Is single-incision laparoscopic cholecystectomy safe? Results of a systematic review and meta-analysis

Is single-incision laparoscopic cholecystectomy safe? Results of a systematic review and meta-analysis

Alberto Arezzo[1], Gitana Scozzari[1], Federico Famiglietti[1], Roberto Passera[2] and Mario Morino[1]

(1)
Department of Surgical Sciences, University of Turin, Corso Dogliotti 14, 10126 Turin, Italy

(2)
Division of Nuclear Medicine, University of Turin, Corso Dogliotti 14, 10126 Turin, Italy

Alberto Arezzo
Email: alberto.arezzo@mac.com

Abstract

Background

Single-incision laparoscopic cholecystectomy (SILC) is gaining popularity. It is not evident whether the benefits of this procedure overcome the potential increased risk. We performed a systematic review and meta-analysis to compare SILC with conventional multi-incision laparoscopic cholecystectomy (MILC).

Methods

Data from randomized, controlled trials published up to December 2011 and comparing SILC versus MILC were extracted. The primary end point was overall morbidity. A fixed-effect model was applied to summarize the study outcomes in the meta-analysis, and a random-effect model was used in the sensitivity analysis. The outcome measures were relative risk (RR) and mean difference (MD); a RR of <1.0 or a negative MD indicated a more favorable outcome after SILC. Publication bias was assessed by a funnel plot, and heterogeneity was tested by the I^2 measure and subgroup analyses.

Results

A total of 12 trials (996 patients) were included. Mortality was nil in both treatment groups; the overall RR for morbidity was 1.36 ($p = 0.098$). The mean operating time was 47.2 min for MILC and 58.1 min for SILC (MD 9.47 min; $p < 0.001$). The visual analog scale pain

score at 24 h after surgery was 2.96 in MILC and 2.34 in SILC (MD −0.64; p = 0.058), but sensitivity analysis of the four studies deemed at low risk of bias for pain assessment, according to blinding and postoperative analgesic protocols, showed significance at −0.43 points (95 % confidence interval −0.87 to 0.00; p = 0.049). Cosmetic outcome scored better in the SILC group, with its standardized MD being equal to 1.16 (95 % confidence interval 0.57 to 1.75; p < 0.001).
Conclusions
In selected patients, SILC has similar overall morbidity compared with MILC; further, it results in better cosmetic satisfaction and reduced postoperative pain despite longer operative time.
Keywords
Cholecystectomy Instruments Systematic review Meta-analysis Single-port laparoscopy

Although the first single-incision laparoscopic cholecystectomy (SILC) was described in 1997 by Navarra et al. [*1*], this technique has spread slowly until more recent years. One of the main problems was concern about its safety. Several authors claimed that an uncontrolled dissemination of SILC would lead to a significant complication rate, in particular an increased number of bile duct injuries, as occurred during the early dissemination of conventional multi-incision laparoscopic cholecystectomy (MILC) [*2*, *3*]. Several recently published studies failed to demonstrate major differences in clinical results between the single-incision laparoscopic technique and standard multiport laparoscopy [*4-9*]. Furthermore, there is increasing doubt about whether the new technique actually fulfills its initial promises. The premises for the interest in single-incision access were that it could improve cosmetic results, reduce postoperative pain, allow earlier return to work, and result in greater patient satisfaction [*10-12*]. Nevertheless, well before enhanced cosmesis, the crucial issue for any new technique is to prove its safety versus the established technique [*13*].
The aim of this systematic review was to examine currently available evidence on the feasibility and safety of SILC and to compare short-term outcomes after SILC and MILC reported in randomized, controlled trials (RCT) and quasirandomized clinical trials (qRCT).

Methods

The methods for the analysis and generation of inclusion criteria were based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA) recommendations [*14*]. According to population, interventions, comparators, outcome measures, and setting (PICOS) criteria, patients were included if they had benign gallbladder pathologies for which laparoscopic cholecystectomy was indicated. The study methods were documented in a protocol registered and accessible at http://www.crd.york.ac.uk/prospero/ (registration CRD42011001880).

Types of studies, participants, and interventions

Only RCTs or qRCTs, defined as those reporting nonrandom, nonconcealed allocation, were considered for this analysis, regardless of inflammatory status (acute or chronic cholecystitis, gallstone pancreatitis) or etiology (symptomatic gallstone disease, suspected common bile duct stones, asymptomatic gallbladder polyps, gallbladder dyskinesia, gallbladder adenomyomatosis).
Trials where the SILC technique included routine use of any additional trocar other than the transumbilical trocar were excluded. The control group was composed of patients undergoing MILC, with no restrictions on the dimension of the laparoscopic instruments, the number of trocars (three-port or four-port laparoscopic cholecystectomy), or any additional intraoperative procedure (e.g., intraoperative cholangiography). Trials including gasless techniques were excluded.

Types of outcome measures

The primary outcome measure was defined as the overall perioperative complications rate, i.e., intraoperative and early (<30 days) postoperative complications. The secondary outcome measures were parietal access–related complications, operating time, conversion to open surgery, need for further postoperative treatments, hospital stay, cosmetic results, and postoperative pain score as measured on a visual analog scale (VAS) at 24 h after the operation.

Search strategy and data collection

Three databases were searched: Medline, Embase, and Central (Cochrane clinical trials database). The U.S. National Institutes of Health (NIH) trial registry (ClinicalTrials.gov) was also examined for potentially relevant results, and the authors were contacted to obtain preliminary unpublished data. Abstracts and posters from the annual meetings of the European Association for Endoscopic Surgery (EAES) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) from 2008 to 2011 were also examined and the authors asked for preliminary unpublished data. The literature search was closed on December 31, 2011.

The search strategy was performed using the following terms: ("single incision" [All Fields] OR "single port" [All Fields] OR "single site" [All Fields] OR "SILS" [All Fields] OR "single access" [All Fields] OR "laparoendoscopic" [All Fields]) AND "cholecystectomy" [All Fields].

All abstracts retrieved from the electronic databases were screened independently by two authors (G.S. and F.F.); when an abstract was deemed relevant by at least one of them, the full text was retrieved. The reference lists of all relevant articles were manually searched for potentially relevant studies for inclusion.

Data extraction was carried out in duplicate independently by two authors (G.S. and F.F.). Disagreements were resolved by discussion with a third author (A.A.). Data collection included patient characteristics (sex, age, body mass index [BMI], American Society of Anesthesiologists [ASA] score); cause of gallbladder disease; intraoperative data (operating time, intraoperative complications, conversion to MILC or open surgery, number and type of laparoscopic instruments, number and type of any additional instruments, gallbladder perforations, intraoperative bleeding and blood loss, cystic duct injuries, common bile duct injuries, bile leaks, intraoperative-associated procedures, wound length); short-term postoperative complications and mortality, including retained common bile duct stones (CBDS), abdominal collections, urinary retention or infection, parietal access–related complications, lipase increase, and need for further treatments defined as any postoperative intervention; analgesic protocol; VAS score; length of hospital stay; cosmetic scores; and costs. Parietal access–related complications were defined as wound infection, suture-related complications, seroma, bleeding, and postoperative hernia. Conversion to multiple-incision laparoscopy was defined as the unplanned placement of any additional trocar other than the transumbilical one during the operation.

Assessment of risk of bias

All studies that met the selection criteria were assessed for methodological quality according to the Cochrane Collaboration guidelines [15].

Statistical analysis

All analyses were performed according to the original treatment allocation (intention-to-treat analysis). For the binary outcome data, the relative risk (RR) and 95 % confidence interval (CI) were estimated by the Mantel-Haenszel method; a RR of <1 indicated a more favorable outcome after SILC. For the continuous outcome data, the mean differences (MD) and 95 % CIs were estimated by inverse variance weighting; a negative MD value indicated a more favorable outcome after SILC. When means and/or standard deviations were not reported in the original article, they were estimated from the reported medians, ranges, and sample sizes as described by Hozo et al. [16]. A fixed-effects model was used in all meta-analyses, repeating the same analyses using a random-effects model as described by DerSimonian and Laird [17]. Publication bias was assessed by generating a funnel plot and performing the rank correlation test of funnel plot asymmetry. Heterogeneity was assessed by the I^2 measure of inconsistency, statistically significant if I^2 was >50 %; whenever I^2 was <50 %, the fixed-effects model results were used; otherwise, the random-effects model results were preferred. Potential sources of heterogeneity were explored by different sensitivity analyses: comparing fixed- versus random-effects models (incorporating heterogeneity by using the random-effect method); and checking the results of cumulative (sequentially including studies by date of publication) and influence of meta-analyses (calculating pooled estimates by omitting one study at a time). All analyses were performed by the R 2.15.1 meta software package.

Results

Study selection

The database search retrieved 926 records. Additional records were retrieved from the NIH trials registry (ClinicalTrials.gov) (n = 6) and the EAES and SAGES annual meetings (n = 8). No further records were identified in the reference lists. Figure 1 illustrates the PRISMA flow chart for study inclusion and exclusion. After deleting duplicate results, a total of 702 records remained for title and abstract review. Of these, 29 studies were selected for full-text examination. Seventeen of these were excluded, as follows:

retrospective or prospective observational study (n = 5); systematic review (n = 3); meta-analysis (n = 1); and study protocol of a double-blind RCT for which the results were not yet available (n = 1). Of the six remaining RCTs excluded, two did not meet the inclusion criteria (one described a hybrid SILC technique and the other a gasless laparoscopy technique). Contacting the authors of three completed RCTs listed in the NIH trials registry to obtain preliminary unpublished results produced a negative response in one case and no response in two cases. One last trial was initially excluded because it was published as the preliminary results of a multicenter RCT, but it was later included [9-18]. Twelve studies in all fulfilled the inclusion criteria and were suitable for the meta-analysis [*4-8*,18-24].

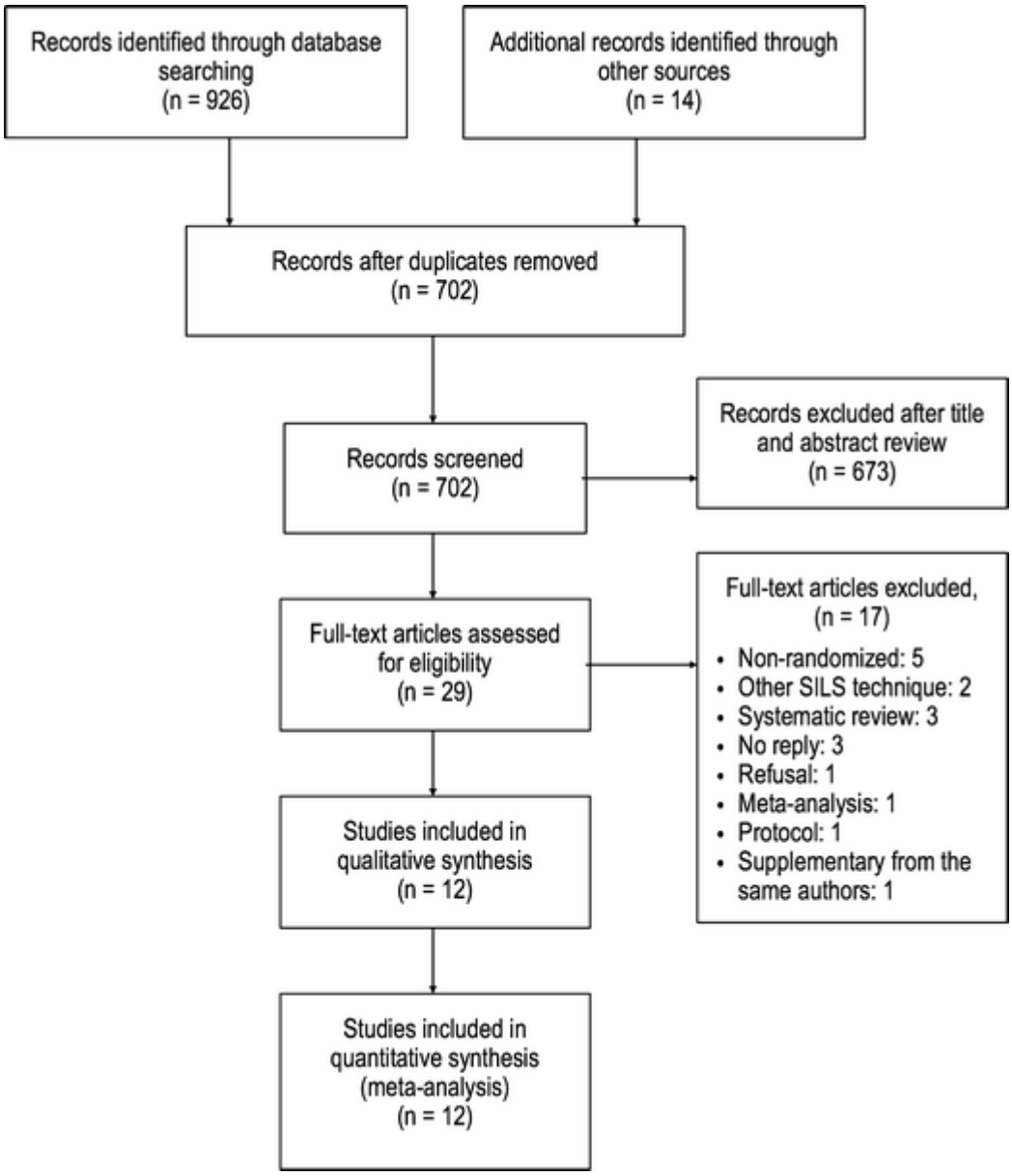

Fig. 1

Flow chart for the systematic search and study selection strategy

Characteristics of included studies

Table 1 summarizes the characteristics of the 12 selected studies, including study period, study design, MILC technique, number of patients, exclusion criteria, primary end points, and follow-up. Of 996 patients included, 515 underwent SILC and 481 MILC. The main exclusion criteria were as follows: age younger than 18 years; obesity (BMI >28, 30, 40, and 45 kg/m²); emergency presentations (retained CBDS, pancreatitis, cholecystitis); and poor general condition (ASA score of >III). Although acute gallbladder disease was indicated as exclusion criteria in all studies, three of 12 trials reported some cases of acute cholecystitis in their results, without any imbalance between groups [5,19,20]. Six studies reported the use of a TriPort (Advanced Surgical Concepts, Wicklow, Ireland) [4,6,8,19,23,24], three the use of a SILS Port (Covidien, Inc., Norwalk, CT, USA) [16,21,24], two the use of three standard trocars through a single skin incision [20,22], one the use of a QuadraPort (Advanced Surgical Concepts, Wicklow, Ireland) [7], and one the use of a surgical glove port [5]. As a consequence, a TriPort was used in 177 patients (34 %), the SILS port in 204 (39 %), three trocars through a single incision in 77 (15 %), a QuadraPort in 35 (7 %), and a surgical glove port in 24 patients (5 %). All but 24 procedures (95 %) in the SILC group were attempted with the use of only two surgical instruments in addition to the optics. On the other side, nine trials described a four-port MILC technique for 341 patients (71 %), while in four studies, a three-port MILC technique was used for 140 patients (29 %) [4,20,23,24]. In five studies comprising 161 patients (31 %), a trans-abdominal suture was placed in the epigastric area to lift either the gallbladder or the falciform ligament as part of the SILC procedure [4,5,7,20,22]. In eight studies, at least one SILC procedure required the addition of at least one further instrument for a total of 26 procedures (5.0 %, range 1–67 %) [4,6-8,18-20,23]. Postoperative pain was evaluated in all trials; more specifically, all but three studies reported VAS pain scores at 24 h after surgery [6,21,23]. Nine studies reported cosmetic results using different time points and scales [4,6-8,18,19,21,23,24]. Six of them recorded cosmetic results at the 30th postoperative day, resulting in comparable data suitable for analysis [7,8,18,19,23,24]. Only six trials stated the materials and/or methods used for skin closure, which all varied among studies [7,19,20,22-24]. Four studies reported having performed a quality-of-life assessment, but the evaluation was based on different types of questionnaires [8,18,19] or data were omitted in the text [6] that precluded this outcome from being included in the analysis. Overall reporting on the duration of follow-up was

generally poor: at least 1 month's follow-up was performed in nine trials [5-8,18,19,21,23,24], but the duration in the other three trials was unclear. Finally, only two trials reported the operative costs [5,17], leading us to exclude this outcome in our meta-analysis.

Table 1

Summary of characteristics of included studies

Study	Study period	Study design	Country	MILC technique	SILC device	No. of patients SILC	MILC	Exclusion criteria	Primary end point	Follow-up (weeks)
Lee 2010 [7]	2008–2009	RCT	Taiwan	4 ports	QuadraPort Laparoscopic Access Device	35	35	Acute cholecystitis, CBDS, severe obesity, previous upper abdominal surgery, ASA score III/IV	Postoperative pain	24
Tsimoyiannis 2010 [22]	NA	RCT	Greece	4 ports	3 VersaStep trocars Covidien through single skin incision	20	20	Acute cholecystitis, CBDS, acute pancreatitis, BMI >30 kg/m^2, ASA score III/IV	Postoperative pain	<1
Aprea 2011 [4]	2009–2010	RCT	Italy	3 ports	TriPort Laparoscopic Access Device	25	25	Acute cholecystitis, CBDS, acute pancreatitis, BMI >30 kg/m^2, ASA score III/IV, previous abdominal surgery	NA	1
Asakuma 2011 [5]	2009	qRCT	Japan	4 ports	Surgical glove port	24	25	Emergency presentation, CBDS, previous upper abdominal surgery	Postoperative pain	72[a]
Bucher 2011 [19]	2009–2010	RCT	Switzerland	4 ports	TriPort Advanced Surgical Concepts	75	75	Acute gallbladder disease, cirrhosis	Cosmetic result	4
Cao 2011 [20]	2010	RCT	China	3 ports	3 trocars through single skin incision	57	51	CBDS, acute pancreatitis, previous upper abdominal surgery, ASA	NA	NA

Study	Study period	Study design	Country	MILC technique	SILC device	No. of patients SILC	MILC	Exclusion criteria	Primary end point	Follow-up (weeks)
								score III/IV, BMI >30 kg/m^2		
Lai 2011 [*21*]	2009–2010	RCT	China	4 ports	SILS port Covidien	24	27	Mirizzi syndrome, CBDS, suspected malignancy, previous upper abdominal surgery, previous cholangitis, acute/chronic cholecystitis, gallstone >3 cm	Postoperative pain	12
Lirici 2011 [8]	2009	Multicenter RCT	Italy	4 ports	TriPort Olympus America	20	20	Acute cholecystitis, CBDS, acute pancreatitis, previous upper abdominal surgery, ASA score III/IV, BMI >30 kg/m^2	QoL	4
Ma 2011 [6]	2009–2010	RCT	USA	4 ports	TriPort Advanced Surgical Concepts	21	22	Acute cholecystitis, CBDS, BMI >40 kg/m^2, gallstone >2.5 cm	Postoperative pain	NA
Phillips 2012 [18]	NA	Multicenter RCT	USA, UK, Italy	4 ports	SILS port Covidien	117	80	Acute cholecystitis, CBDS, previous upper abdominal and umbilical surgery, ASA score >III	Morbidity	48
Vilallonga 2011 [24]	2009–2010	Multicenter qRCT	Spain, Turkey	3 ports,4 ports[b]	TriPort Advanced Surgical Concepts and SILS port Covidien[c]	69	71	NA	NA	NA
Zheng 2012 [23]	2008–2010	RCT	China	3 ports	TriPort Advanced Surgical Concepts	28	30	Acute cholecystitis, CBDS, BMI >28 kg/m^2, previous abdominal surgery	NA	24

RCT randomized controlled trial, qRCT quasi–randomized controlled trial, SILC single-incision laparoscopic cholecystectomy, MILC multi-incision laparoscopic cholecystectomy, NA not available, BMI body mass index, ASA American Society of Anesthesiologists physical classification score, CBDS common bile duct stone, QoL quality of life

[a]Median

[b]Three ports in 34 patients, 4 ports in 37 patients

[c]SILS port was used in 63 patients and TriPort in 6 patients

Risk of publication bias

Assessment of quality according to the Cochrane Collaboration's tool for assessing risk of bias shows a relative low quality of the studies, with five of them not scoring more than 2. A funnel plot for global complications demonstrates the absence of publication bias. In two trials, the methods of sequence generation were inadequate—for example, assignment based on the day of the week [5] or alternation [24]. Two trials gave insufficient information about the sequence generation process [18] and allocation concealment [6], so the risk of bias was deemed unclear. Blinding of the outcome assessors was attempted in four RCTs [7,20-22] and was unclear in one [8]. Conversely, blinding of patients was attempted in only two trials [8,18]. Loss to follow-up and number of dropouts were not reported in five trials [6,8,19,22,24]. In one study, two patients in the SILC treatment group were excluded from the analysis of key outcomes because of conversion to MILC [23]. One or more outcomes of interest were not reported or were reported incompletely in two trials, rendering them unsuitable for the analysis [6,23]. Analgesia protocols and needs were specifically evaluated. Five trials provided the same perioperative analgesic therapy for both treatment groups or stated the analgesic needs in the results [4,7,8,19,22]. Finally, a baseline imbalance was found in one study because of a significantly lower BMI in the SILC treatment group [18].

Primary outcome

The meta-analysis of the primary outcome investigated overall morbidity (11.0 %) in 11 studies (Fig. 2). The raw incidence of global complications was lower in the MILC than in the SILC treatment group (9.0 vs. 12.8 %). The RR was 1.37 (95 % CI 0.94 to 1.98; $p = 0.098$). No publication bias was found ($p = 0.697$), and heterogeneity was absent

(0 %). On cumulative meta-analysis, the RR increased over time from 0.50 to 1.36, while on influential meta-analysis, it varied slightly between 1.19 and 1.46 for the whole time frame.

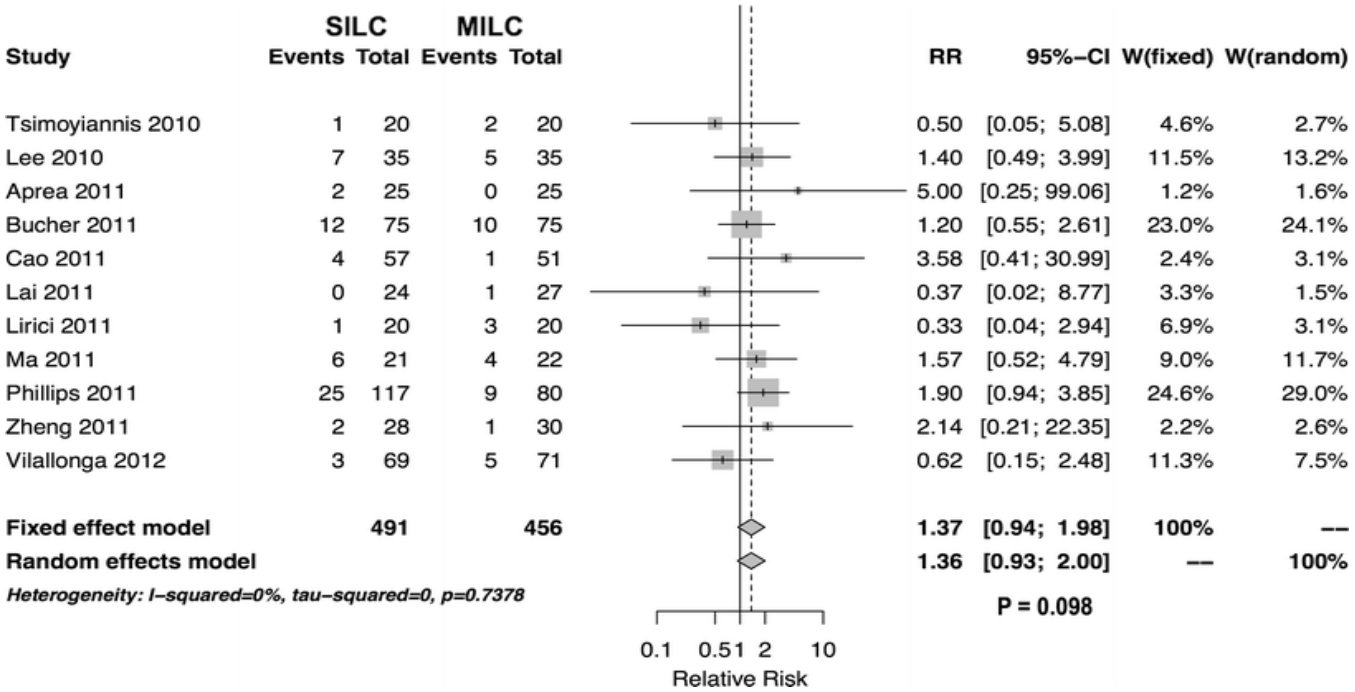

Fig. 2

Overall perioperative complications rate after cholecystectomy by SILC and MILC

With regard to biliary complications, two bile leaks were reported for each group [20,22], which were treated conservatively; one partial cystic duct avulsion was reported during MILC [8], which required conversion to open surgery for a safe repair. No endoscopic stenting or hepaticojejunostomy was needed in these patients.

Secondary outcomes

On analysis of the incidence of parietal access–related complications as reported in six studies [6,18-21,24], the overall rate was 7.0 % (5.5 and 8.3 % for MILC and SILC, respectively) (Fig.3). The RR was 1.44 (95 % CI 0.81 to 2.57; p = 0.095), with low heterogeneity (16.9 %) and no publication bias (p = 0.573). On cumulative meta-analysis, the RR rose from 0.75 to 1.44 and ranged between 0.82 and 1.74 on influence meta-analysis. With regard to port-site incisional hernias, there were reported six and three hernias after SILC and MILC, respectively [6,18,24], while seven wound infections were described after SILC and five after MILC [6,18,20,21].

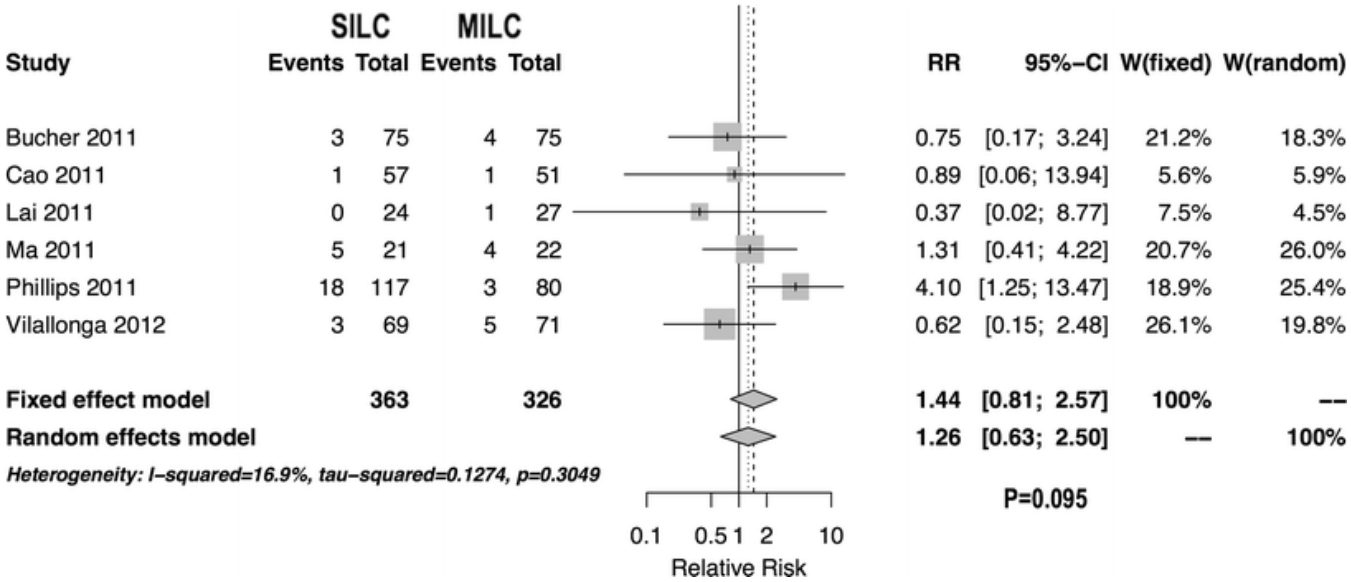

Fig. 3

Parietal access–related complications rate after cholecystectomy by SILC and MILC

The raw incidence of further interventions in four trials was 1.7 % overall (0.5 and 2.7 % for MILC and SILC, respectively). The RR was 2.74 (95 % CI 0.77 to 24.96; p = 0.097) in the absence of heterogeneity (0 %) and publication bias (p = 0.497). The RR ranged from 2.69 to 2.74 and from 2.19 to 4.37 on the cumulative and influential analyses, respectively. Further postoperative treatments consisted of endoscopic retrograde cholangiopancreatography for CBDS in four cases [6,18,20], ultrasound-guided drainage of abdominal collections in two cases [23], and hernia repair in one case [6].

The mean operating time was reported in 10 studies (overall, 52.7 min; 47.2 min for MILC and 58.1 min for SILC) (Fig. 4). The MD was 9.47 min (95 % CI 4.55 to 14.39; p < 0.001), with a very high heterogeneity (82.9 %) but without publication bias (p = 0.531). On cumulative meta-analysis, the MD progressively decreased over time from 23.3 to 9.47 min; on influential meta-analysis, the MD ranged between 7.4 and 10.6 min, with MILC consistently the faster of the two techniques.

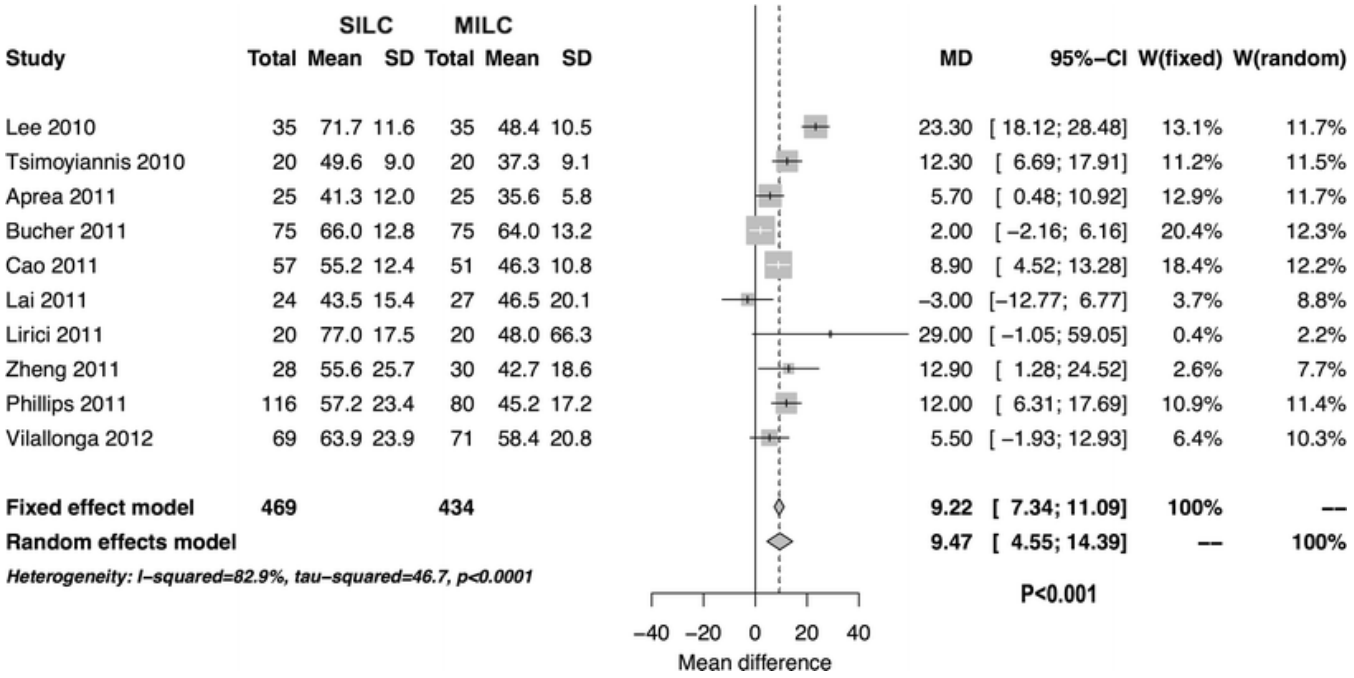

Fig. 4

Operating time for cholecystectomy by SILC and MILC ($p < 0.001$)

Mean length of hospital stay was very similar for both treatment groups (2.16 vs. 2.13 days for MILC and SILC, respectively), as reported in eight studies (overall length of stay, 2.14 days). The MD was −0.06 days (95 % CI −0.38 to 0.27; $p = 0.727$), with high heterogeneity across trials (85.8 %) but no publication bias ($p = 0.805$). On cumulative meta-analysis, the MD decreased progressively from −0.50 to −0.06 days and ranged between 0.01 and −0.18 days on influence meta-analysis.

Mean VAS pain score at 24 h after surgery showed a trend toward lower postoperative pain, resulting 2.96 after MILC and 2.34 after SILC (overall, 2.65 points), as reported in nine studies (Fig. 5). The MD was −0.64 points (95 % CI −1.31 to 0.02; $p = 0.058$), with extreme heterogeneity (96.0 %) but without publication bias ($p = 0.297$). On cumulative meta-analysis, the MD ranged between −0.54 and −0.64 points, and between −0.79 and −0.46 points on influence meta-analysis. On sensitivity analysis of the four studies deemed at low risk of bias [7,8,20,22] for pain assessment, according to blinding and postoperative analgesic protocols, the MD had the same direction of effect but reached significance at −0.43 points (95 % CI −0.87 to 0.00; $p = 0.049$).

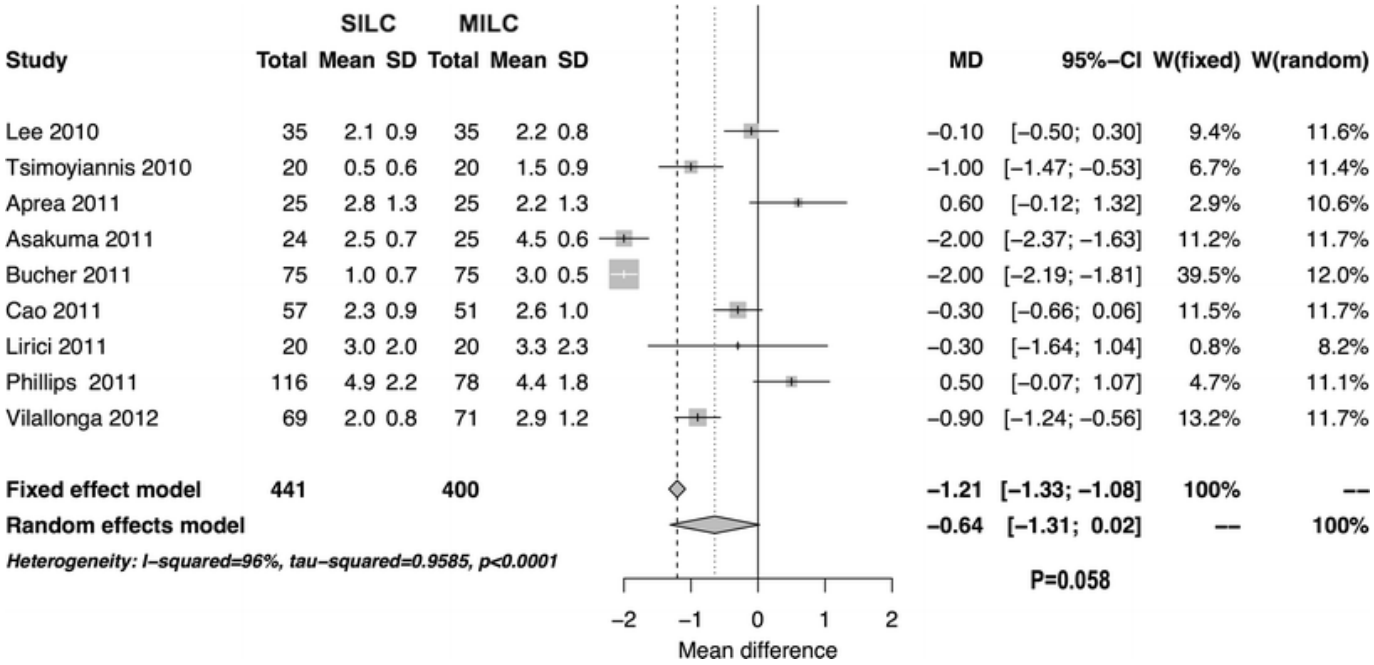

Fig. 5

VAS pain scores at 24 h after cholecystectomy by SILC and MILC

Finally, as a result of the different cosmetic scores employed, we used the standardized mean difference (SMD) to make data comparable. There was a statistically significant better cosmetic outcome at the 30th postoperative day in the SILC group, with its SMD equal to 1.16 (95 % CI 0.57 to 1.75; $p < 0.001$), with an extreme heterogeneity (91.0 %) but without publication bias ($p = 0.932$) (Fig. 6). On cumulative meta-analysis, the SMD widely varied over time from 0.67 to 2.66; on influential meta-analysis, the SMD ranged between 1.09 and 1.22, with the results from Bucher et al. [19] being the only outlier (0.86).

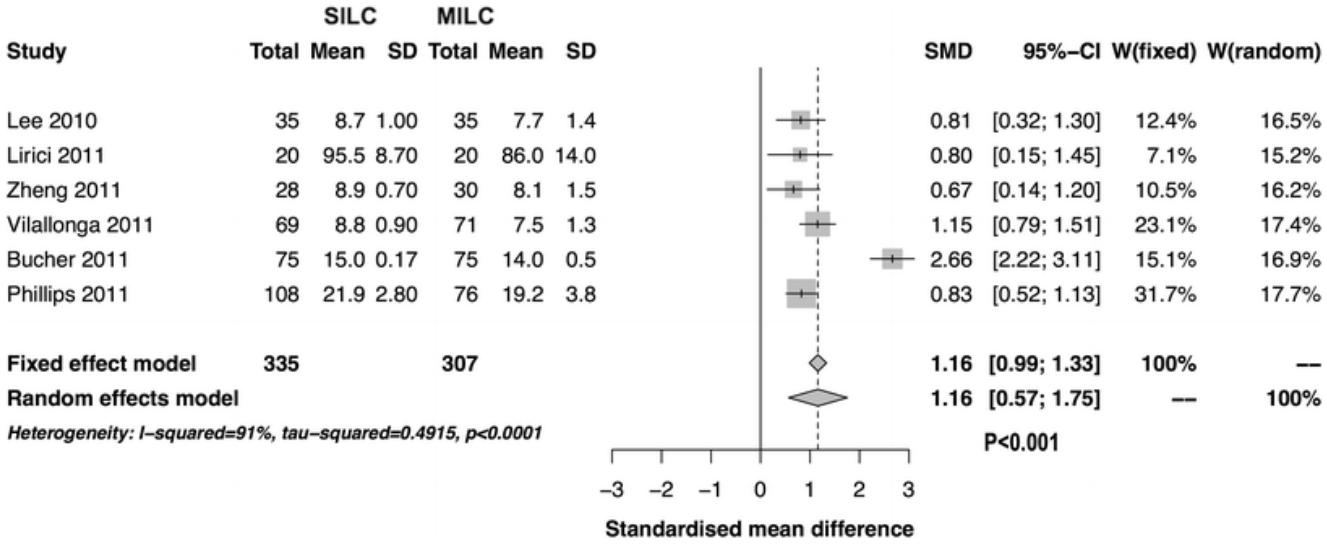

Fig. 6

Cosmetic result score after cholecystectomy by SILC and MILC ($p < 0.001$)

A meta-analysis of outcomes of interest is summarized in Table 2.

Table 2

Meta-analysis of outcomes of interest

Outcome of interest	No. of studies	Incidence/duration score		RR, MD, or SMD	95 % CI	P	I^2 (%)
		SILC	MILC				
Global complications	11	12.8 %	9.0 %	RR 1.37	0.94–1.98	0.098	0
Intraoperative complications	5	7.3 %	5.9 %	RR 1.35	0.71–2.54	0.361	0
Postoperative complications	10	9.2 %	6.3 %	RR 1.37	0.86–2.16	0.184	0
Conversion to open surgery	4	1.2 %	2.4 %	RR 0.63	0.17–2.39	0.498	0
Access-related complications	6	8.3 %	5.5 %	RR 1.44	0.81–2.57	0.211	16.9
Need for further treatment	4	2.7 %	0.5 %	RR 2.74	0.77–24.96	0.097	0
Operating time (min)	10	58.1	47.2	MD 9.47	4.55–14.39	<0.001	82.9

Outcome of interest	No. of studies	Incidence/duration score		RR, MD, or SMD	95 % CI	P	I^2 (%)
		SILC	MILC				
Hospital stay (days)	8	2.13	2.16	MD −0.06	−0.38 to 0.27	0.727	85.8
Postoperative pain at 24 h (VAS)	9	2.34	2.96	MD −0.64	1.31–0.02	0.058	96.0
Cosmetic results	6	–	–	SMD 1.16	0.57–1.75	<0.001	91.0

RR relative risk, MD mean difference, CI confidence interval, SILC single-incision laparoscopic cholecystectomy, MILC multi-incision laparoscopic cholecystectomy, VAS visual analog scale, SMD standardized mean difference

Sensitivity analysis

A first sensitivity analysis of intraoperative complications rates was performed on the five studies that reported such events. The global intraoperative complications rate was 6.7 % (5.9 % for MILC and 7.3 % for SILC). The RR was 1.35 (95 % CI 0.71 to 2.54; p = 0.361), was substantially the same for both treatment groups, and was without a publication bias (p = 0.624).

A second sensitivity analysis was performed on the risk of conversion to open surgery in the four trials reporting such events. The global conversion rate was 1.8 % (2.4 % for MILC and 1.2 % for SILC). The overall RR was 0.63 (95 % CI 0.17 to 2.39; p = 0.498) without a publication bias (p = 1.000); the RR was again fairly similar for both treatment groups. The reasons for conversion during MILC were cholecystitis [5] in two cases, cystic duct injury [8], and technical difficulties [24], while cholecystitis [5] and dense adhesions [20] accounted for the two conversions during SILC.

A third sensitivity analysis of postoperative complications was performed on the results of 10 studies. The overall rate was 7.8 % for both treatment groups (6.3 % for MILC group and 9.2 % for SILC). The RR was 1.36 (95 % CI 0.86 to 2.16; p = 0.184). No publication bias was found (p = 0.788), once again confirming the comparability of the safety profiles of the two techniques.

Discussion

As laparoscopic skills improve and technologies advance, the search continues for ways to make laparoscopic surgery less invasive. One approach documented throughout the recent literature is single-incision laparoscopic surgery. Although applied in a variety of general surgery cases, including appendectomy [25], sleeve gastrectomy [26], splenectomy [17], and colectomy [28], its test bed is cholecystectomy, just as it was for the introduction of laparoscopy about 20 years ago. SILC was first described in 1997 by Navarra et al. [1] in a report on 30 patients with favorable outcomes.

Although the technique is gaining increasing acceptance, only small trials have been completed to date, and not all have the expected results in favor of SILC. A recent review also claimed an increased risk of bile duct injury during SILC when compared with historic rates during MILC [3]. This prompted us to systematically review the available literature and carry out a meta-analysis on the published data. Unfortunately, the techniques described are notoriously heterogeneous. To limit inevitable biases, we restricted our analysis not only to RCTs and qRCTs, but also to those trials that reported on the most standard techniques, i.e., we excluded any study in which a supplementary instrument through a further trocar was routinely used or abdominal distention was obtained by a gasless technique. This highly selective policy translated into a high homogeneity of results, as demonstrated by the risk of bias analysis. The narrower study selection criteria and a threefold increase in the number of patients included in the analysis represent a consistent improvement over a previous systematic review and meta-analysis published by Markar et al. [29].

Analysis of the published data showed that many of the currently held assumptions lack a firm evidence base. SILC does not appear to carry a higher risk of global complications. No mortality was reported, and although the incidence of complications reported for SILC was higher by about half, the difference was not statistically significant. This observation is made stronger by the consistent number of cases included in the analysis. Conversion to open surgery was found to be substantially similar for both techniques, with the addition of at least one instrument in 5 % of SILC procedures.

Intraoperative complications rates were also the same for both treatment groups; the increase by about a half observed in the postoperative complications rate associated with SILC was not statistically significant. This difference may depend in part on an increased risk of parietal access–related complications. However, it should be noted that the length

of follow-up was generally insufficient to accurately measure the rate of late complications. The incisional hernia rate was in fact difficult to interpret, and definitive conclusions cannot be drawn on this topic. Similarly, the raw incidence of further postoperative treatments was more than five times higher for SILC, and again, no conclusions can be drawn from the very low incidence of the event.

No common bile duct injury—the most threatening complication during cholecystectomy procedure—was observed in any of the studies considered. Two bile leaks were reported for each group [20,22], all treated conservatively, while one partial cystic duct avulsion occurred during MILC [8]. These were considered as biliary complications rather than injuries, as no endoscopic stenting or hepaticojejunostomy was needed [30].

VAS pain scores at 24 h after surgery were slightly lower after SILC but not significantly different from those reported after MILC. Blinding and postoperative analgesic protocols were considered the most important sources of bias and were therefore specifically evaluated. In fact, some authors reporting a benefit of reduced pain in SILC group suggested that their study could contain a bias because the patients, because of the dressings applied, were not blinded to the type of operation and that this might have influenced the results [19]. Moreover, different or unclear postoperative analgesic protocols between groups may have led to bias of VAS assessment. On subsequent sensitivity analysis of the data selected from only the studies at low risk of bias for pain assessment [7,8,20,22], lower postoperative pain scores were confirmed for SILC, reaching a statistical significance.

SILC was associated with better cosmetic satisfaction at 1 month's follow-up. Although statistically significant, this difference may have been affected from selection bias. In fact, only half of the studies stated the materials and/or methods of skin closure, and even when this was declared, materials and methods differed among studies.

Operative time was found to be significantly longer in SILC group. Despite its statistical significance, it must be noted that the MD in time was less than 10 min when comparing the two groups. Nevertheless, this might be due to a steep learning curve, which is further complicated by the variety of technical options available, including different single-access ports and a wide range of laparoscopic,instruments such as conventional straight laparoscopic instruments, precurved instruments, and bendable instruments. Rather than offering an opportunity, such variety becomes a substantial obstacle to the rapid acquisition of knowledge along the learning curve. Nevertheless, the MD in operating time

between the treatment groups decreased progressively over time, confirming a clear learning-curve effect in the SILC treatment group.

In some ways, this conflicts with the finding that the RR for global complications progressively increased over time from 0.50 to 1.36, which might have been due to overconfidence with the novel technique. Indeed, while earlier studies consistently applied fairly narrow inclusion criteria—limiting eligibility to patients with a BMI of <30 kg/m^2, for instance—later studies were less restrictive in their patient selection, including those with a BMI of up to <45 kg/m^2.

There are several limitations to be considered when interpreting these results. It has to be observed that although almost all the SILC procedures analyzed were attempted with just two surgical instruments in addition to the optics, in more than two-thirds of the procedures included in the MILC group, three surgical instruments were used. In truth, about a third of the SILC procedures were performed with the aid of a transabdominal suture in the epigastric area to lift either the gallbladder or the falciform ligament; this was done in an attempt to compensate for the lack of a further instrument. Nevertheless, this observation implies that any of the present results may be influenced not only by the different technique, as intended by the authors, but also by the different number of instruments used [31]. For this reason, better retracting systems are currently used, such as the EndoGrab Port-Free Endocavity Retractor (Virtual Ports, Ltd., Caesarea, Israel) [32], or are under development [33].

Patients affected by inflammatory and obstructive disease as well as severe obesity were excluded from these trials. However, it should be noted that in four studies, a various degree of gallbladder inflammation was found at pathology [5,7,19,20] for a total of 215 patients. Although well balanced between groups, it was unfortunately not possible to extract specific outcomes and to analyze them.

All trials had a high risk of bias due to lack of blinding, missing or incomplete outcomes data, and/or inadequate random-sequence generation (i.e., qRCT). However, sensitivity analyses and subgroup analyses of higher-quality studies showed results consistent with our overall analysis.

Although we made a great effort to contact the corresponding authors so that the data would be as complete as possible, and so our analysis could be as accurate as possible, some data still were missing, leading to the exclusion of several trials from the analysis of some outcomes of interest, such as perioperative complications and postoperative VAS.

Overall reporting on follow-up duration was generally poor; this could have led to an underestimation of late complication rate.

Finally, outcomes of great interest, such as operative costs and quality-of-life assessment, were excluded from this meta-analysis because the data were not comparable or limited.

Although surgeons develop techniques for reduced-port surgery, patient safety should remain a concern. The present meta-analysis shows that in selected patients and in a limited number of randomized cases, SILC does not significantly increase morbidity compared to MILC. Nevertheless, only time and further data will tell us whether single-incision surgery really does improve clinical outcome. Robust studies showing a difference in benefit without compromising safety are needed before such techniques can be widely advocated. Efficacy studies on the many new devices on the market and those in the development pipeline may serve to simplify the bewildering multiplicity of novel products designed for this purpose.

With this goal, a novel multicenter randomized trial entitled MUSIC (MUlti-port vs. SIngle-port Cholecystectomy) just started; it plans to recruit 300 patients per group in a 12-month time frame [34]. The aim is to compare the two approaches in terms of overall morbidity, skin incision–related morbidity, postoperative pain, and cosmetic results. Promoted by the Technology Committee and supported by the European Association for Endoscopic Surgery, the study received local ethical committee approval and is registered with Clinical Trials (U.S. International Clinical Trials Databank, U.S. NIH, ID code NCT01104727).

In conclusion, this meta-analysis affirms that SILC in selected patients is as feasible and safe when compared to MILC, with better cosmetic results but with a longer operative time. We await high-quality, double-blind RCTs. These should include clear statements on analgesic protocols, standard scores of cosmetic results, longer follow-up assessment, and cost–benefit analysis.

Acknowledgments

Supported in part by the European Commission within the STIFF-FLOP FP7 European project FP7/ICT-2011-7-287728.

Disclosures

Prof. Alberto Arezzo is consultant for Johnson & Johnson Medical, Cincinnati, OH. Dr. Roberto Passera, Dr. Gitana Scozzari, Dr. Federico Famiglietti, and Prof. Mario Morino have no conflicts of interest or financial ties to disclose.

References

1.
Navarra G, Pozza E, Occhionorelli S (1997) Short note: one wound laparoscopic cholecystectomy. Br J Surg 84:695–697

2.
Allemann P, Schafer M, Demartines N (2010) Critical appraisal of single port access cholecystectomy. Br J Surg 97:1476–1480

3.
Joseph M, Phillips MR, Farrell TM, Rupp CC (2012) Single incision laparoscopic cholecystectomy is associated with a higher bile duct injury rate. A review and a word of caution. Ann Surg 256:1195–1200

4.
Aprea G, Coppola Bottazzi E, Guida F, Masone S, Persico G (2011) Laparoendoscopic single site (LESS) versus classic video-laparoscopic cholecystectomy: a randomized prospective study. J Surg Res 166:e109–e112

5.
Asakuma M, Hayashi M, Komeda K, Shimizu T, Hirokawa F, Miyamoto Y, Okuda J, Tanigawa N (2011) Impact of single-port cholecystectomy on postoperative pain. Br J Surg 98:991–995

6.
Ma J, Cassera MA, Spaun GO, Hammill CW, Hansen PD, Aliabadi-Wahle S (2011) Randomized controlled trial comparing single-port laparoscopic cholecystectomy and four-port laparoscopic cholecystectomy. Ann Surg 254:22–27

7.
Lee PC, Lo C, Lai PS, Chang JJ, Huang SJ, Lin MT, Lee PH (2010) Randomized clinical trial of single-incision laparoscopic cholecystectomy versus minilaparoscopic cholecystectomy. Br J Surg 97:1007–1012

8.
Lirici MM, Califano AD, Angelini P, Corcione F (2011) Laparo-endoscopic single site cholecystectomy versus standard laparoscopic cholecystectomy: results of a pilot randomized trial. Am J Surg 202:45–52

9.
Marks J, Tacchino R, Roberts K, Onders R, Denoto G, Paraskeva P, Rivas H, Soper N, Rosemurgy A, Shah S (2011) Prospective randomized controlled trial of traditional

laparoscopic cholecystectomy versus single-incision laparoscopic cholecystectomy: report of preliminary data. Am J Surg 201:369–372
10.
Edwards C, Bradshaw A, Ahearne P, Dematos P, Humble T, Johnson R, Mauterer D, Soosaar P (2010) Single-incision laparoscopic cholecystectomy is feasible: initial experience with 80 cases. Surg Endosc 24:2241–2247
11.
Vettoretto N, Arezzo A (2010) Human natural orifice translumenal endoscopic surgery: on the way to two different philosophies? Surg Endosc 24:490–492
12.
Lirici MM, Arezzo A (2006) Surgery without scars: the new frontier of minimally invasive surgery? Controversies, concerns and expectations in advanced operative endoscopy. Minim Invasive Ther Allied Technol 15:323–324
13.
Rocchietto S, Scozzari G, Arezzo A, Morino M (2012) Obese women's perception of bariatric trans-vaginal NOTES. Obes Surg 22:452–459
14.
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151:65–94
15.
Higgins JPT, Green S (eds) (2011) Cochrane handbook for systematic reviews of interventions, version 5.1.0. Available at: http://www.cochrane-handbook.org. Accessed January 1, 2012
16.
Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5:13
17.
DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188

18.
Phillips MS, Marks JM, Roberts K, Tacchino R, Onders R, DeNoto G, Rivas H, Islam A, Soper N, Gecelter G, Rubach E, Paraskeva P, Shah S (2012) Intermediate results of a prospective randomized controlled trial of traditional four-port laparoscopic cholecystectomy versus single-incision laparoscopic cholecystectomy. Surg Endosc 26(5):1296–1303
19.
Bucher P, Pugin F, Buchs NC, Ostermann S, Morel P (2011) Randomized clinical trial of laparoendoscopic single-site versus conventional laparoscopic cholecystectomy. Br J Surg 98:1695–1702
20.
Cao ZG, Cai W, Qin MF, Zhao HZ, Yue P, Li Y (2011) Randomized clinical trial of single-incision versus conventional laparoscopic cholecystectomy: short-term operative outcomes. Surg Laparosc Endosc Percutan Tech 21:311–313
21.
Lai EC, Yang GP, Tang CN, Yih PC, Chan OC, Li MK (2011) Prospective randomized comparative study of single incision laparoscopic cholecystectomy versus conventional four-port laparoscopic cholecystectomy. Am J Surg 202:254–258
22.
Tsimoyiannis EC, Tsimogiannis KE, Pappas-Gogos G, Farantos C, Benetatos N, Mavridou P, Manataki A (2010) Different pain scores in single transumbilical incision laparoscopic cholecystectomy versus classic laparoscopic cholecystectomy: a randomized controlled trial. Surg Endosc 24:1842–1848
23.
Zheng M, Qin M, Zhao H (2012) Laparoendoscopic single-site cholecystectomy: a randomized controlled study. Minim Invasive Ther Allied Technol 21(2):113–117
24.
Vilallonga R, Barbaros U, Sümer A, Demirel T, Fort JM, González O, Rodriguez N, Carrasco MA (2011) Laparoscopic single-site surgery for cholecystectomy. Initial experience. Surg Endosc 25(suppl 1, S35)
25.
Ponsky TA, Diluciano J, Chwals W, Parry R, Boulanger S (2009) Early experience with single port laparoscopic surgery in children. J Laparoendosc Adv Surg Tech A 19:551–553

26.
Saber AA, El-Ghazaly TH, Dewoolkar AV (2010) Single-incision laparoscopic bariatric surgery: a comprehensive review. Surg Obes Relat Dis 6:575–582
27.
Targarona EM, Balague C, Martinez C, Pallares L, Estalella L, Trias M (2009) Single-port access: a feasible alternative to conventional laparoscopic splenectomy. Surg Innov 16:348–352
28.
Chow AG, Purkayastha S, Zacharakis E, Paraskeva P (2011) Single-incision laparoscopic surgery for right hemicolectomy. Arch Surg 146:183–186
29.
Markar SR, Karthikesalingam A, Thrumurthy S, Muirhead L, Kinross J, Paraskeva P (2012) Single-incision laparoscopic surgery (SILS) vs conventional multiport cholecystectomy: systematic review and meta-analysis. Surg Endosc 26(5):1205–1213
30.
Connor S, Garden OJ (2006) Bile duct injury in the era of laparoscopic cholecystectomy. Br J Surg 93:158–168
31.
Saccomani G, Arezzo A, Percivale A, Baldo S, Pellicci R (2009) Laparoscopic cholecystectomy can be performed safely with only three ports in the majority of cases. Chir Ital 61:613–616
32.
Schlager A, Khalaileh A, Shussman N, Elazary R, Keidar A, Pikarsky AJ, Ben-Shushan A, Shibolet O, Horgan S, Talamini M, Zamir G, Rivkind AI, Mintz Y (2010) Providing more through less: current methods of retraction in SIMIS and NOTES cholecystectomy. Surg Endosc 24:1542–1546
33.
Tognarelli S, Pensabene V, Condino S, Valdastri P, Menciassi A, Arezzo A, Dario P (2011) A pilot study on a new anchoring mechanism for surgical applications based on mucoadhesives. Minim Invasive Ther Allied Technol 20:3–13
34.
Arezzo A, Morino M (2011) Endoscopic surgery through single-port incision: time for a trial? Surg Endosc 25:1709–1711