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Single-incision versus conventional laparoscopic cholecystectomy: A systematic review and meta-analysis

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Abstract

Background: This review aims to evaluate the feasibility and safety of single-incision laparoscopic cholecystectomy (SILC) as compared to conventional laparoscopic cholecystectomy (CLC). *Methods:* A literature search for studies comparing the feasibility and safety of SILC with CLC was performed. Perioperative complications, postoperative pain, cosmetic satisfaction, conversion rates operative time, length of stay (LOS), estimated blood loss (EBL), total incision length, time to return to work / normal activity, and cost of stay were extracted. Weighted mean differences (WMDs) and odds ratios (ORs) were calculated for continuous and dichotomous variables, respectively. *Results:* Forty-three studies, including 2291 cases for SILC and 2281 cases for CLC, were included. Our analysis showed that compared with CLC, SILC was associated with significantly reduced postoperative pain on the day of surgery (WMD, -0.47; $p = 0.005$), lower rate of analgesic use (26.5% vs. 36.1%; $p = 0.004$), better cosmetic satisfaction scores (WMD, 0.84; $p = 0.0006$), shorter LOS (WMD, -0.18d; $p = 0.03$), and shorter incision length (WMD, -9.67 mm; $p = 0.004$). However, SILC was associated with significantly longer operative time compared to CLC (WMD, 13.65min; $p < 0.00001$). No significant differences were observed in perioperative complications, analgesic requirement, conversions to open surgery, EBL, time to return to work / normal activity, or cost of stay. *Conclusions:* In this analysis, which included the largest number of patients thus far, SILC appeared to be feasible and safe. Whether SILC benefits LOS over CLC remains to be further investigated, as well as cost of stay.

Keywords

Laparoscopic Cholecystectomy, Single-Incision, Single-Port Access, Laparoendoscopic Single-Site, Single-Incision Laparoscopic Surgery

1. Introduction

Open cholecystectomy (OC), as first described by Langenbuch in 1882, has remained mainly unchanged until German surgeon Muhe performed the first laparoscopic cholecystectomy (LC) using a modified laparoscope ("Galloscope") in 1985.[1] Following this, Mouret performed the first electronic video-assisted LC in 1987.[2] Since then, LC has gained widespread popularity for the treatment of gallstone-related diseases, with reduced postoperative pain, shorter hospital stay, better cosmetic outcome, and quicker convalescence compared to OC.[3] Although small-incision cholecystectomy, also called mini-laparotomy cholecystectomy, seems to be equivalent with LC in terms of complications, hospital stay and postoperative recovery with a shorter operative time,[4] this has not stopped LC from being introduced into widespread clinical practice. As an "innovative procedure" and gold standard surgical treatment for removing the gallbladder, LC is applicable to nearly all patients with symptomatic cholelithiasis in experienced hands and the contraindications to attempting LC diminishes with increasing experience of the procedure.[5] For those healthcare

providers without the financial resources for laparoscopic equipment and appropriately trained surgical teams and patients unable to tolerate general anesthesia, small-incision cholecystectomy may be a viable and safe option.

At the end of the 1990s, a second "innovative procedure" in this field has been the introduction of single-incision laparoscopic cholecystectomy (SILC).[6-8] Since this procedure needs only one skin incision with the scar masked in the umbilicus and not evident in the abdomen, this aesthetic advantage may attract more attention in SILC than conventional multi-port (three or four port) laparoscopic cholecystectomy among patients when a better "scarless" option is shown.[7] However, due to the coaxiality of the instruments, markedly reduced working space, and difficulty to achieve the critical view of safety and to perform cholangiography, its widespread use is restricted by the limitations of the technology. In recent years, with the development of the technique and instrumentation, SILC has become the focus of renewed interest and has gained much popularity. From 2008 and thereafter, numerous studies examined its feasibility and safety and compared it with conventional laparoscopic cholecystectomy (CLC). Previous meta-analyses have demonstrated that SILC was associated with a significantly longer operative time with postoperative complications, postoperative pain and length of hospital stay comparable with CLC.[9-11] However, these studies were limited by the relatively small number of patients (approximately 400 in each group). Thus, it may not be sufficient to recognize small differences in outcomes with wide confidence intervals (CIs). For example, Joseph et al.[12] found bile duct injury rate with SILC (0.72%) was relatively high when compared with a rate of 0.5% for CLC. It was impossible to detect the difference of bile duct injury rate with only a few hundred patients (~ 800) because even if the injury rates were 1% for SILC and 0.5% for CLC, only 6 bile duct injuries would have occurred in total. As expected, none of these studies examined this major complication. In addition, some of the outcomes, such as the cosmetic results, varied from these studies. Garg et al.[9] and Pisanu et al.[10] found that SILC had significantly favorable cosmetic scoring compared to CLC, while Sajid et al.[11] found the cosmetic scoring was comparable between the two cholecystectomy techniques.

To overcome these limitations, we performed the present meta-analysis and included the largest number of patients from all eligible comparative studies of SILC and CLC in the literature. The aim of this study was to evaluate and validate the feasibility and safety of SILC as compared to CLC. The specific questions our study aims to answer are: (1) Is the perioperative complications following SILC statistically comparable with CLC, especially the incidence of bile duct injuries, which is higher than CLC as stated by Joseph et al.[12]?; (2) Does SILC significantly reduce postoperative pain in comparison with CLC?; (3) Is there a really significant difference in cosmetic results with SILC as compared to CLC?; (4) Does SILC have more conversions to open surgery?; (5) Is SILC associated with a reduced length of hospital stay?; and (6) Does SILC cost more than CLC?

2. Materials and Methods

A prospective protocol of this systematic review was registered at: www.crd.york.ac.uk/PROSPERO (Registration number: CRD42012002775) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[13] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[14]

2.1. Literature Search Strategy

A literature search was performed in August 2014 using PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) databases, on all published studies comparing efficacy and safety of SILC with CLC. The following Medical Subject Headings (MeSH) terms and keywords were used in searching: single incision / port / site laparoscopic cholecystectomy, natural orifice transluminal endoscopic surgery, conventional / classic / standard / traditional laparoscopic cholecystectomy, multi-port / three-port / four-port laparoscopic cholecystectomy, single incision laparoscopic surgery (SILS), SILC, laparo-endoscopic single-site surgery (LESS), CLC, and standard laparoscopic cholecystectomy. The electronic search was supplemented by a hand search of ClinicalTrials.gov and the Current Controlled Trials registry. Reference lists for all relevant studies, recent editorials, and related review articles were also checked for further eligible studies. The search was conducted without any region or language restrictions.

2.2. Inclusion and Exclusion Criteria

Articles were selected if they met the following inclusion criteria: (1) compared SILC and CLC techniques in adults; (2) reported at least one of the outcome measures mentioned below; (3) when two studies were reported by the same institution and/or authors, we included either the one of the better quality, or the most recently published. Studies were excluded from the meta-analysis if: (1) it was impossible to extract the necessary data from the outcomes of interest; (2) the study sample size was too small ($n < 30$); and (3) the study compared SILC with CLC in a pediatric population. Review articles, case reports, comments, editorials, letters, and animal model studies were also excluded.

2.3. Data Extraction

Two authors (J.H. and J.G.) independently screened all of the abstracts and articles. The following data from each included study were extracted: first author, year of publication, country where the study was performed, study design, number of patients operated on with each technique, study population characteristics, surgical technique, and intraoperative and postoperative outcomes. Any disagreement was resolved through discussion and arbitrated by the senior author (Z.S.).

2.4. Outcomes of Interest and Definitions

The primary outcomes were perioperative complication rates, postoperative pain, cosmetic satisfaction, and

conversion rates. If sufficient data were available, perioperative complications were subdivided into intraoperative complications and postoperative complications. All reported complications were graded according to the Clavien-Dindo Classification of Surgical Complications System.[15] Grades I and II complications were classified as minor, and grades III to V were classified as major. Postoperative pain was measured using a 10-point visual analog scale (VAS) on the same day of surgery (day 0), postoperative day 1, and postoperative day 2 together with analgesia requirement and rate of analgesic use. Cosmetic satisfaction was rated on a scale ranging from 1 (poor) to 10 (excellent). Other scales reported on cosmetic satisfaction were converted to a 1-10 scale for comparison. Conversions in the SILC group were defined as follows: (1) to cholecystectomy requiring an additional trocar; (2) to conventional three-port or four-port laparoscopic cholecystectomy; or (3) to open surgery.

The secondary outcomes were operative time, length of stay (LOS), estimated blood loss (EBL), total incision length, time to return to work or normal activity, and cost of hospital stay. Operative time was defined as the interval between the initial skin incision and skin closure. LOS was defined as the number of days spent in the hospital postoperatively. Time to return to work or normal activity was defined as the interval from the date of discharge to the date of return to work or normal activity. Cost of hospital stay was defined as the total hospital charges for a patient from admission to discharge.

2.5. Quality Assessment and Levels of Evidence

The methodological quality of randomized controlled trials was assessed based on the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0.[16] Each included randomized controlled trial (RCT) was assessed regarding sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. The methodological quality of nonrandomized studies was assessed by the Newcastle-Ottawa Scale, [17] in which a study is judged on three dimensions: the selection of the study groups, the comparability of the groups, and the assessment of outcome of interest. RCTs and nonrandomized studies achieving six or more stars were considered to be of high quality. In addition, studies were rated for levels of evidence according to the Centre for Evidence-Based Medicine in Oxford in the UK.[18]

2.6. Statistical Analysis

Statistical analysis was performed using Review Manager version 5.0.0 for Windows (2008; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and Intercooled Stata version 7.0 for Windows (StataCorp, College Station, TX, USA). Dichotomous effect estimates were presented as odds ratios (ORs) with 95% CIs using the Mantel-Haenszel method and we considered a p-value < 0.05 (two-sided) as significant. For continuous estimates, weighted mean difference (WMD) with 95% CI was presented using the Inverse-Variance method. We estimated the degree of heterogeneity among results using the Cochrane Q statistic (with $p \leq 0.10$ considered significantly heterogenetic), and the I^2 statistic (with an $I^2 > 50\%$ regarded as significantly heterogenetic).[19] We used a random-effects model, if either of the two statistics was significant. Otherwise, we used a fixed-effects model. Sensitivity analyses were performed for RCTs and high quality studies. Publication bias was evaluated by inspection of the funnel plot.

2.7. Sample Size Considerations

Sample power analysis was performed using PS Software (Power and Sample Size Calculation version 3.0) .[20] The overall complication rates were 8.4% and 7.5% in the SILC and CLC groups, respectively. To examine this difference with a 5% significance level and 80% power, it was calculated that 14405 patients would be required in each arm of a RCT. For the complication of bile duct injury, the number of patients required would be even higher (~ 20,000 patients in each arm).

3. Results

Through the electronic database search, we found 710 citations: 488 from PubMed, 201 from Embase, and 21 from the Cochrane Library. In addition, the searches of ClinicalTrials.gov and the Current Controlled Trials registry yielded 24 more records. Examinations of reference lists for all relevant studies, editorials, and related review articles did not yield any further studies. In total, 43 studies,[21-63] including 2291 cases of SILC and 2281 cases of CLC, matched the selection criteria and were included in final meta-analysis (Fig. 1). On review of study selection, there was 96% agreement between the two reviewers (J.H. and J.G.), and the agreements on data extraction and quality assessment were 96% and 98%, respectively.

3.1. Characteristics of Selected Studies

The characteristics of included studies are presented in Table 1. Among the 43 studies, there were 17 retrospective studies[21-37] (level of evidence: 3b), 12 prospective nonrandomized studies[38-49] (level of evidence: 3b), 13 RCTs[50-62], and one quasi-RCT[63] (level of evidence: 2b). Twenty-three out the 43 studies used commercial single-port devices (e.g., SILS port, TriPort, GelPOINT, OCTO Port, and Quadra Port), three used a self-designed glove port, and the remaining 17 used adjacent trocars inserted through separate fascial sites in a single umbilical skin incision. Approximately half of the included studies mentioned the length of follow-up, whereas the remaining studies only provided perioperative data.

3.2. Methodological Quality of Included Studies

The methodological quality of randomized trials is shown

in Fig. S1. The quality assessment and scores of both prospective nonrandomized and retrospective studies are summarized in Table 1. In total, 14 non-randomized studies[23-25, 28, 30, 32, 38-40, 43-45, 49, 59] achieving six or more stars, 13 RCTs[50-62] and one quasi-RCT[63] were regarded as high quality studies.

3.3. Primary Outcomes

3.3.1. Perioperative Complications

Perioperative complications were reported in 39 studies (Table 2), but the incidence was not significantly different between the SILC and CLC groups (8.4% vs. 7.5%; OR: 1.11; 95%CI: 0.88-1.41; p = 0.38) (Fig. 2). Intraoperative and postoperative complication rates were available in 22 and 39 studies, respectively, but the results were not significantly different between the two groups (3.3% vs. 3.0%; OR, 1.08; 95% CI, 0.69-1.69; p = 0.75; and 5.1% vs. 4.5%; OR, 1.20; 95% CI, 0.90-1.61; p = 0.22). When all reported complications were graded according to the Clavien-Dindo Classification of Surgical Complications System and divided into minor and major complications, there were still no significant differences between the two groups (5.5% vs. 5.6%; OR, 1.05; 95% CI, 0.79-1.40; p = 0.71; and 1.6% vs. 0.9%; OR, 1.51; 95% CI, 0.89-2.54; p = 0.12).

3.3.2. Postoperative Pain

Twenty-five studies reported postoperative pain using the VAS, with 17 on day 0, 17 on day 1, and 10 studies on day 2. Meta-analysis of 17 studies showed a significantly reduced pain scores on day 0 in the SILC group compared with the CLC group (WMD, -0.47; 95% CI, -0.79 to -0.15; p = 0.005) (Fig. 3), while the pain scores on postoperative days 1 and 2 failed to reach statistical significance between the two groups (WMD, -0.28; 95% CI, -0.71 to 0.15; p = 0.20; and WMD, -0.16; 95% CI, -0.44 to 0.13; p = 0.27, respectively).

Meta-analysis of the five studies that reported analgesic requirement in 696 patients showed no significant difference between the SILC and CLC groups (WMD, 1.06; 95% CI, -4.52 to 6.64; p=0.71). However, the pooled data of eight studies including 902 patients showed that the SILC group had a significantly lower rate of analgesic use than the CLC group (26.5% vs. 36.1%; OR, 0.38; 95% CI, 0.19-0.73; p = 0.004).

3.3.3. Cosmetic Satisfaction

Seven studies evaluated the cosmetic satisfaction on a 1-10 scale and the pooled data of these studies showed better cosmetic satisfactory scores in the SILC group compared with the CLC group (WMD, 0.91; 95% CI, 0.27-1.56; p = 0.006). The results of another six studies that reported cosmetic satisfaction on different scales (three studies on a 1-5 scale, one study on a 3-15 scale, one study on a 3-24 scale, and one study on a Likert scale) were converted to a 1-10 scale for comparison. Pooling the data from these 13 studies still showed significantly better cosmetic satisfactory scores in the SILC group (WMD, 0.84; 95% CI, 0.36- 1.32; p = 0.0006) (Fig. 4).

3.3.4. Conversion Rate

Thirty-nine studies, including 4317 patients, reported the number of conversions. A total of 174 patients (8%) in the SILC group required conversions, with 64 to cholecystectomy requiring an additional trocar, 96 to CLC, and 13 to open surgery. Reasons for conversions are shown in Table S1. The conversion rate was significantly higher in the SILC group (incidence of 8.0%; 174 of 2163) than the CLC group (1.5%; 33 of 2154), with an OR of 4.58 and corresponding 95% CI of 3.25 to 6.45. When only conversions to open surgery were analyzed, there was no significant difference between the two groups (OR, 0.57; 95% CI: 0.30-1.08; p = 0.08) (Fig. 5).

3.4. Secondary Outcomes

3.4.1. Operative Time

Thirty-eight studies that reported operative time in the SILC group versus CLC group were included in this outcome analysis. The results of pooled data showed a significantly longer operative time in the SILC group than the CLC group, with random-effects WMD of 13.65 (95% CI, 7.9 to 19.39; p < 0.00001) (Fig. S2).

3.4.2. Length of Hospital Stay

Thirty of 43 studies, including 2921 patients, reported postoperative length of stay. The results showed a significant reduced length of hospital stay in the SILC group versus the CLC group (WMD, -0.18d; 95% CI, -0.35 to -0.02; p = 0.03) (Fig. S3).

3.4.3. Estimated Blood Loss

Nine studies reported estimated blood loss during the operation of SILC and CLC. Although the EBL was lower in the SILC group than the CLC group, the difference was not significantly different (WMD, -3.53ml; 95% CI, -7.85 to 0.78; p = 0.11).

3.4.4. Total Incision Length

Only five studies reported the data of skin incision length, with one reporting the umbilical skin incision length, which was significantly longer in the SILC patients (18.8 ± 3.47 vs.14.31 ± 4.14 mm; p = 0.002). Meta-analysis of the remaining four studies that reported total incision length showed a significantly shorter skin incision length in the SILC group compared with the CLC group (WMD, -9.67 mm; 95% CI, -16.32 to -3.01; p = 0.004).

3.4.5. Time to Return to Work/Normal Activity

Seven studies reported postoperative time to return to work or normal activity in 584 patients. Pooling the data of these studies showed no significant difference between the two groups (WMD, -0.78d; 95% CI, -0.17 to 0.14; p = 0.09).

3.4.6. Cost of Hospital Stay

Only five studies including 640 patients compared cost of hospital stay in SILC and CLC groups. The mean cost between these studies varied and no significant difference was found, with a reduction of $205.92 in the SILC group versus the CLC group, but a wide CI of -$1346.82 to $934.98.

Table 1. *Characteristics of included studies*

Study	Year	Design	Cases		Matching*	Single-port devices for SILC	Follow-up, mo†, SILC/CLC	Level of evidence	NOS score
			SILC	CLC					
Aprea *et al.*	2011	RCT	25	25	1,2,3,4,5,7	TriPort	Perioperative	2b	RCT
Asakuma *et al.*	2011	Quasi-RCT	24	25	1,2,3,5,6	Homemade (Glove port)	18	2b	Quasi-RCT
Barband *et al.*	2012	PNR	25	30	1,2,3,5,7	Homemade (Glove port)	3	3b	★★★★★★★
Beck *et al.*	2012	R	50	50	5,7	GelPOINT/SILS port/TriPort	Perioperative	3b	★★★★
Bucher *et al.*	2011	RCT	75	75	1,3,4,5,6	TriPort	1	2b	RCT
Cao ZG *et al.*	2011	RCT	57	51	1,2,3,4,5,6,7	No	Perioperative	2b	RCT
Cao LP *et al.*	2011	R	36	24	1,2,5	No	0.5	3b	★★★★★
Chang *et al.*	2011	R	30	30	1,2,7	SILS port	7	3b	★★★★★★★
Chow *et al.*	2010	R	41	58	1,2,3,5,7	No	Perioperative	3b	★★★★★★
Fronza *et al.*	2010	R	25	25	1,2,3,4,5,6	TriPort/SILS port/No	1	3b	★★★★★★★
Gangl *et al.*	2011	PNR	67	67	1,2,3,4,5	SILS port	17-26	3b	★★★★★★★
Gang *et al.*	2012	PNR	35	29	1,2,3,4,7	No	10.5	3b	★★★★★★★★
Han *et al.*	2012	PNR	31	30	2,3,5	Homemade (Glove port)	Perioperative	3b	★★★★★
Hernandez *et al.*	2009	R	100	30	1,2,3	No	Perioperative	3b	★★★★★
Hodgett *et al.*	2009	R	29	29	1,2,3,7	No	Perioperative	3b	★★★★★
Jacob *et al.*	2011	R	36	37	1,2,3,4,5	TriPort	11/14	3b	★★★★★★★★
Joseph *et al.*	2011	R	108	177	1,2,3,4,5,7	No	NA	3b	★★★★★
Karim *et al.*	2012	R	45	62	1,2,3,4,5	GelPOINT/SILS port/TriPort/SSLAS	2	3b	★★★★★★
Khaimook *et al.*	2012	R	107	108	1,2,3,5	SILS port	Perioperative	3b	★★★★★
Khambaty *et al.*	2011	PNR	107	44	1,3,4	SILS port	11	3b	★★★★★
Kim *et al.*	2012	R	96	94	1,2,3,4,5,6,7	OCTO Port	Perioperative	3b	★★★★★★
Lai *et al.*	2011	RCT	24	27	1,2,3,4,5,6	SILS port	3	2b	RCT
Lee *et al.*	2010	RCT	35	35	1,2,3,6,7	Quadra Port	6	2b	RCT
Leung *et al.*	2012	RCT	36	43	1,2,3,6	NA	3.3/3	2b	RCT
Lirici *et al.*	2011	RCT	20	20	1,2,3,4,5	TriPort	1	2b	RCT
Love *et al.*	2011	R	68	48	NA	No	Perioperative	3b	★★★
Ma *et al.*	2011	RCT	21	22	1,3,5,6	TriPort	Perioperative	2b	RCT
McGregor *et al.*	2011	PNR	11	24	1,4,5,6	Endopath Xcel Trocar	2	3b	★★★★★★
Philipp *et al.*	2009	R	29	22	1,2,3,4,5,6	No	1	3b	★★★★★
Phillips *et al.*	2012	RCT	117	80	1,2,3,4,5	SILS port	12	2b	RCT
Prasad *et al.*	2011	PNR	100	100	1,2,3	No	Perioperative	3b	★★★★★★
Rasic *et al.*	2012	R	48	50	1,2,3	No	Perioperative	3b	★★★★
Rupp *et al.*	2011	PNR	101	100	1,2,3,7	No	Perioperative	3b	★★★★★
Sasaki *et al.*	2012	R	114	201	1,2,3,4,5,6	No	Perioperative	3b	★★★★★★★
Sinan *et al.*	2012	RCT	17	17	1,2,3,5	SILS port	7/5.3	2b	RCT
Solomon *et al.*	2012	PNR	22	11	1,2,3,5,7	SILS port	Perioperative	3b	★★★★★★
Thapa *et al.*	2010	PNR	20	20	1,2	SILS port	Perioperative	3b	★★★★★
Tsimoyiannis *et al.*	2010	RCT	20	20	1,2,4,7	No	Perioperative	2b	RCT
Vidal *et al.*	2011	PNR	120	120	1,2,4	SILS port	24	3b	★★★
Vilallonga *et al.*	2012	RCT	69	71	1,2	SILS port/TriPort	7.3	2b	RCT
Wong *et al.*	2012	PNR	20	20	1,2,3,4,6	No	Perioperative	3b	★★★★★★
Wu *et al.*	2011	R	100	100	1,2,5,7	No	Perioperative	3b	★★★★
Zheng *et al.*	2012	RCT	30	30	1,2,3,5,6	TriPort	9.4/11.6	2b	RCT

*Matching: 1 = age; 2 = gender; 3 = body mass index; 4 = American Society of Anesthesiologists score; 5 = history of upper abdominal surgery; 6 = indications for cholecystectomy; 7 = single surgeon.

†Mean or median.

Abbreviations: RCT: randomized controlled trial; PNR: prospective nonrandomized; R: retrospective; SILC: single-incision laparoscopic cholecystectomy; CLC: conventional laparoscopic cholecystectomy; SSLAS: Single Site Laparoscopy Assess System; NOS: Newcastle-Ottawa Scale.

Table 2. *Meta-analysis of single-incision laparoscopic cholecystectomy and conventional laparoscopic cholecystectomy*

Outcomes of Interest	Studies, No.	SILC patients, no.	CLC patients, no.	Effect Estimate WMD/OR(95%CI)	Z test	*P* value¶	Heterogeneity			
							χ^2	*df*	*p* value	I^2, %
Primary outcomes										
Perioperative complications	39	2107	2110	1.11(0.88-1.41)	0.88	0.38	24.94	32	0.81	0
Intraoperative complications	22	1250	1316	1.08(0.69-1.69)	0.32	0.75	7.55	11	0.75	0
Postoperative complications	39	2107	2110	1.20(0.90-1.61)	1.24	0.22	26.61	32	0.74	0
Minor complications*	38	1987	1990	1.05(0.79-1.40)	0.37	0.71	32.69	29	0.29	11
Major complications†	38	1987	1990	1.51(0.89-2.54)	1.54	0.12	8.36	20	0.99	0
Postoperative pain‡ at day0	17	783	767	-0.47(-0.79 to -0.15)	2.84	0.005	113.21	16	<0.00001	86
Postoperative pain at day1	17	625	593	-0.28(-0.71 to 0.15)	1.29	0.20	361.18	16	<0.00001	96
Postoperative pain at day2	10	385	370	-0.16(-0.44 to 0.13)	1.09	0.27	64.57	9	<0.00001	86
Analgesic requirement, mg§	5	345	351	1.06(-4.52 to 6.64)	0.37	0.71	35.74	4	<0.00001	89
Rate of analgesic use	8	415	487	0.38(0.19-0.73)	2.90	0.004	15.98	7	0.03	56
Cosmetic satisfaction score	13	573	523	0.84(0.36-1.32)	3.43	0.0006	333.41	12	<0.00001	96
Conversion rate	39	2163	2154	4.58(3.25-6.45)	8.72	<0.00001	37.41	32	0.23	14
Secondary outcomes										
Operative time	38	1999	2038	13.65(7.92-19.39)	4.66	<0.00001	2267.23	37	<0.00001	98
Length of hospital stay	30	1479	1442	-0.18(-0.35 to -0.02)	2.23	0.03	246.43	29	<0.00001	88
Estimated blood loss	9	481	539	-3.53(-7.85 to 0.78)	1.60	0.11	57.71	8	<0.00001	86
Total incision length	4	127	137	-9.67(-16.32 to -3.01)	2.85	0.004	717.91	3	<0.00001	100
Time to return to work/normal activity	7	291	293	-0.78(-1.70 to 0.14)	1.67	0.09	41.22	6	<0.00001	85
Cost of hospital stay	5	292	348	-205.92(-1346.82 to 934.98)	0.13	0.90	54.68	4	<0.00001	93

*Minor complications: Clavien-Dindo grade I-II.
†Major complications: Clavien-Dindo grade III-V.
‡Postoperative pain was evaluated by visual analogue scale (VAS).
§Morphine equivalents in milligrams.
¶Statistically significant *p* values are shown in bold.
Abbreviations: SILC: single-incision laparoscopic cholecystectomy; CLC: conventional laparoscopic cholecystectomy; WMD/OR: weighted mean difference/odds ratio; CI: confidence interval; *df*: degrees of freedom.

Table 3. *Sensitivity analysis of primary and secondary outcomes*

Outcomes of Interest	RCT					High-quality studies				
	Studies, No.	SILC patients, no.	CLC patients, no.	Effect Estimate WMD/OR (95%CI)	*P* value¶	Studies, No.	SILC Patients, no.	CLC Patients, no.	Effect Estimate WMD/OR (95%CI)	*P* value¶
Primary outcomes										
Perioperative complications	12	510	473	1.14(0.78-1.67)	0.51	26	1171	1256	1.05(0.80-1.38)	0.74
Intraoperative complications	7	365	333	1.17(0.54-2.52)	0.70	18	893	966	1.10(0.68-1.79)	0.70
Postoperative complications	12	510	473	1.41(0.82-2.40)	0.21	26	1171	1256	1.11(0.78-1.58)	0.55
Minor complications*	12	510	473	1.15(0.71-1.85)	0.57	26	1171	1256	0.99(0.72-1.35)	0.93
Major complications†	12	510	473	2.19(0.80-5.98)	0.13	26	1171	1256	1.87(0.94-3.74)	0.08
Postoperative pain‡ at day0	8	280	285	-0.41(-0.80 to -0.02)	0.04	12	460	463	-0.59(-0.98 to -0.20)	0.003
Postoperative pain at day1	7	249	243	-0.41(-1.28 to 0.46)	0.36	15	569	549	-0.31(-0.85 to 0.23)	0.26
Postoperative pain at day2	4	114	108	-0.34(-0.84 to 0.16)	0.18	9	354	340	-0.18(-0.48 to 0.11)	0.23
Analgesic requirement,	2	110	110	3.08(-9.26 to	0.62	3	130	130	2.10(-9.69 to	0.73

Outcomes of Interest	RCT					High-quality studies				
	Studies, No.	SILC patients, no.	CLC patients, no.	Effect Estimate WMD/OR (95%CI)	*P* value[¶]	Studies, No.	SILC Patients, no.	CLC Patients, no.	Effect Estimate WMD/OR (95%CI)	*P* value[¶]
mg[§]				15.42)					13.89)	
Rate of analgesic use	3	115	115	0.26(0.12-0.54)	0.0003	5	159	160	0.24(0.13-0.44)	<0.00001
Cosmetic satisfaction score	8	395	363	1.26(0.64-1.87)	<0.0001	11	517	479	1.04(0.55-1.53)	<0.0001
Conversion rate	11	529	499	3.10(1.35-7.15)	0.008	26	1190	1282	3.12(2.02-4.82)	<0.00001
Secondary outcomes										
Operative time	10	372	371	12.48(5.96-19.00)	0.0002	25	1063	1184	15.55(8.10-23.01)	<0.0001
Length of hospital stay	9	355	354	-0.25(-0.71 to 0.21)	0.29	19	744	788	-0.22(-0.45 to 0.02)	0.07
Estimated blood loss	4	118	115	1.69(-0.92 to 4.29)	0.20	5	143	140	1.82(-0.94 to 4.58)	0.20
Total incision length	3	116	113	-6.43(-9.07 to -3.79)	<0.00001	4	127	137	-9.67(-16.32 to -3.01)	0.004
Time to return to work/normal activity	3	134	137	-0.70(-2.40 to 1.00)	0.42	7	291	293	-0.78(-1.70 to 0.14)	0.09

[*]Minor complications: Clavien-Dindo grade I-II.
[†]Major complications: Clavien-Dindo grade III-V.
[‡]Postoperative pain was evaluated by visual analogue scale (VAS).
[§]Morphine equivalents in milligrams.
[¶]*P* values of changed significance in sensitivity analysis are shown in bold.
Abbreviations: RCT: randomized controlled trials; SILC: single-incision laparoscopic cholecystectomy; CLC: conventional laparoscopic cholecystectomy; WMD/OR: weighted mean difference/odds ratio; CI: confidence interval.

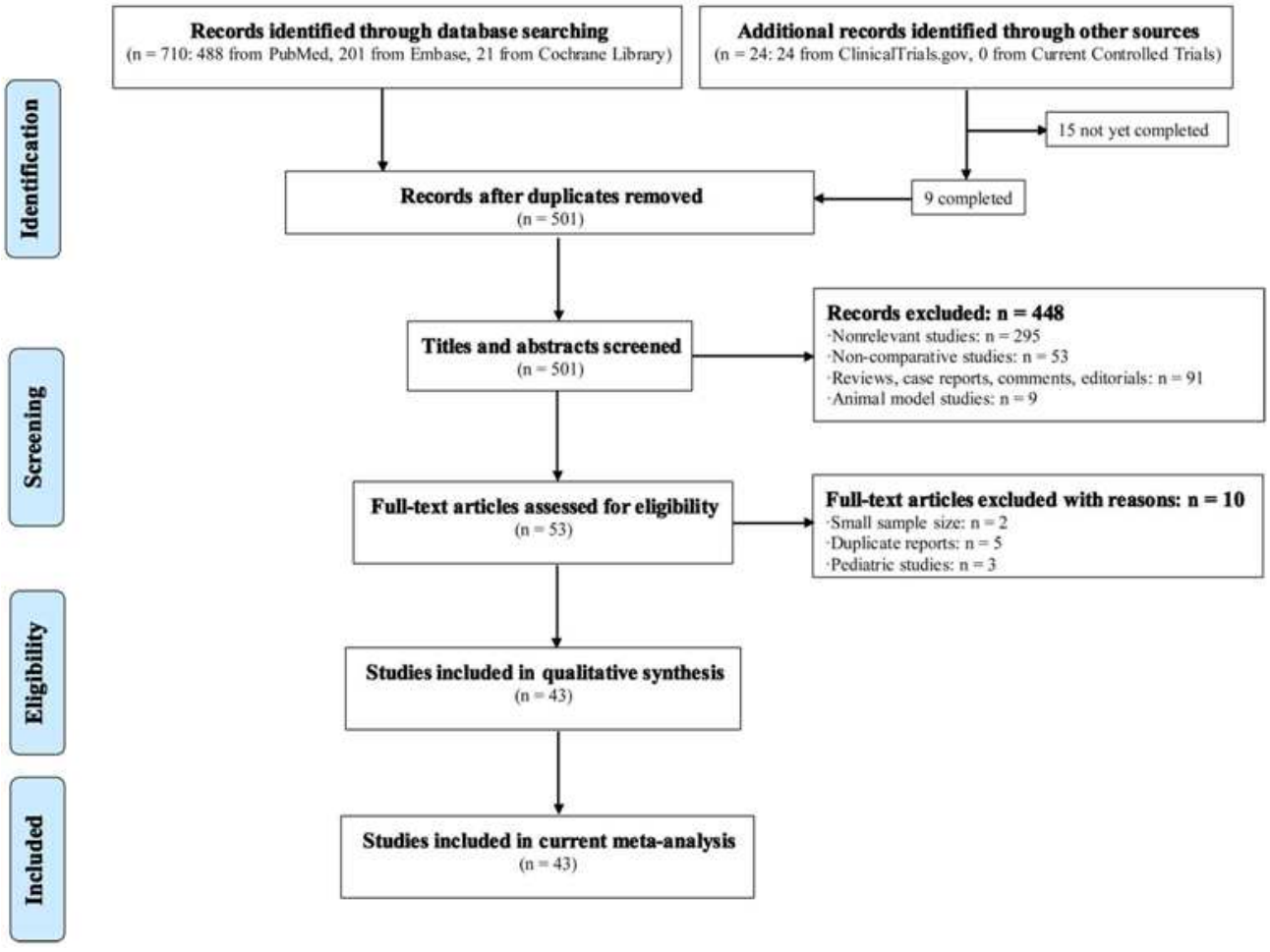

Figure 1. *Flow diagram of study identification, inclusion and exclusion.*

Table S1. *Reasons for conversions*

Reasons for conversions	SILC		CLC	
	No. of patients (ratio %)	Rate (%)	No. of patients (ratio %)	Rate (%)
Adhesions/inflammation/unclear or abnormal anatomy	59 (33.9)	2.6	11 (33.3)	0.48
Inadequate visualization of the critical view	26 (15.0)	1.1	1 (3.0)	0.04
Bleeding	11 (6.3)	0.5	2 (6.1)	0.09
Choledocholithiasis	7 (4.0)	0.3	2 (6.1)	0.09
Inability to maintain pneumoperitoneum	3 (1.7)	0.1	0 (0)	0
Others	6 (3.5)	0.2	4 (12.1)	0.17
Unclear	62 (35.6)	2.7	13 (39.4)	0.57
Total	174	7.6	33	1.44

Abbreviations: SILC: single-incision laparoscopic cholecystectomy; CLC: conventional laparoscopic cholecystectomy.

Table S2. *Perioperative complications*

Complications	SILC		CLC	
	No. of patients (Ratio %)	Rate (%)	No. of patients (Ratio %)	Rate (%)
Wound complications*	65 (36.7)	3.08	60 (38.0)	2.84
Gallbladder perforation/Bile spillage	36 (20.3)	1.71	32 (20.2)	1.52
Incisional hernia	11 (6.2)	0.52	5 (3.2)	0.24
Intra-abdominal hematoma	10 (5.7)	0.47	6 (3.8)	0.28
Bile leak	8 (4.6)	0.38	4 (2.5)	0.19
Severe bleeding	5 (2.8)	0.24	6 (3.8)	0.28
Retained bile duct stones	5 (2.8)	0.24	5 (3.2)	0.24
Common bile duct injury	4 (2.3)	0.19	5 (3.2)	0.24
Other minor complications	33 (18.6)	1.57	35 (22.2)	1.66
Total	177	8.40	158	7.49

*Wound complications: wound infection; abdominal hematoma/seroma.
Abbreviations: SILC: single-incision laparoscopic cholecystectomy; CLC: conventional laparoscopic cholecystectomy.

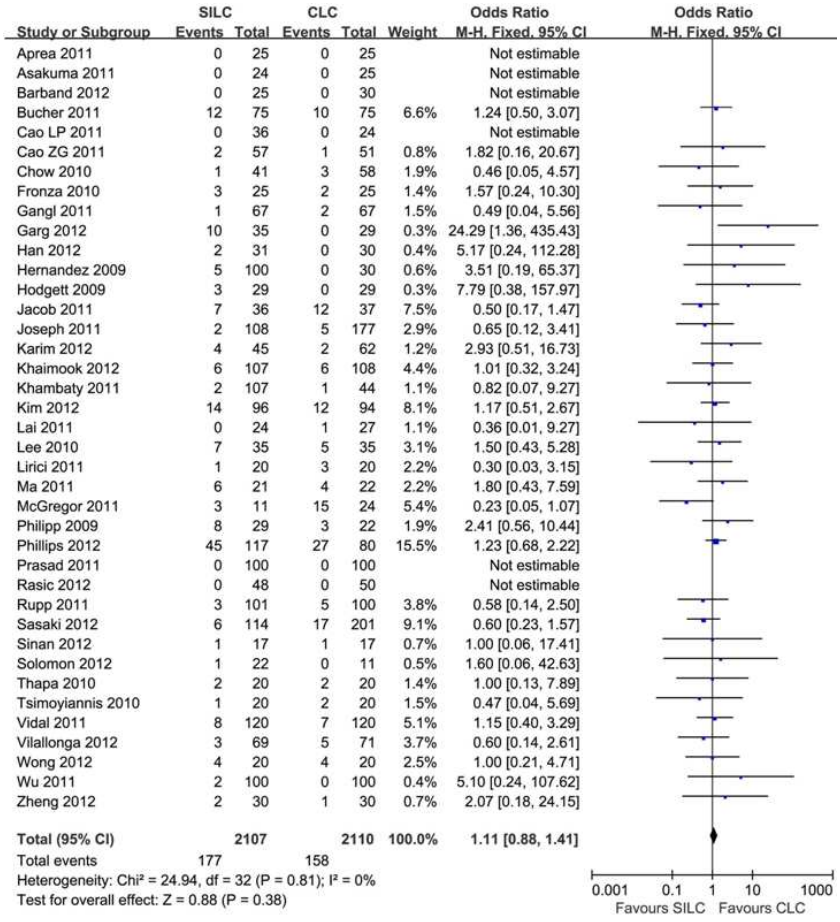

Figure 2. *Forest plot and meta-analysis of perioperative complications. SILC, single-incision laparoscopic cholecystectomy; CLC, conventional laparoscopic cholecystectomy; M-H, Mantel-Haenszel method; CI, confidence interval.*

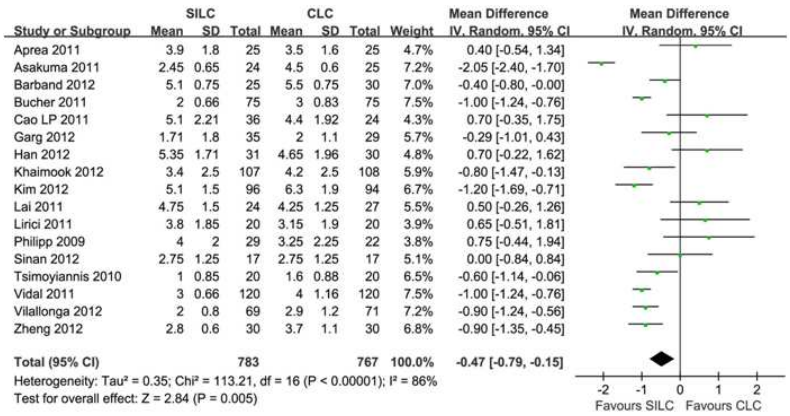

Figure 3. *Forest plot and meta-analysis of postoperative pain on the day of surgery. SILC, single-incision laparoscopic cholecystectomy; CLC, conventional laparoscopic cholecystectomy; IV, inverse-variance method; CI, confidence interval; SD, standard deviation.*

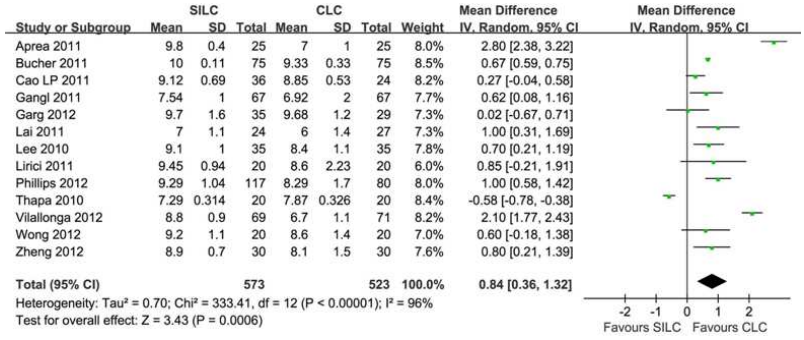

Figure 4. *Forest plot and meta-analysis of cosmetic satisfactory scores. SILC, single-incision laparoscopic cholecystectomy; CLC, conventional laparoscopic cholecystectomy; IV, inverse-variance method; CI, confidence interval; SD, standard deviation.*

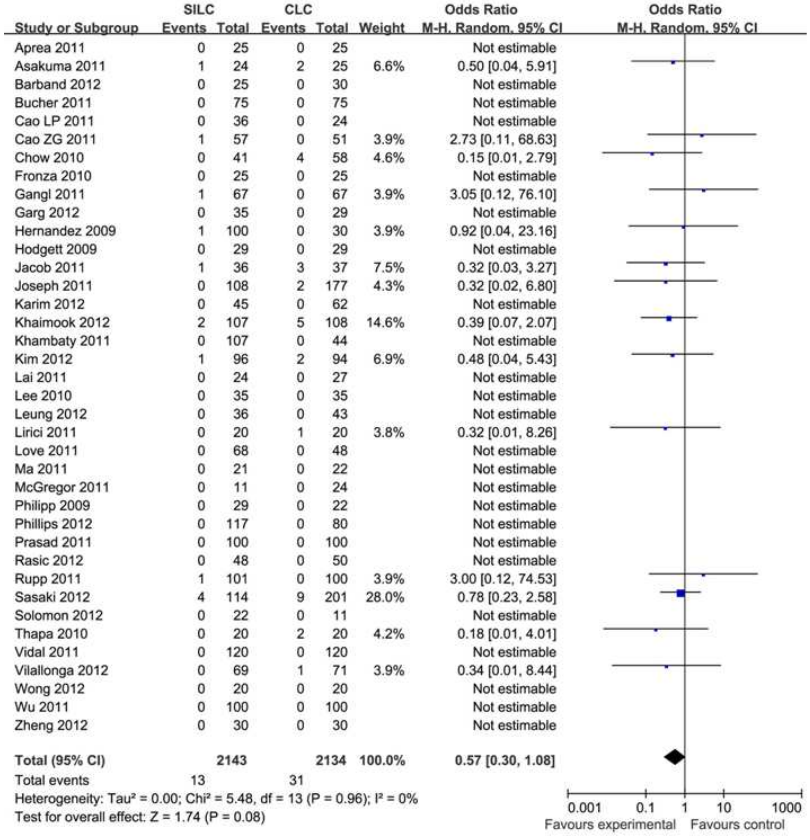

Figure 5. *Forest plot and meta-analysis of conversions to open surgery. SILC, single-incision laparoscopic cholecystectomy; CLC, conventional laparoscopic cholecystectomy; M-H, Mantel-Haenszel method; CI, confidence interval.*

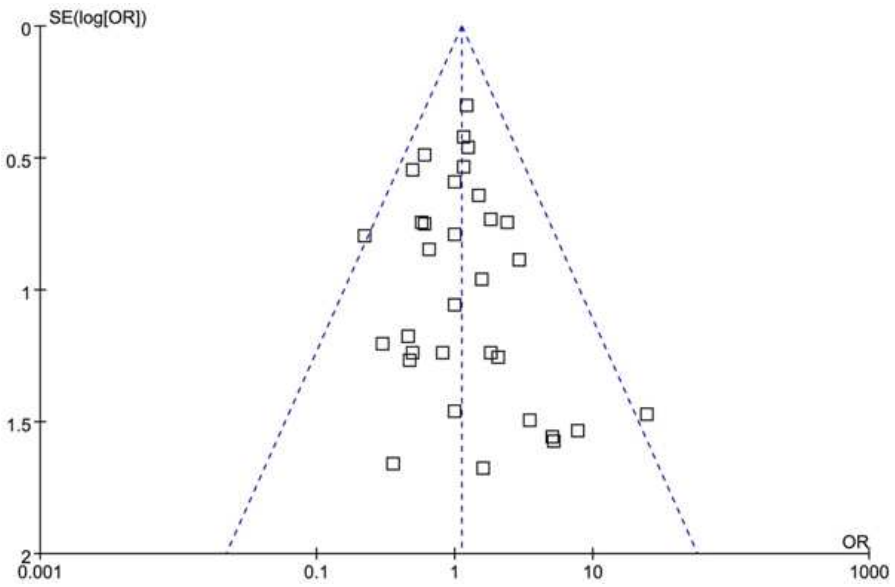

Figure 6. *Funnel plot of a publication bias test for perioperative complication rates. OR, odds ratio; SE (log [OR]), standard error of the natural logarithm of the odds ratio.*

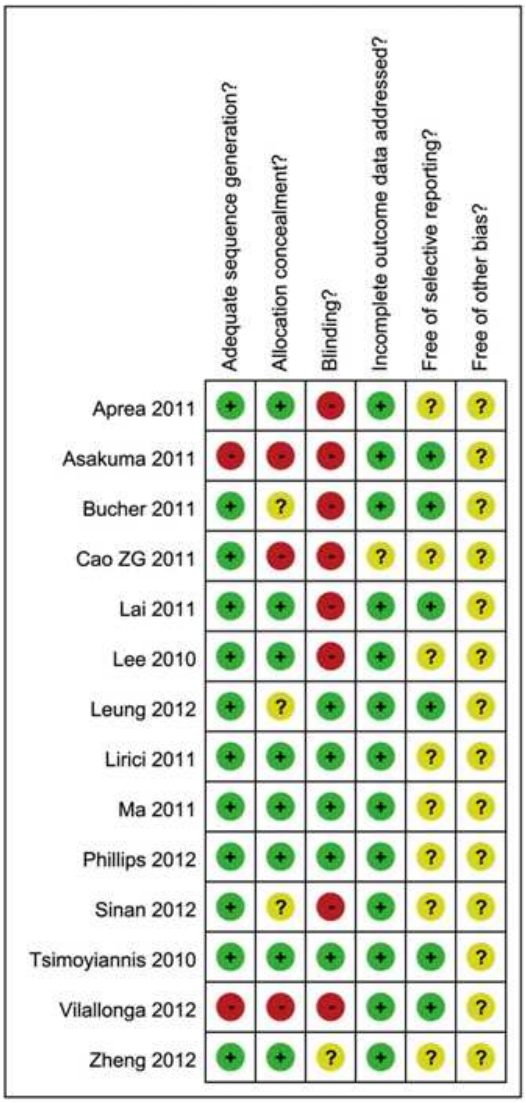

Figure S1. *The methodological quality of randomized trials. Each domain has 3 selectable judgments: Yes (low risk of bias), Unclear, and No (high risk of bias).*

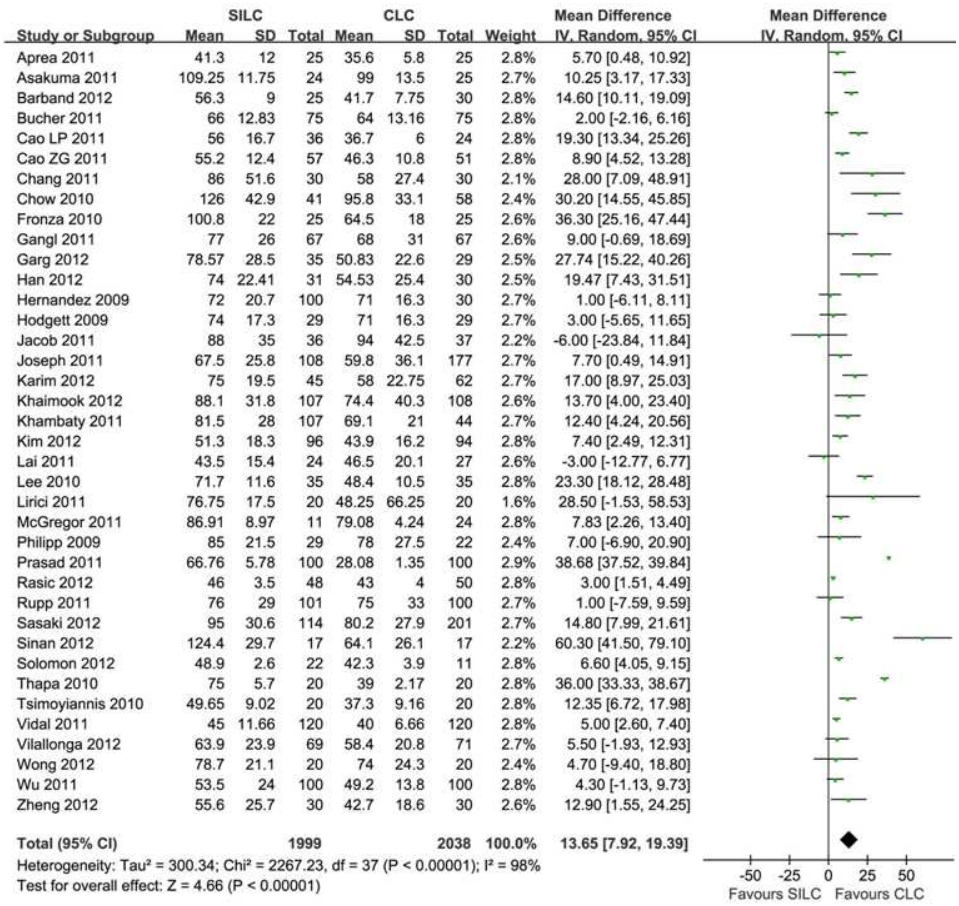

Figure S2. *Forest plot and meta-analysis of operative time. SILC, single-incision laparoscopic cholecystectomy; CLC, conventional laparoscopic cholecystectomy; IV, inverse-variance method; CI, confidence interval; SD, standard deviation.*

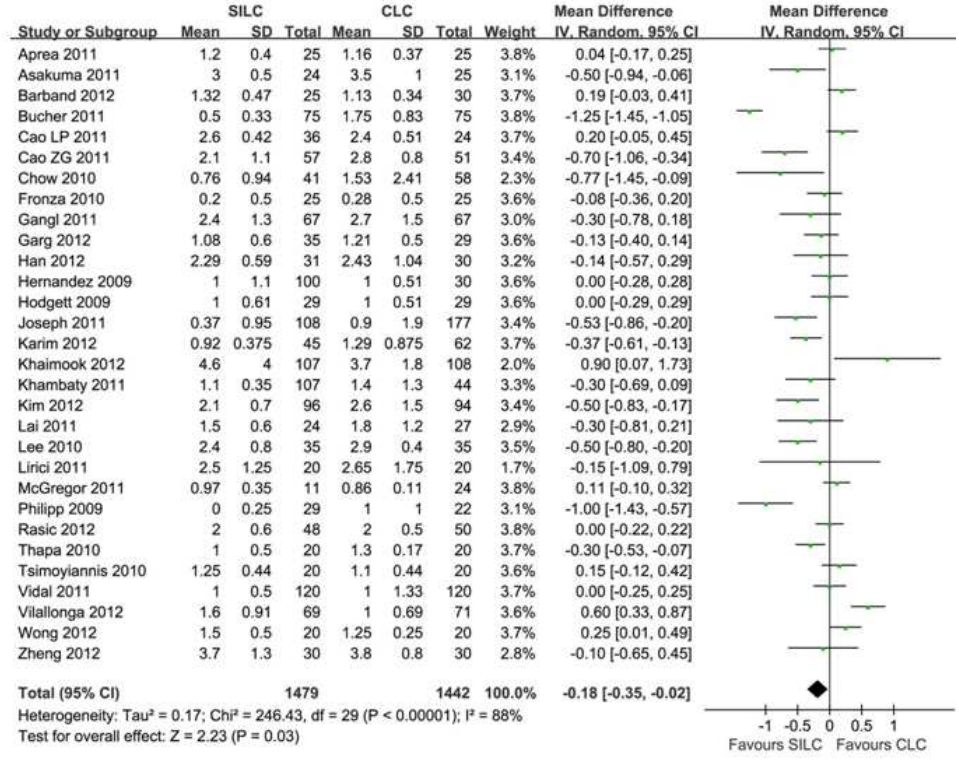

Figure S3. *Forest plot and meta-analysis of length of hospital stay. SILC, single-incision laparoscopic cholecystectomy; CLC, conventional laparoscopic cholecystectomy; IV, inverse-variance method; CI, confidence interval; SD, standard deviation.*

3.5. Sensitivity Analysis

In meta-analysis of RCTs or 28 high quality studies, there was no change in the significance of any of the outcomes except for LOS, which showed no significant difference between the two cholecystectomy techniques (WMD, -0.25d; 95% CI, -0.71 to 0.21; $p = 0.29$ and WMD, -0.22d; 95% CI, -0.45 to 0.02; $p = 0.07$, respectively) (Table 3). Because the necessary data were not available, sensitivity analysis on cost of hospital stay could not be performed.

3.6. Publication Bias

A funnel plot of perioperative complications was used in our meta-analysis to assess publication bias. Figure 6 is a scatter plot of the treatment effects estimated from individual studies on the horizontal axis (OR), against a measure of study size using SE (log [OR]) on the vertical axis. The shape of the funnel plot did not reveal any evidence of asymmetry in perioperative complication rates, indicating no obvious publication bias.

4. Discussion

To the best of our knowledge, this meta-analysis of 43 studies comparing the efficacy and safety of SILC and CLC included the largest number of patients in the literature. Our analysis showed that compared with CLC, SILC was feasible and safe, with significantly reduced postoperative pain on day 0, lower rate of analgesic use, better cosmetic satisfaction scores, shorter LOS, and shorter incision length. Postoperative pain on days 1 and 2 were statistically comparable between the two groups. There were also no statistically significant differences between the two groups in perioperative complications, analgesic requirement, conversions to open surgery, EBL, time to return to work or normal activity, and cost of hospital stay. However, SILC was associated with longer operative time compared to CLC. Sensitivity analysis of only RCTs or high-quality studies revealed no change in the significance of any of the outcomes except for LOS, suggesting that most of the results in our analysis were stable.

As a second "innovative procedure", SILC went a long way towards overcoming the existing performance problems. Until recently, due to the development of the technique and instrumentation, it has been common procedure worldwide for the management of benign gallbladder disorders. Cosmesis and postoperative pain are thought to be the two main factors driving the introduction of SILC into wide clinical practice. A previous study showed that when presented with cosmetic appearance, patients' initial preference was for SILC.[64] Women and younger patients were more likely to select SILC after their initial inspection of the images. These characteristics may define a potential target group for the wider introduction of SILC. Thus, better cosmetic outcomes have been expected from SILC because of the reduced number of ports and a transumbilical incision. Our analysis demonstrated that the cosmetic satisfactory scores after the operation favored the SILC group with a statistically significant difference. However, a questionnaire study by Bignell et al.[65] revealed that patients perceived the cosmetic results after CLC as excellent. Following this, Monkhouse et al.[66] also found that the overall satisfaction with CLC was high (93%). These studies suggest that there is little that can be done to improve the cosmetic results, hence our findings can also be interpreted as there is possibly only a small cosmetic benefit in SILC compared to CLC. Therefore, in order for SILC to be widely accepted, it may need more time and more studies with large numbers of patients to prove other aspects to be comparable with CLC.

Many factors can affect postoperative pain, such as incision length, pnemoperitonum pressure, etc. The current meta-analysis found a reduction in postoperative pain on day 0 in the SILC group, together with a lower rate of analgesic use. Thus, it is likely that subcostal/right upper quadrant pain, as well as concurrent pain in the umbilical port site, in the CLC group gave rise to the higher VAS scores on the day of surgery. This may also lead to more patients requiring analgesic use. However, there were no differences in terms of postoperative pain on days 1 and 2 and analgesic requirement. As shown in an interesting study, Blinman et al.[67] demonstrated that total tension rose nonlinearly with increasing incision length. Thus, tension across multiple incisions was always less than the total tension for an incision of the same total length, which may possibly explain why pain after CLC was significantly less than the OC, while the pain on days 1 and 2 were not significantly different between SILC and CLC, although SILC was associated with shorter skin incision length.

When comparing new to standard procedures, the safety of the patients is always of paramount importance. The pooled data of perioperative complications indicates that the single port approach is safe and effective for cholecystectomy. Even when we examined the details of perioperative complications, there were no significant differences in any of the detailed complications between the two groups (Table S2). However, the operative time was significantly longer in the SILC group than in the CLC group, which was probably due to the learning curve of SILC. As there is a learning curve of any new surgical procedure, this may explain the current results of the operative time because of the initial data of SILC approach. A recent study[68] suggests that for CLC-proficient surgeons, the learning curve for SILC begins near proficiency. Joseph et al.[69] also prospectively recorded several metrics of both attending and resident surgeons and found operative time was shorter in residents who were proficient in CLC along the learning curve and SILC had a short learning curve for resident surgeons who were proficient in CLC. Thus, decreased operative time can be expected with increasing experience of SILC in further studies.

Another concern of the safety of SILC that surgeons raised was the conversion rate. Due to the loss of triangulation, markedly reduced working space, and in-line vision of SILC, there is a technical obstacle for surgeons who are proficient with CLC. In the current meta-analysis, the conversion rate was significantly higher for SILC than CLC. Most reasons for

conversions were adhesions/inflammation/unclear or abnormal anatomy (33.9%), inadequate visualization of the critical view (15.0%), and bleeding (6.3%). However, large numbers of conversions were to cholecystectomy requiring an additional trocar or to CLC and when only conversions to open surgery were compared, there was no significant difference between the two techniques ($p = 0.08$).

The analysis of outcome of interest showed that SILC was associated with shorter LOS when pooling the data of 43 studies. However, sensitivity analysis of RCTs or high quality studies revealed that there was no significant difference in terms of LOS between the SILC and CLC groups. As compared to OC, CLC has a significantly shorter LOS (3 days less than OC) and patients usually stay in the hospital only 1 or 2 days postoperatively. Many studies[70, 71] even demonstrated the safety and feasibility of day-care LC. Therefore, SILC may not offer any benefit of LOS because CLC is hard to improve upon.

The cost associated with the technique must also be taken into account when considering the introduction of SILC. The hypothesis of higher operative costs of SILC may be the particular dedicated instruments used. However, a previous study[72] demonstrated that the cost of SILC did not differ significantly from that for CLC. Only converted cases were significantly more expensive than completed SILC and LC cases. This result may not be applicable universally because the result was based on data from a single institution and single single-incision technique. As over recent years, many companies have developed different single-port devices, such as SILS port, TriPort Access System and GelPOINT system, all of which vary in cost, the exact cost comparison of SILC and CLC needs further investigation and future studies should focus on the true cost effectiveness of different single-port devices. The different costs of various devices may also possibly explain the varied mean cost of hospital stay and wide CI values in our meta-analysis. Thus, whether the cost of SILC is comparable to that of CLC remains unknown.

The current meta-analysis has some advantages. First, this study, comparing SILC with CLC, included the largest number of patients in the literature, thereby increasing the statistical power and making it possible to recognize small differences in outcomes of interest. Secondly, the overall results did not change remarkably (except for LOS) after sensitivity analysis was performed, indicating that most of the results in our analysis were stable. Thirdly, no publication bias was detected, indicating that the pooled results may be unbiased. However, several limitations of this current meta-analysis should also be acknowledged. First, the follow-up period was generally short, so long-term outcomes of SILC, such as the prevalence of incisional hernia, remain to be further studied. Secondly, there was variation in study design, inclusion criteria, treatment protocols, and outcome assessment between studies. Thirdly, the varying surgical expertise levels and surgical devices in the included studies may have also influenced the outcomes. Finally, there was uneliminatable heterogeneity between studies in some outcomes of interest.

In summary, the results from this meta-analysis demonstrated that SILC was associated with reduced postoperative pain on the day of surgery, lower rate of analgesic use, better cosmetic satisfaction, and shorter incision length, whereas CLC was associated with decreased conversion rate and shorter operative time. The two techniques appeared to be equivalent in terms of operative complications, postoperative pain on days 1 and 2, analgesic requirements, conversions to open surgery, EBL, and time to return to work or normal activity. SILC appeared to be feasible and safe, but whether SILC has a benefit on LOS or is just similar to CLC remains to be further investigated, as well as the cost of hospital stay.

Acknowledgments

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