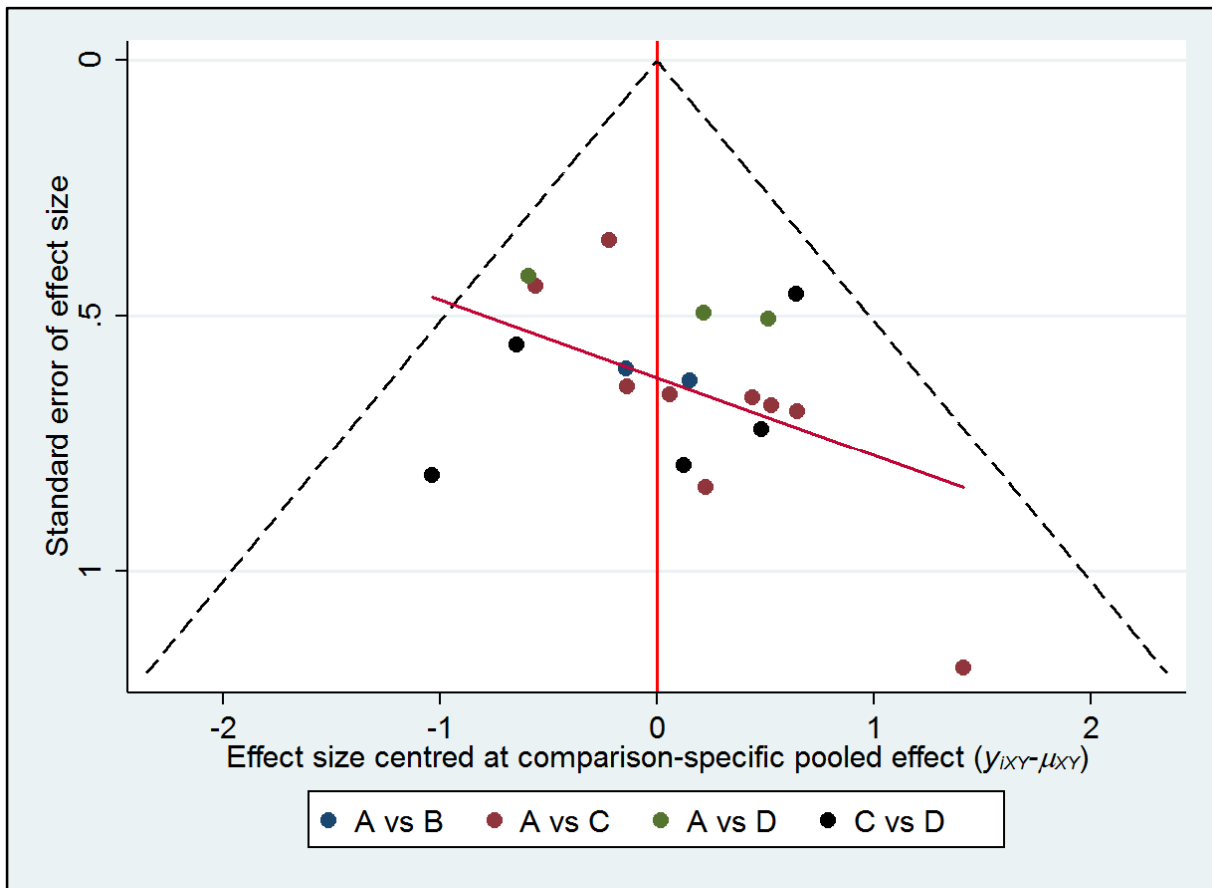ntraoperative Endoscopic Retrograde Cholangiopancreatography LOS: Length of Postoperative Hospital Stay; $: Dollars; NA: not applicable.

eFigure 6. Cluster rank combined the surface under the cumulative ranking curve (SUCRA) values, success rate and mortality rate. The y axis reports the SUCRA values as a percentage of "safety" (mortality rate). The x axis reports the efficacy (success rate). Different colors identify the different clusters.

Legend: LC: Laparoscopic Cholecystectomy; LCDBE: Laparoscopic Common Bile Duct Exploration; PostERCP: Postoperative Endoscopic Retrograde Cholangiopancreatography; PreERCP: Preoperative Endoscopic Retrograde Cholangiopancreatography; IntraERCP: Intraoperative Endoscopic Retrograde Cholangiopancreatography.

37

eFigure 7. Funnel plots of the network estimates of all outcomes

Panel A. Success rate

Legend: Funnel plots of the network estimates of all outcomes. In the comparison-adjusted funnel plot, the horizontal axis shows the difference of each i-study estimate YiXY from the summary effect for the respective comparison (YiXY-μXY) while the vertical axis presents the measure of dispersion of YiXY, namely the standard error of the effect size. The red line shows the null hypothesis. Each point represents a direct comparison; different colors correspond to different comparisons. The dashed black line represents the 95% confidence interval. The horizontal line represents the regression line; the dark red regression line demonstrates that no asymmetry is present; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).
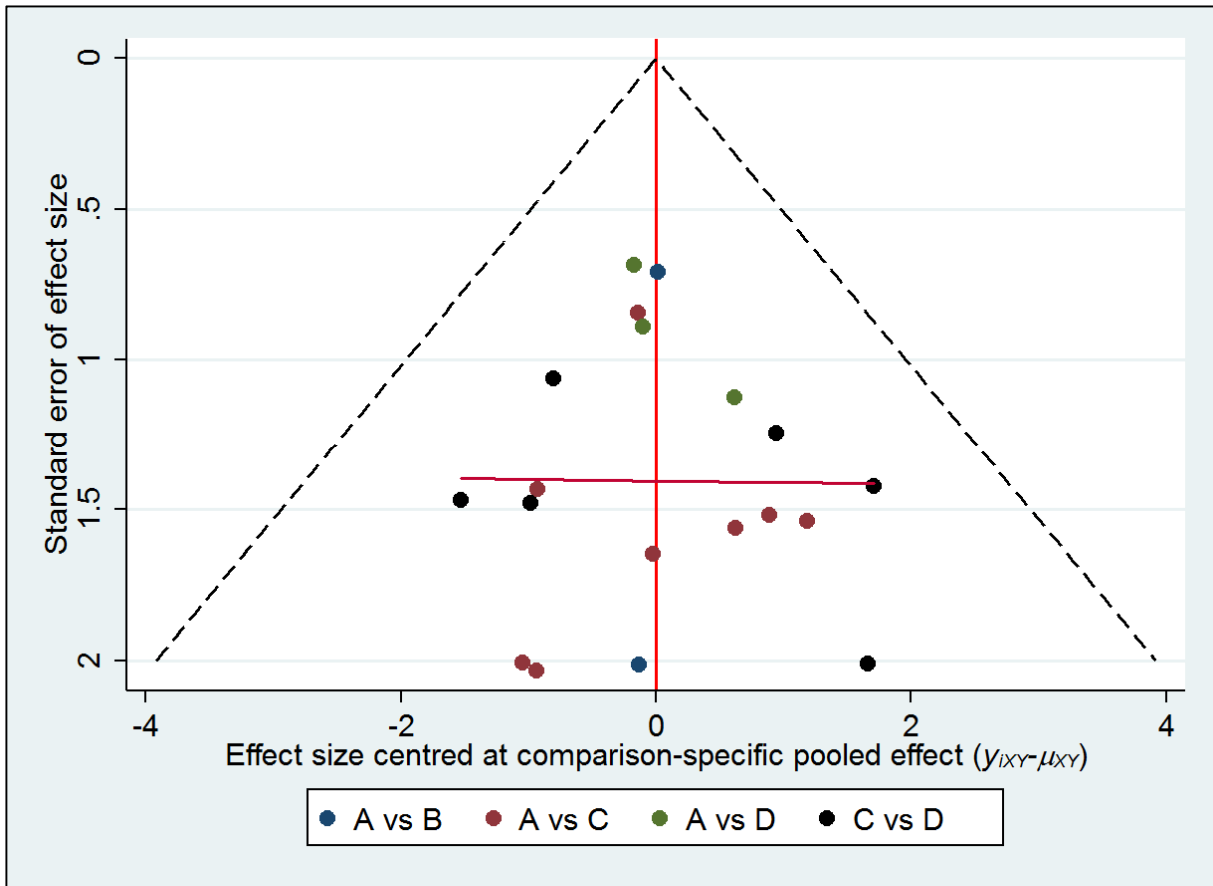
Panel B. Overall mortality rate

Legend: Funnel plots of the network estimates of all outcomes. In the comparison-adjusted funnel plot, the horizontal axis shows the difference of each i-study estimate YiXY from the summary effect for the respective comparison (YiXY-μXY) while the vertical axis presents the measure of dispersion of YiXY, namely the standard error of the effect size. The red line shows the null hypothesis. Each point represents a direct comparison; different colors correspond to different comparisons. The dashed black line represents the 95% confidence interval. The horizontal line represents the regression line; the dark red regression line demonstrates that asymmetry is present and it was confirmed by Begg's test for "LC + PreERCP versus LC + IntraERCP" comparison (P=0.086) ; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).
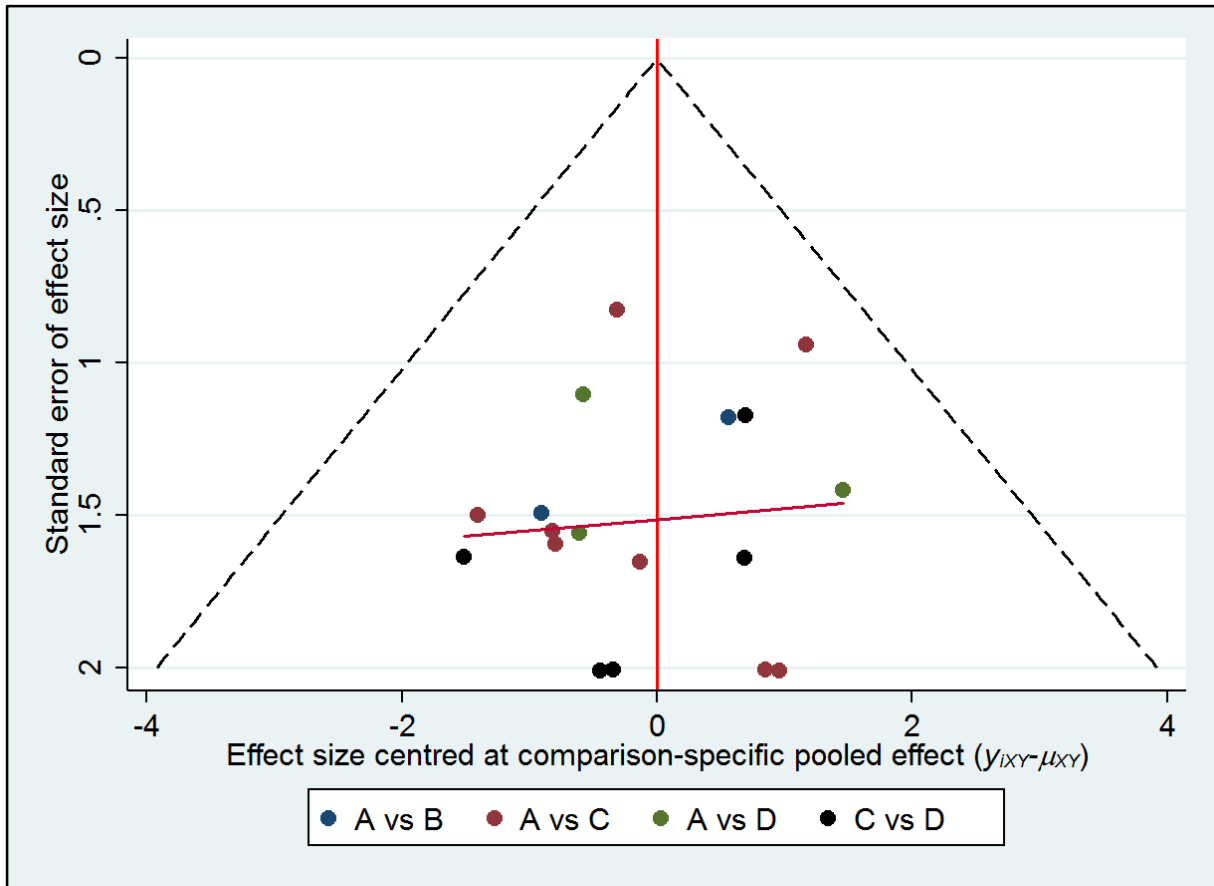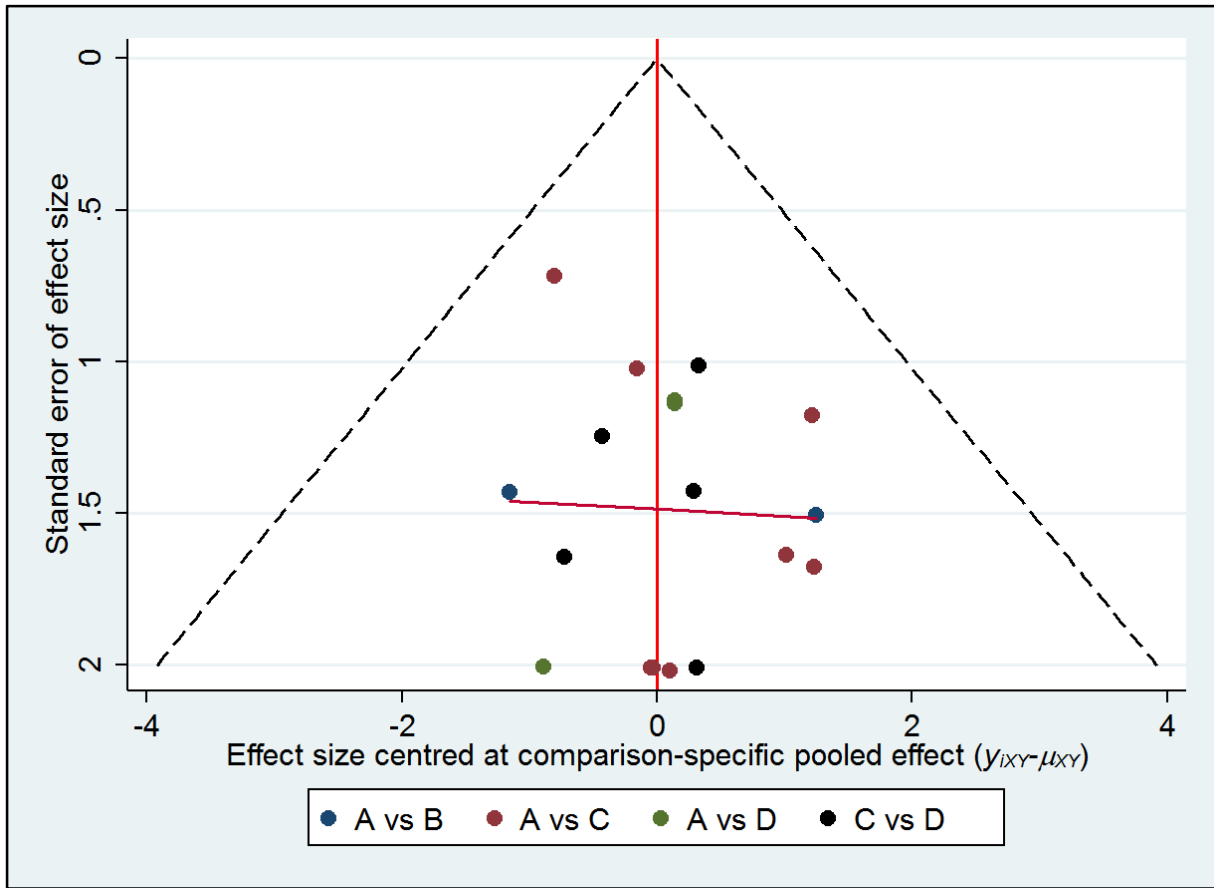
Panel C. Overall morbidity rate

Legend: Funnel plots of the network estimates of all outcomes. In the comparison-adjusted funnel plot, the horizontal axis shows the difference of each i-study estimate YiXY from the summary effect for the respective comparison (YiXY-µXY) while the vertical axis presents the measure of dispersion of YiXY, namely the standard error of the effect size. The red line shows the null hypothesis. Each point represents a direct comparison; different colors correspond to different comparisons. The dashed black line represents the 95% confidence interval. The horizontal line represents the regression line; the dark red regression line demonstrates that asymmetry is present but it did not is confirmed by Begg's test; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).
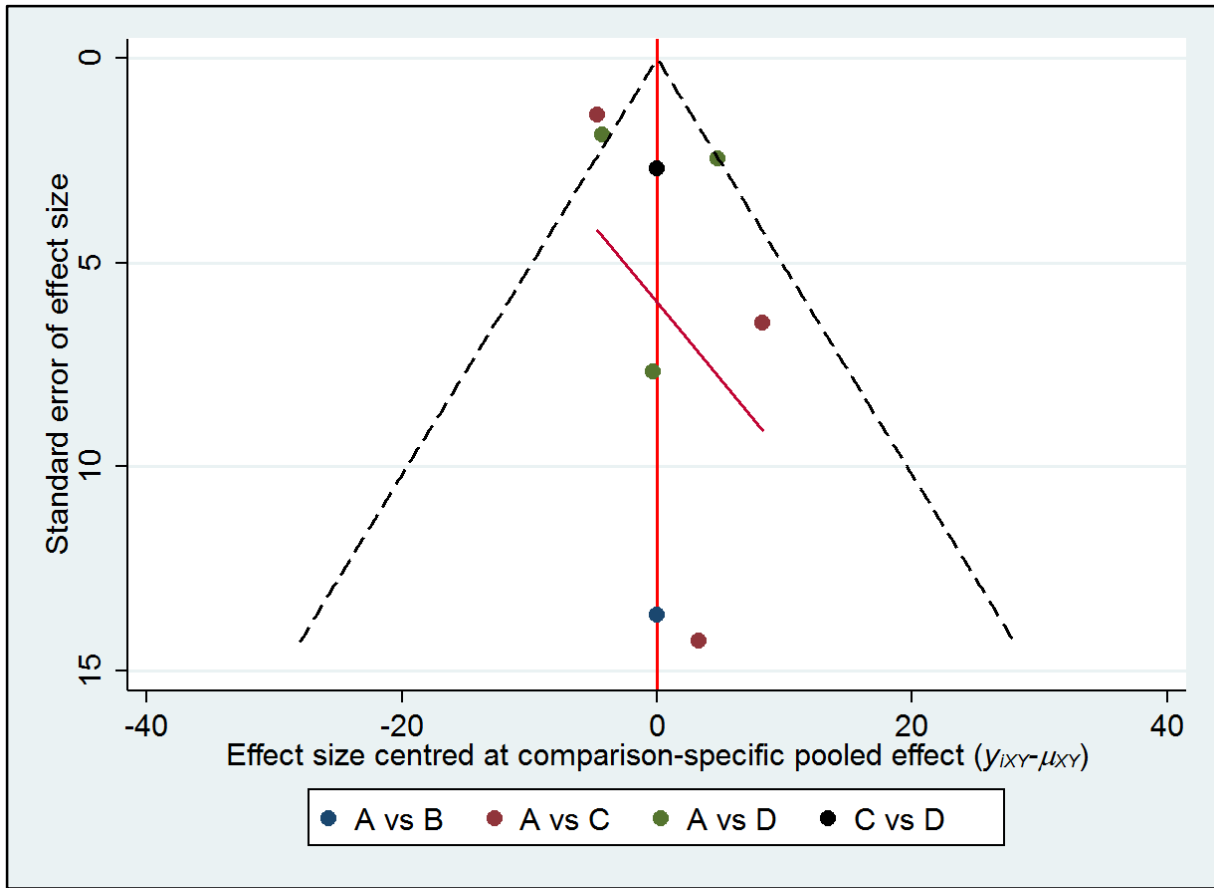
Panel D. Acute pancreatitis

Legend: Funnel plots of the network estimates of all outcomes. In the comparison-adjusted funnel plot, the horizontal axis shows the difference of each i-study estimate YiXY from the summary effect for the respective comparison (YiXY-μXY) while the vertical axis presents the measure of dispersion of YiXY, namely the standard error of the effect size. The red line shows the null hypothesis. Each point represents a direct comparison; different colors correspond to different comparisons. The dashed black line represents the 95% confidence interval. The horizontal line represents the regression line; the dark red regression line demonstrates that no asymmetry is present but Begg's test shows that "LC + LCBDE versus LC + IntraERCP" had a significant small study effect (P=0.029); arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).

Panel E. Biliary leak

Legend: Funnel plots of the network estimates of all outcomes. In the comparison-adjusted funnel plot, the horizontal axis shows the difference of each i-study estimate YiXY from the summary effect for the respective comparison (YiXY-μXY) while the vertical axis presents the measure of dispersion of YiXY, namely the standard error of the effect size. The red line shows the null hypothesis. Each point represents a direct comparison; different colors correspond to different comparisons. The dashed black line represents the 95% confidence interval. The horizontal line represents the regression line; the dark red regression line demonstrates that no asymmetry is present; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).

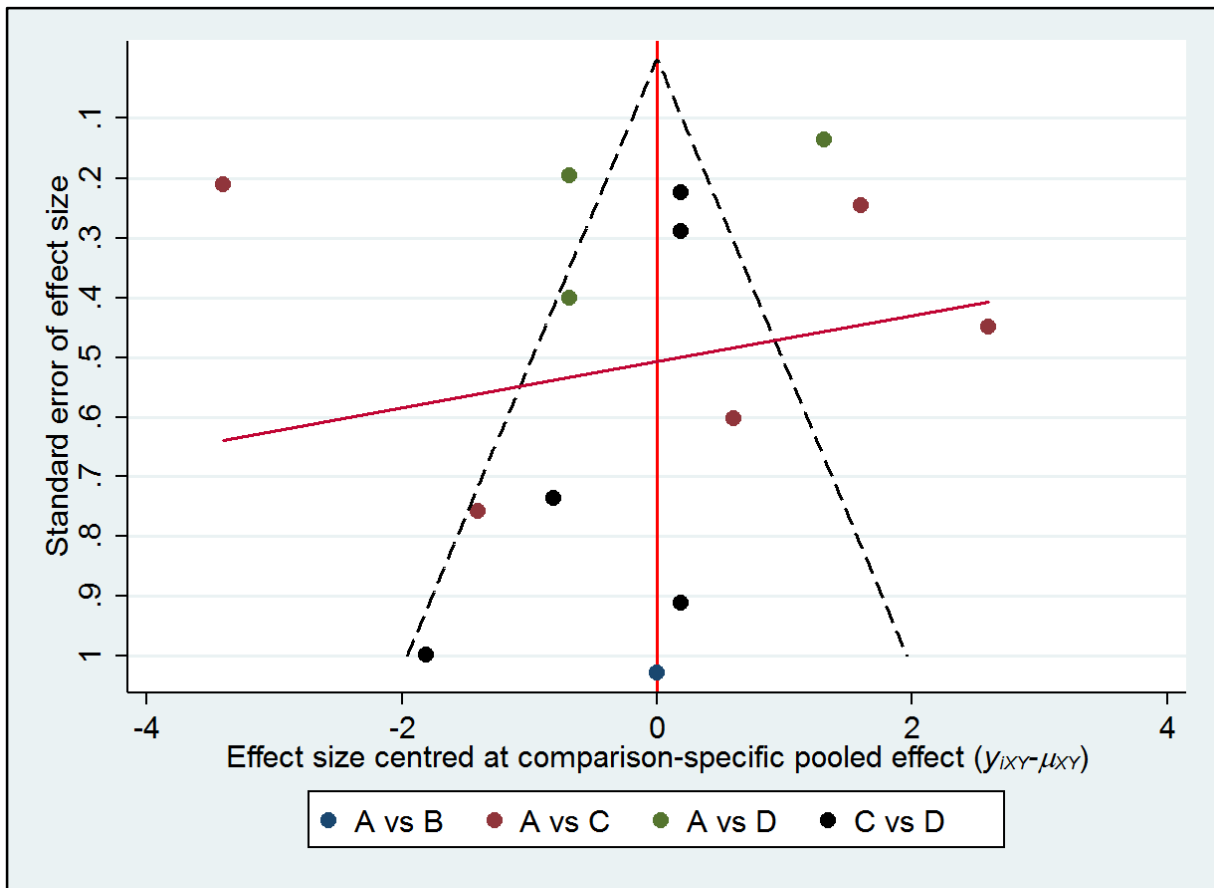**Panel F.** Overall bleeding

Legend: Funnel plots of the network estimates of all outcomes. In the comparison-adjusted funnel plot, the horizontal axis shows the difference of each i-study estimate YiXY from the summary effect for the respective comparison (YiXY-μXY) while the vertical axis presents the measure of dispersion of YiXY, namely the standard error of the effect size. The red line shows the null hypothesis. Each point represents a direct comparison; different colors correspond to different comparisons. The dashed black line represents the 95% confidence interval. The horizontal line represents the regression line; the dark red regression line demonstrates that no asymmetry is present; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).
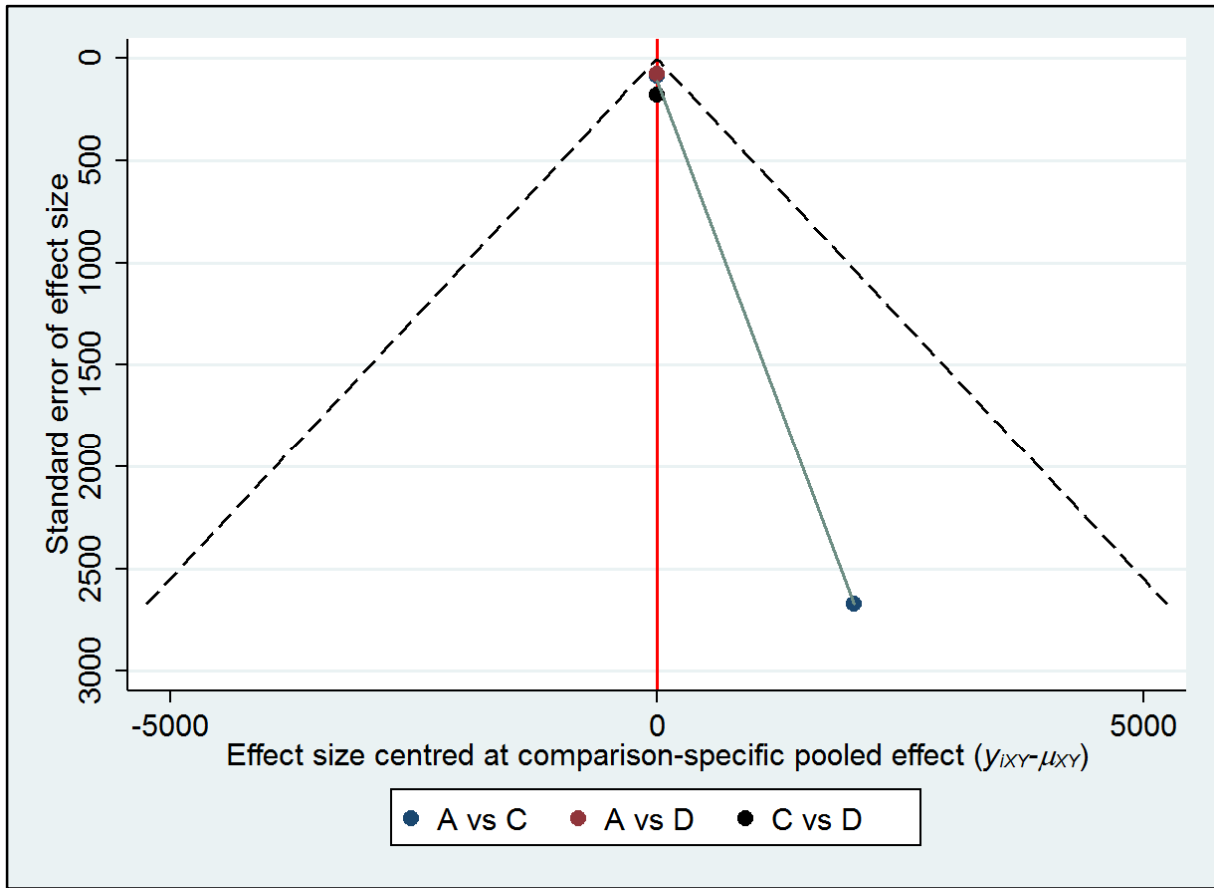
Panel G. Overall operative time

Legend: Funnel plots of the network estimates of all outcomes. In the comparison-adjusted funnel plot, the horizontal axis shows the difference of each i-study estimate YiXY from the summary effect for the respective comparison (YiXY-μXY) while the vertical axis presents the measure of dispersion of YiXY, namely the standard error of the effect size. The red line shows the null hypothesis. Each point represents a direct comparison; different colors correspond to different comparisons. The dashed black line represents the 95% confidence interval. The horizontal line represents the regression line; the dark regression line demonstrates that asymmetry is present; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).

Panel H. Length of hospital stay

Legend: Funnel plots of the network estimates of all outcomes. In the comparison-adjusted funnel plot, the horizontal axis shows the difference of each i-study estimate YiXY from the summary effect for the respective comparison (YiXY-μXY) while the vertical axis presents the measure of dispersion of YiXY, namely the standard error of the effect size. The red line shows the null hypothesis. Each point represents a direct comparison; different colors correspond to different comparisons. The dashed black line represents the 95% confidence interval. The horizontal line represents the regression line; the dark regression line demonstrates that asymmetry is present; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP).

Panel I. Total cost

Legend: Funnel plots of the network estimates of all outcomes. In the comparison-adjusted funnel plot, the horizontal axis shows the difference of each i-study estimate YiXY from the summary effect for the respective comparison (YiXY-μXY) while the vertical axis presents the measure of dispersion of YiXY, namely the standard error of the effect size. The red line shows the null hypothesis. Each point represents a direct comparison; different colors correspond to different comparisons. The dashed black line represents the 95% confidence interval. The horizontal line represents the regression line; the dark regression line demonstrates that asymmetry is present; arm A= Laparoscopic Cholecystectomy (LC) plus Laparoscopic Common Bile Duct Exploration (LCDBE); Arm B= LC plus Postoperative Endoscopic Retrograde Cholangiopancreatography (PostERCP); arm C= LC plus Preoperative Endoscopic Retrograde Cholangiopancreatography (PreERCP); arm D= LC plus Intraoperative Endoscopic Retrograde Cholangiopancreatography (IntraERCP)

eTable 3. Meta-regression of confounding covariates influencing heterogeneity

Covariates	Success rate (β, p value)			Operative time in min (β, p value)			LOS in days (β, p value)		
	B vs A	C vs A	D vs A	B vs A	C vs A	D vs A	B vs A	C vs A	D vs A
Years (increasing year)	-0.92, 0.020	0.25,0.065	0.10, 0.616	*	*	-2.3,0.186	*	0.9,0.060	1.5,0.100
Country (Western vs Eastern)	*	0.25,0,796	2.8,0.016	*	*	-11.7,0.186	*	*	-2.9,0.508
Patients (Proven vs Suspected stones)	*	2.63, <0.001	1.62,0.243	*	8.1,0.138	*	*	2.1,0.412	1.1,0.781
Matching for Age (Yes vs No)	*	-0,67,0.402	-0,80,0.382	*	-27.1,0.139	*	*	5.6,0.316	6.9,0.124
Matching for Sex (Yes vs No)	*	-0.31,0.678	-2.01,0.152	*	*	*	*	5.9,0.114	6.3,0.216
Risk of Bias (Yes vs No)	*	-0.18,0.715	*	*	*	*	*	4.9,0.296	*
Trans-cystic approach (increasing %)	3.98, 0.082	1.82, 0.081	0.91,0.644	*	-13,0.221	-3,4,0.856	*	3.1,0.217	1.1,0.673

Legend: β=regression coefficient; Arm A= Laparoscopic cholecystectomy plus laparoscopic common bile duct exploration; Arm B =Laparoscopic cholecystectomy plus post-operative endoscopic retrograde cholangio-pancreatography; Arm C= Preoperative endoscopic retrograde cholangio-pancreatography plus cholecystectomy; ; Arm D= Laparoscopic cholecystectomy plus endoscopic retrograde cholangio-pancreatography.

References

1. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ*. 2005;331:897-900.

2. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gøtzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;11:777-784.

3. Mills EJ, Ioannidis JP, Thorlund K, Schünemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA*. 2012:26;308:1246-1253.

4. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One*. 2013;8:e76654.

5. Bucher HC, Guyatt GH, Griffith LE, Walter SD.The results of direct and indirect treatment comparisons in meta-analysis of randomised controlled trials. *J Clin Epidemiol*. 1997;50:683-691.

6. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011;64:163-171.

7. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *Int J Epidemiol*. 2012;41:818-827.

8. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997:315:629-634.