Single-incision versus conventional laparoscopic surgery for rectal cancer: a meta-analysis of clinical and pathological outcomes

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Abstract

Introduction: *Single-incision laparoscopic surgery (SILS) for rectal cancer is technically challenging. There is a lack of high-level evidence for the feasibility and safety of SILS for rectal cancer.*
Aim: *To compare clinical and pathological outcomes of SILS versus conventional laparoscopic surgery (CLS) for rectal cancer.*
Material and methods: *The PubMed, Embase, CENTRAL, and Web of Science databases were searched systematically up to November 2021. Eligibility criteria included randomized controlled trials and non-randomized clinical trials that compared the outcomes of SILS and CLS for rectal cancer. Outcomes of interest included operative, postoperative, and pathologic outcomes.*
Results: *Meta-analysis was performed on 6 studies involving 417 patients. In total 181 patients underwent SILS and 236 underwent CLS. SILS had better outcomes for the incision length (MD = –49.58, 95% CI: –72.43 to –26.73), postoperative pain (visual analogue scale on postoperative day 1, MD = –0.96, 95% CI: –1.18 to –0.74; postoperative day 2, MD = –1.43, 95% CI: –2.29 to –0.57), and hospital stay (MD = –1.17, 95% CI: –1.84 to –0.50). Operative outcomes, including operation time, blood loss, conversion to laparotomy, and ileostomy rate, were similar. Perioperative mortality, overall complications, reoperation, and readmission were similar. Numbers of harvested lymph nodes, lengths of proximal and distal margin, circumferential resection margin involvements, incomplete mesorectal grade, and R0 resection rates were similar.*
Conclusions: *SILS for rectal cancer presented superior outcomes for incision length, postoperative pain, and hospital stays. Perioperative mortality, morbidity, and pathologic outcomes of SILS were comparable to CLS. Future studies are required to determine the long-term oncologic outcomes of SILS for rectal cancer.*

Key words: *single-incision, laparoscopic, minimally invasive surgery, rectal cancer, total mesorectal excision.*

Introduction

Laparoscopic surgery was introduced for colorectal cancer treatment in the 1990s [1–4] and today is performed worldwide. Minimally invasive surgery (MIS), including laparoscopic surgery, was adopted for colorectal cancer treatment because it provides rapid postoperative recovery due to less surgical trauma and guarantees oncological safety. Thus, the scope of MIS is widening, and several different modalities have been developed over the past dec-

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ades, such as laparoscopic surgery, robotic surgery, natural orifice transluminal endoscopic surgery, and single-incision laparoscopic surgery (SILS).

SILS for colon cancer was first reported in 2008 [5] and for rectal cancer in 2010 [6], and since then clinical studies have been conducted to establish its safety and feasibility for colorectal surgery. Although some meta-analyses have been performed on the topic, the studies were heterogeneous because both colon and rectal cancers were included. Rectal cancer surgery is more technically challenging than colon cancer surgery because space is limited in the narrow pelvic cavity. Before adopting SILS for rectal cancer surgery, we need to determine whether this technical issue could be overcome to guarantee surgical and oncological safety.

Aim

We performed this meta-analysis to compare SILS and conventional laparoscopic surgery (CLS) regarding operative and pathologic outcomes and to verify the feasibility and safety of SILS for rectal cancer treatment.

Material and methods

Search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [7]. The PubMed, Embase, CENTRAL, and Web of Science databases were searched systematically until November 2021. Search terms included rectal cancer, rectal carcinoma, rectal neoplasm, single incision, single port, single access, single site, laparoscopic, and laparoscopy. Additional articles from references provided in previous systematic reviews were added. After database searching, duplicates were removed, and the identified articles were screened by reviewing titles and abstracts. Then, full texts of screened articles were reviewed, and ineligible articles were excluded. Two authors (G Kim and KY Lee) independently conducted the screening and review and decided on the articles included in the meta-analysis. Disagreements were resolved by discussion.

Eligibility criteria and outcomes of interest

Eligibility criteria included randomized controlled trials (RCTs) or controlled clinical trials comparing outcomes of single-incision versus conventional laparoscopic surgery for rectal cancer. Exclusion criteria were studies on reduced port laparoscopic surgery or single-incision plus one-port laparoscopic surgery. The primary outcome was an overall perioperative complication rate. The secondary outcomes included operative outcomes (operative time, blood loss, conversion rate, incision length, and ileostomy rate), postoperative outcomes (mortality, complications, hospital stay, reoperation, readmission, postoperative pain, postoperative analgesics requirement, and bowel motility recovery), and pathologic outcomes (number of harvested lymph nodes, specimen length, resection margins, positive circumferential margin, and mesorectal grade).

Risk of bias assessment

Risk of bias of the selected studies was assessed using the Cochrane Collaboration tool for assessing risk of bias [8] for randomized controlled trials and the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) [9] for controlled clinical trials. The Cochrane Collaboration's risk of bias tool evaluated seven independent sources of bias: i) random sequence generation, ii) allocation concealment, iii) blinding of participants and personnel, iv) blinding of outcome assessment, v) incomplete outcome data, vi) selective reporting, and vii) other bias [8]. The RoBANS tool evaluated 6 independent sources of bias: i) selection of participants, ii) confounding variables, iii) measurement of exposure, iv) blinding of outcome assessments, v) incomplete outcome data, and vi) selective outcome reporting [9]. For the studies included in the meta-analysis, the sources of bias were assessed as being of high, low, or unclear risk.

Data extraction

Two authors independently extracted relevant data from the eligible full-text articles. Extracted data included identification information (name of first author, year of publication, country where the study was conducted, study design, type of surgery, sample size, and follow-up period), patients demographics (age, gender, body mass index (BMI), the American Society of Anesthesiologists (ASA) score, and history of previous abdominal surgery), operative outcomes (operative time, blood loss, conversion, incision length, additional trocar insertions, and ileostomy), postoperative outcomes (perioperative

mortality, complications, hospital stay, reoperation, readmission, postoperative pain score, analgesic requirements, recovery of gastrointestinal motility, and diet build-up), pathologic outcomes (number of harvested lymph nodes, tumour size, specimen length, length of resection margins, number of positive margins, mesorectal grade, and R0 resection rate), and oncologic outcomes (overall survival (OS) and disease-free survival (DFS)). The extracted data were cross-checked for discrepancies.

Statistical analysis

Pooled effects are presented as mean differences and 95% confidence intervals for continuous variables and as odds ratios and 95% confidence intervals for dichotomous variables. Heterogeneity among studies was measured using I^2 statistic: $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic, and df is the degree of freedom [10]. When the included studies showed high heterogeneity, a random-effects model was applied for meta-analysis, and when they presented low heterogeneity, a fixed-effects model was applied. The statistical analysis was performed using Review Manager 5.4.1.

Results

Article search results

Database searching identified 728 articles (161 from PubMed, 220 from Embase, 118 from CENTRAL, and 329 from Web of Science), and additional searching, as described in the search strategy, added one article. After removing duplicates from the 729 articles using citation manager, 572 articles remained. Title and abstract reviews resulted in the exclusion of 556 irrelevant articles. A full-text review revealed that one of the remaining 16 articles was written in Chinese, and this article was excluded because full text was not available in English. In addition, one duplicate not detected by the citation manager was also excluded. Thus, we reviewed the full text of 14 articles (Table I) [11–24]. Two studies by Sirikurnpiboon [11, 12] had overlapping study populations, and only the most recent study was included for analysis. Also, 2 studies by Tei *et al*. [14, 15] had overlapping populations, and the most recent study was included. Three studies conducted in Denmark [17–19] had overlapping populations, and only the most recent study (a randomized controlled study) was included. The other 2 articles were a non-randomized study and a poster abstract. A study by Bracale *et al*. [20]

Table I. A list of the 14 full-text reviewed studies

Publication year	Author	Country	No. of patients		Study period	Disease besides rectal cancer	Final selection
			SILS	CLS			
2021	Sirikurnpiboon [11]	Thailand	41	43	2011–2014	–	Included
2016	Sirikurnpiboon [12]	Thailand	35	36	2011–2014	–	Excluded
2020	Jiang *et al*. [13]	China	51	51	2013–2017	–	Included
2018	Tei *et al*. [14]	Japan	44	49	2011–2015	–	Included
2015	Tei *et al*. [15]	Japan	50	50	2010–2014	–	Excluded
2018	Nerup *et al*. [16]	Denmark	12	41	2009–2012	–	Included
2015	Bulut *et al*. [17]	Denmark	20	20	2011–2012	–	Included
2014	Levic and Bulut [18]	Denmark	36	194	2009–2012	–	Excluded
2013	Levic *et al*. [19]	Denmark	40, in total		not presented	–	Excluded
2015	Bracale *et al*. [20]	Italy	21	21	2010–2012	Benign diseases	Excluded
2014	Kim *et al*. [21]	Korea	67	49	2006–2013	Sigmoid and rectosigmoid cancer	Excluded
2013	Choi and Lee [22]	Korea	31	49	2006–2013		Excluded
2013	Choi [23]	Korea	31	49	2006–2013		Excluded
2013	Sourrouille *et al*. [24]	France	13	32	2008–2012	–	Included

SILS – single-incision laparoscopic surgery, CLS – conventional laparoscopic surgery.

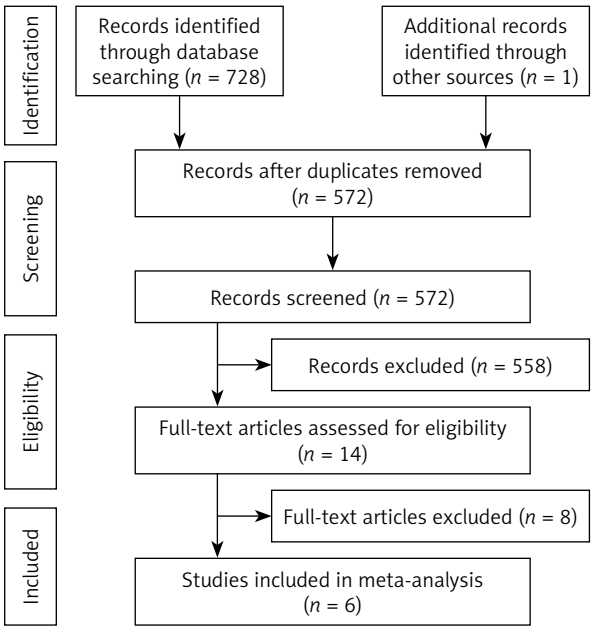


Figure 1. PRISMA flow diagram

included benign diseases other than rectal cancer and thus was also excluded. Finally, 3 Korean studies [21–23] shared the same population and included sigmoid and rectosigmoid colon cancer, and thus all 3 were excluded. After exclusions, 6 eligible studies remained for meta-analysis [11, 13, 14, 16, 17, 24]. A flow diagram of the article selection is provided in Figure 1.

Characteristics of included studies

Table II shows the characteristics of the 6 studies included in the meta-analysis [11, 13, 14, 16, 17, 24]. These studies included a total of 417 patients who were enrolled in 6 clinical trials. All articles were published between 2013 and 2021. Reported outcomes included; i) operative outcomes (operative times, blood losses, conversions to laparotomy, incision lengths, additional trocar insertions, and ileostomy rates), ii) postoperative outcomes (perioperative mortality, perioperative complications, hospital stays, reoperation and readmission rates, pain scores, analgesic requirements, recovery of gastrointestinal motility, and diet build-up), iii) pathologic outcomes (numbers of harvested lymph nodes, specimen length, length of resection margin, circumferential resection margin (CRM) involvement, mesorectal grade, and R0 resection), and iv) oncologic outcomes (OSs, DFSs, and recurrence rates) (Table III).

Risk of bias assessment

For non-randomized studies, the risk of bias was assessed in 6 independent sources using RoBANS [9]. For the selection of participants, 3 studies showed a low risk of bias and 2 showed a high risk of bias; for confounding variables, one study showed a low risk of bias and 4 showed an unclear risk of bias; for measurement of exposure, all 5 studies showed a low risk of bias; for blinding of outcome assessments, all showed a low risk of bias; for incomplete outcome data, all showed a low risk of bias; and for selective outcome reporting, 4 showed a low risk of bias and one showed an unclear risk of bias. For the randomized study, the risk of bias was assessed in 7 independent sources using the Cochrane risk of bias tool [8]. This assessment showed a low risk of bias for blinding of participants and personnel, blinding of outcome assessments, and incomplete outcome data; unclear risk for random sequence generation, allocation concealment, and selective reporting, and no risk of other bias. A summary of the risks of bias for selected studies is provided in Figure 2.

Pooled analysis of measured outcomes

Operative outcomes

Figure 3 presents pooled analyses of operative outcomes.

Operative time (min): Pooled analysis of the 6 studies showed no significant difference between the SILS and CLS groups. The weighted mean difference was 18.49 min (95% CI: –4.53 to 41.52; $p = 0.12$), and the included studies showed high heterogeneity ($I^2 = 94$ %). The analysis was conducted using a random-effects model.

Blood loss (ml): Pooled analysis of the 6 studies showed no significant difference between the 2 groups. The weighted mean difference was –41.22 ml (95% CI: –96.82 to 14.38; $p = 0.15$), and the included studies showed high heterogeneity ($I^2 = 94\%$). The analysis was conducted using a random-effects model.

Conversion to laparotomy: Pooled analysis of 5 studies showed no significant difference between the 2 groups. The odds ratio was 0.79 (95% CI: 0.23 to 2.80; $p = 0.72$), and the included studies showed no heterogeneity ($I^2 = 0$ %). The analysis was conducted using a fixed-effects model.

Table II. Characteristics of the included studies

Study ID	Country	Type of procedure	Study type	No. of patients, *n*		Age [years]			Male, *n* (%)			BMI [kg/m²]			ASA ≥ III, *n* (%)			Previous abdominal surgery, *n* (%)			Neoadjuvant CRTx, *n* (%)			Tumour size [mm]			Follow up period [months]		
				SILS	CLS	SILS	CLS	*P*-value	SILS	CLS	*P*-value	SILS	CLS	*P*-value	SILS	CLS	*P*-value	SILS	CLS	*P*-value	SILS	CLS	*P*-value	SILS	CLS	*P*-value	SILS	CLS	P-value
2021 Sirikurnpiboon [11]*	Thiland	LAR, AR, ISR, APR	NCT	41	43	63.97 ±13.05	61.74 ±12.03	NS	19 (46.3%)	20 (46.5%)	NS	22.20 ±4.00	23.14 ±2.89	NS	6 (14.6%)	3 (7.0%)	NS	–	–	–	–	–	–	–	–	–	–	–	–
2020 Jiang [13]**	China	TME	NCT	51	51	62 (15)	62 (14)	NS	30 (58.8%)	27 (52.9%)	NS	23.56 (3.52)	23.18 (3.39)	NS	5 (9.8%)	8 (15.7%)	NS	12 (23.5)	14 (27.5)	NS	–	–	–	30 (20)	30 (20)	NS	32.6 (18.3)	36.8 (23.6)	NS
2018 Tei [14]*	Japan	LAR	NCT	44	49	67.3 ±9.3	65.0 ±10.1	NS	29 (65.9%)	29 (59.2%)	NS	23.6 ±3.5	22.0 ±3.4	0.019	7 (15.9)	3 (6.1)	NS	13 (29.5)	13 (32.7)	NS	–	–	–	39 ±18	41 ±19	NS	40 (5–63)	51 (12–70)	0.017
2018 Nerup [16]***	Denmark	APR	NCT	12	41	76 (59.5–82.5)	69 (59–76)	NS	5 (41.7%)	28 (68.3%)	NS	23.5 (19.3–24.8)	25 (22.5–28.0)	NS	1 (8.3)	12 (29.3)	0.04	2 (16.7)	14 (34.1)	NS	6 (50%)	30 (73.2%)	NS	20 (19.5–27.5)	25 (20–32.5)	NS	9 (5.5–16.5)	14 (8.5–24)	NS
2015 Bulut [17]***	Denmark	LAR, APR, Hartmann	RCT	20	20	69 (50–86)	73 (50–84)	NS	8 (40%)	8 (40%)	NS	24 (16–32)	24 (19–29)	NS	3 (15)	3 (15)	NS	3 (15)	7 (35)	NS	7 (35%)	4 (20%)	NS	25 (10–70)	40 (20–75)	0.026	12 (6–18)	15 (6–20)	NS
2013 Sourrouille [24]**	France	TME	NCT	13	32	60 (56–65)	61 (53–64)	NS	8 (61.5%)	19 (59.4%)	NS	23.0 (21.8–23.8)	24.9 (22.7–26.5)	NS	2 (15.4)	4 (12.5)	NS	–	–	–	9 (69.2%)	22 (68.8%)	NS	–	–	–	–	–	–

*Continuous variables are presented with i) mean ± standard deviation, *; ii) median (interquartile range), **; iii) median (range), ***. BMI – body mass index, ASA – the American Society of Anesthesiologists, CRTx. – chemoradiation therapy, SILS – single-incision laparoscopic surgery, CLS – conventional laparoscopic surgery, LAR – low anterior resection, AR – anterior resection, ISR – intersphincteric resection, APR – abdominoperineal resection, TME – total mesorectal excision, NCT – non-randomized clinical study, RCT – randomized controlled study, NS – non-specific.*

Table III. Reported outcomes from the included studies

Study ID	Operative outcomes					Postoperative outcomes										Pathologic outcomes							Oncologic outcomes			
	Operative time	Blood loss	Conversion to laparotomy	Incision length	Additional trocar(s)	Ileostomy	Perioperative mortality	Perioperative complications	Hospital stay	Reoperation	Readmission	Pain score	Analgesics requirements	Bowel movement recovery	Diet build up	Harvested lymph nodes	Specimen length	PRM	DRM	CRM	CRM involvement	Mesorectal grade	R0 resection	Follow up period	OS	DFS	Recurrence
2021 Sirikurnpiboon [11]	+	+	–	–	–	–	–	+	+	–	–	+	–	+	–	+	–	–	+		+	+	–	–	+	+	-
2020 Jiang [13]	+	+	+	+	+	–	+	+	+	–	+	+	–	–	+	+	–	+	+	–	+	–	–	+	+	+	+
2018 Tei [14]	+	+	+	–	+	–	+	+	+	+	–	–	–	–	–	+	–	+	+	–	+	–	–	+	+	+	+
2018 Nerup [16]	+	+	+	–	–	–	+	+	+	–	+	–	–	–	–	+	+	–	+	+	–	+	–	+	–	–	-
2015 Bulut [17]	+	+	+	+	–	+	–	+	+	+	+	+	+	–	–	+	+	–	+	+	–	+	+	+	–	–	-
2013 Sourrouille [24]	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	+	–	–	–	–	–	+	–	–	–	–	-

PRM – proximal resection margin, DRM – distal resection margin, CRM – circumferential resection margin, OS – overall survival, DFS – disease-free survival.

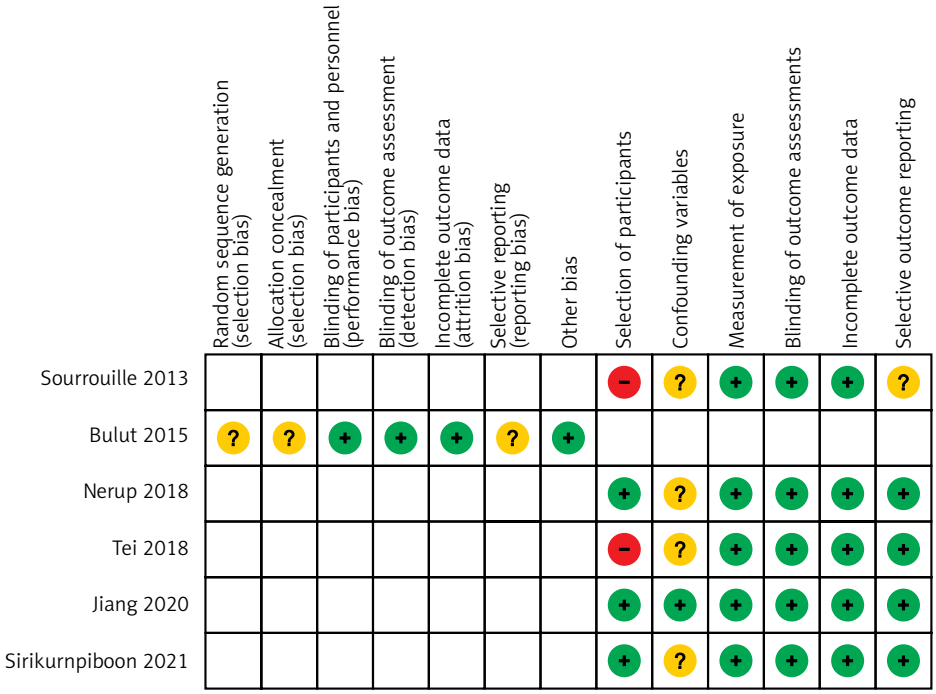


Figure 2. Risk of bias summary: Cochrane risk of bias tool for RCT; RoBANS for non-RCT

Incision length (mm): Pooled analysis of 2 studies showed that the incision length was significantly shorter in the SILS group. The weighted mean difference was –49.36 mm (95% CI: –98.58 to –0.14; $p < 0.00001$), and the included studies showed high heterogeneity (I^2 = 97%). The analysis was conducted using a random-effects model.

Ileostomy rate: Pooled analysis of 2 studies showed no significant difference between the 2 groups. The odds ratio was 0.31 (95% CI: 0.06 to 1.72; $p = 0.18$), and the included studies showed moderate heterogeneity (I^2 = 61 %). The analysis was conducted using a random-effects model.

Postoperative outcomes

Figure 4 presents pooled analyses of postoperative outcomes.

Perioperative mortality: Three studies reported zero perioperative mortality. One study reported 2 perioperative mortalities for SILS and 2 for CLS. The odds ratio was 3.90, and the difference was not statistically significant (95% CI: 0.49 to 31.20).

Overall complications: Pooled analysis of the 6 studies showed no significant difference between the 2 groups. The odds ratio was 0.69 (95% CI: 0.42 to 1.13; $p = 0.14$), and the included studies showed no heterogeneity (I^2 = 0 %). The analysis was conducted using a fixed-effects model.

Hospital stay (days): Pooled analysis of the 6 studies showed that the hospital stays were significantly shorter for SILS than for CLS. The weighted mean difference was –1.20 days (95% CI: –2.02 to –0.39; $p = 0.004$), and the included studies showed moderate heterogeneity (I^2 = 69 %). The analysis was conducted using a random-effects model.

Reoperation rate: Pooled analysis of 3 studies showed no significant difference between the 2 groups. The odds ratio was 1.10 (95% CI: 0.32 to 3.84; $p = 0.88$), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using a fixed-effects model.

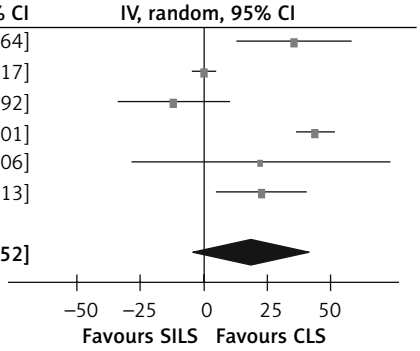
Readmission rate: Pooled analysis of 3 studies showed no significant difference between the 2 groups. The odds ratio was 2.43 (95% CI: 0.64 to 9.14; $p = 0.19$), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using a fixed-effects model.

Pain score (VAS, visual analogue scale): Pooled analysis of 3 studies showed a significantly lower pain score on postoperative day (POD) 1 after SILS than after CLS. The weighted mean difference was –0.96 (95% CI: –1.18 to –0.74; $p < 0.00001$).

A

Study or subgroup	SILS Mean	SILS SD	SILS Total	CLS Mean	CLS SD	CLS Total	Weight (%)	Mean difference IV, random, 95% CI
2021 Sirikurnpiboon	268.29	50.73	41	233	53.8	43	16.6	35.29 [12.94, 57.64]
2020 Jiang	62	11.111	51	62	10.37	51	19.6	0.00 [–4.17, 4.17]
2018 Tei	198	52.8	44	210	55	49	16.7	–12.00 [–33.92, 9.92]
2018 Nerup	312.575	8.756	12	269	18.125	41	19.3	43.57 [36.14, 51.01]
2015 Bulut	290.75	89.25	20	268.5	74	20	10.1	22.25 [–28.56, 73.06]
2013 Sourrouille	302.5	26.964	13	280	28.25	32	17.7	22.50 [4.87, 40.13]
Total (95% CI)			**181**			**236**	**100.0**	**18.49 [–4.53, 41.52]**

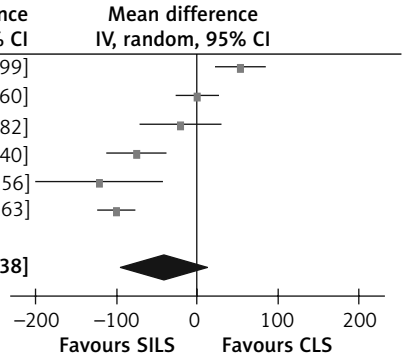
Heterogeneity: $\tau^2 = 700.21$; $\chi^2 = 110.99$, d$f = 5$ ($p < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 1.57$ ($p = 0.12$)



B

Study or subgroup	SILS Mean	SILS SD	SILS Total	CLS Mean	CLS SD	CLS Total	Weight (%)	Mean difference IV, random, 95% CI
2021 Sirikurnpiboon	268.29	50.73	41	215.1	88.99	43	17.5	53.19 [22.39, 83.99]
2020 Jiang	50	66.66667	51	50	70.37037	51	17.8	0.00 [–26.60, 26.60]
2018 Tei	49	120	44	70	125	49	16.1	–21.00 [–70.82, 28.82]
2018 Nerup	75	59.512	12	150	46.875	41	17.1	–75.00 [–111.60, –38.40]
2015 Bulut	91.5	75	20	212.5	162.5	20	13.5	–121.00 [–199.44, –42.56]
2013 Sourrouille	100	28.868	13	200	50	32	17.9	–100.00 [–123.37, –76.63]
Total (95% CI)			**181**			**236**	**100.0**	**–41.22 [–96.82, 14.38]**

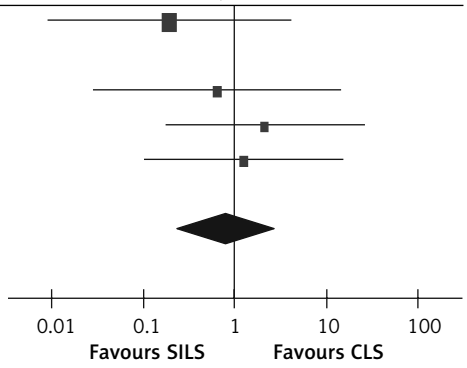
Heterogeneity: $\tau^2 = 4346.26$; $\chi^2 = 77.21$, d$f = 5$ ($p < 0.00001$); $I^2 = 94\%$
Test for overall effect: $Z = 1.45$ ($p = 0.15$)



C

Study or Subgroup	SILS Events	SILS Total	CLS Events	CLS Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
2020 Jiang	0	51	2	51	44.4	0.19 [0.01, 4.11]
2018 Tei	0	44	0	49		Not estimable
2018 Nerup	0	12	2	41	20.4	0.63 [0.03, 14.06]
2015 Bulut	2	20	1	20	16.1	2.11 [0.18, 25.35]
2013 Sourrouille	1	13	2	32	19.1	1.25 [0.10, 15.11]
Total (95% CI)		**140**		**193**	**100.0**	**0.79 [0.23, 2.80]**
Total events	3		7			

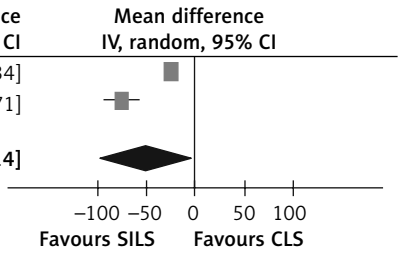
Heterogeneity: $\chi^2 = 1.57$, d$f = 3$ ($p = 0.67$); $I^2 = 0\%$
Test for overall effect $Z = 0.36$ ($p = 0.72$)



D

Study or subgroup	SILS Mean	SILS SD	SILS Total	CLS Mean	CLS SD	CLS Total	Weight (%)	Mean difference IV, random, 95% CI
2020 Jiang	40	7.407407	51	65	11.11111	51	51.5	–25.00 [–28.66, –21.34]
2015 Bulut	57.5	25	20	132.75	31.25	20	48.5	–75.25 [–92.79, –57.71]
Total (95% CI)			**71**			**71**	**100.0**	**–49.36 [–98.58, –0.14]**

Heterogeneity: $\tau^2 = 1220.74$; $\chi^2 = 30.21$, d$f = 1$ ($p < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 1.97$ ($p = 0.05$)



E

Study or Subgroup	SILS Events	SILS Total	CLS Events	CLS Total	Weight (%)	Odds ratio M-H, random, 95% CI
2015 Bulut	4	20	13	20	51.7	0.13 [0.03, 0.56]
2013 Sourrouille	10	13	26	32	48.3	0.77 [0.16, 3.68]
Total (95% CI)		**33**		**52**	**100.0**	**0.31 [0.06, 1.72]**
Total events	14		39			

Heterogeneity: $\tau^2 = 0.93$; $\chi^2 = 2.60$, d$f = 1$ ($p = 0.11$); $I^2 = 61\%$
Test for overall effect: $Z = 1.34$ ($p = 0.18$)

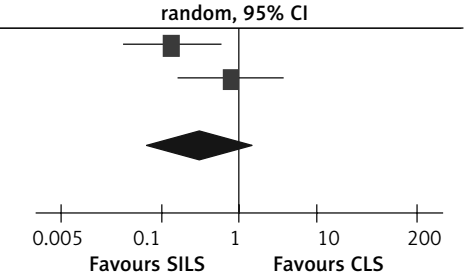


Figure 3. Forest plots comparing operative outcomes of single-incision laparoscopic surgery (SILS) vs. conventional laparoscopic surgery (CLS) for rectal cancer. **A** – Operative time (min). **B** – Blood loss (ml). **C** – Conversion to laparotomy. **D** – Incision length (mm). **E** – Incidence of ileostomy

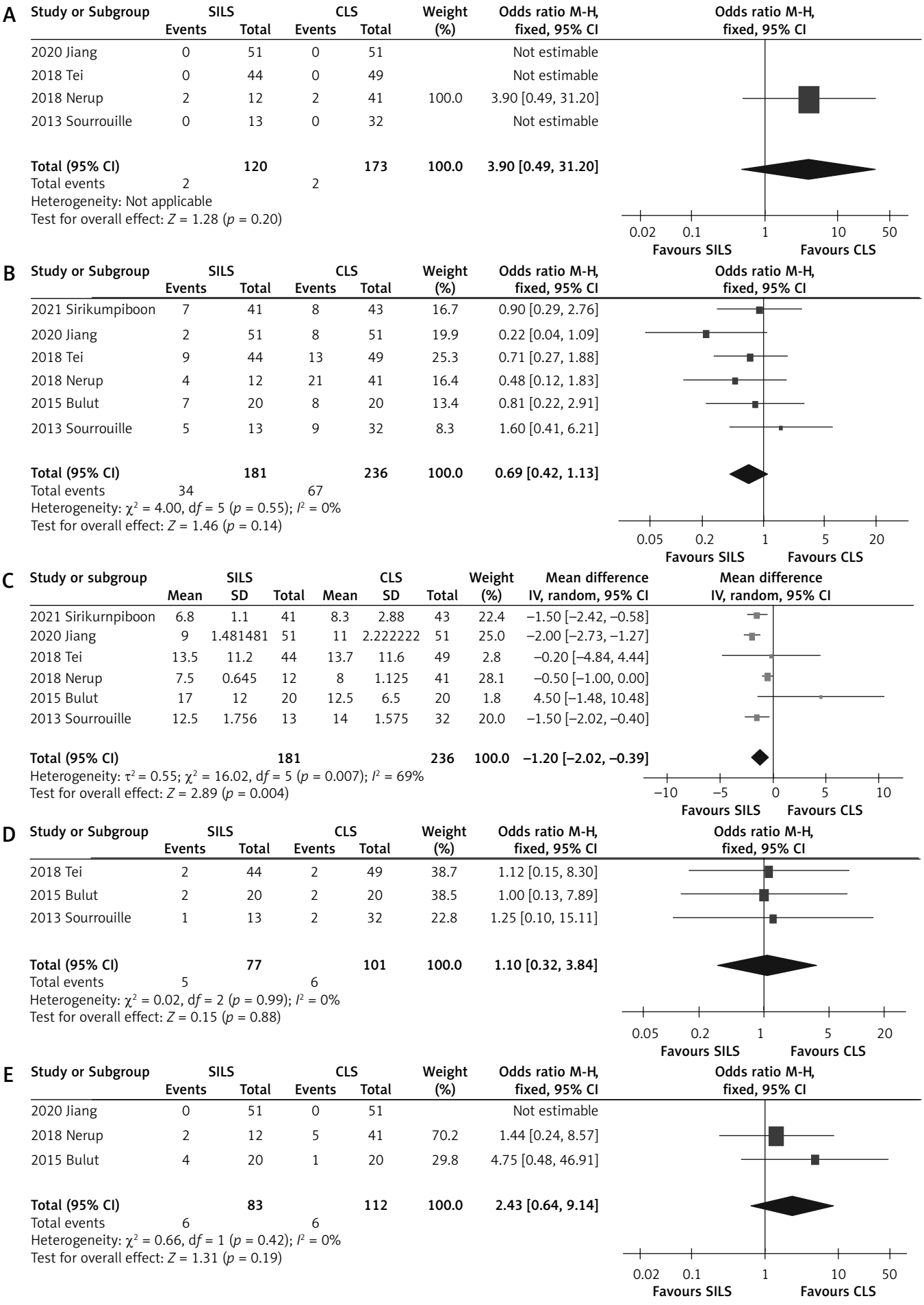


Figure 4. Forest plots comparing postoperative outcomes of single-incision laparoscopic surgery (SILS) vs. conventional laparoscopic surgery (CLS) for rectal cancer. **A** – Perioperative mortality. **B** – Overall complications. **C** – Hospital stay (days). **D** – Reoperations. **E** – Readmissions

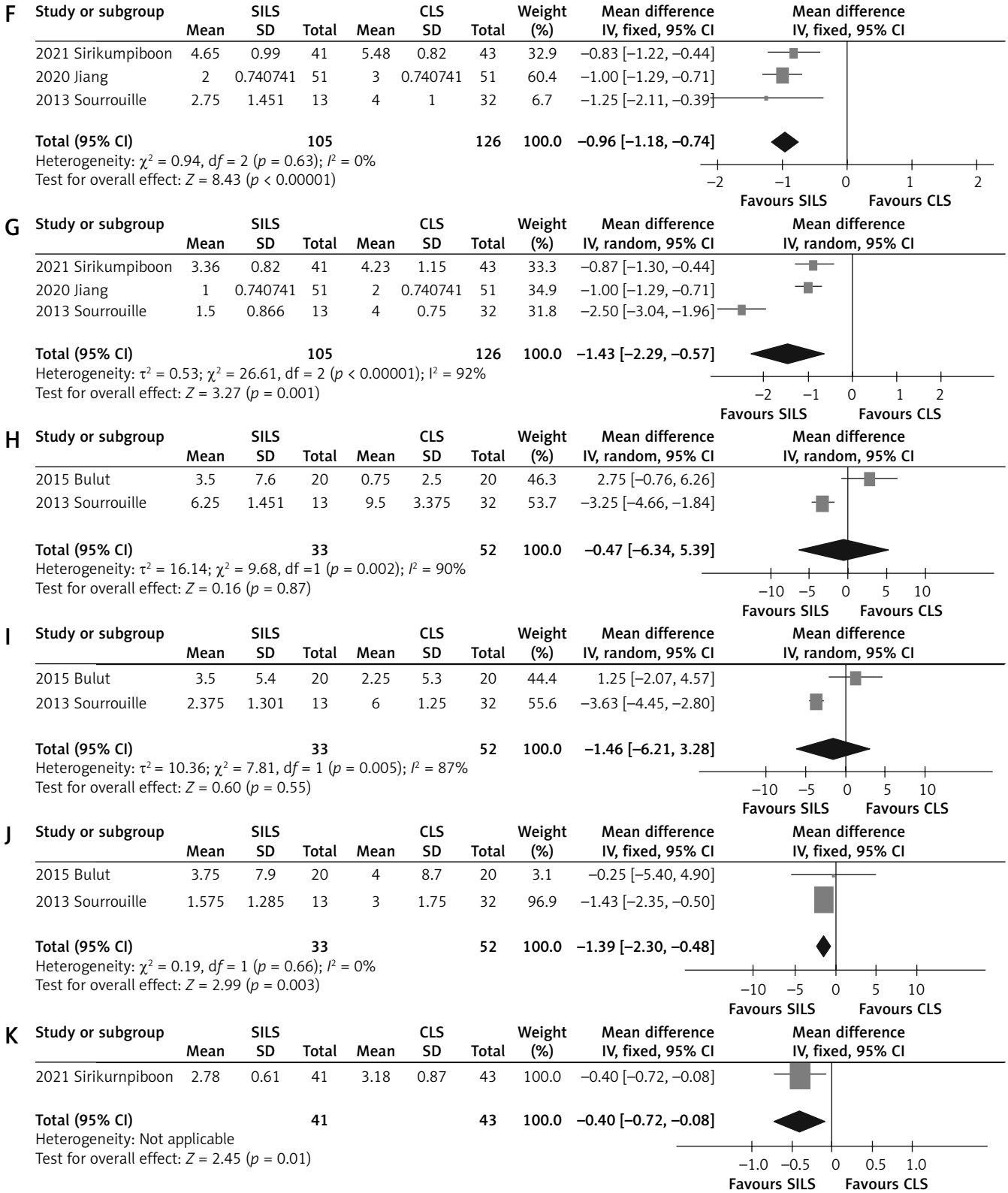


Figure 4. Cont. **F** – Pain score (VAS, visual analog scale), postoperative day 1. **G** – Pain score (VAS, visual analog scale), postoperative day 2. **H** – Morphine requirement (mg), postoperative day 1. **I** – Morphine requirement (mg), postoperative day 2. **J** – Morphine requirement (mg), postoperative day 3. **K** – Time to first bowel movement (days)

The included studies showed no heterogeneity (I^2 = 0%), and the analysis was conducted using the fixed-effects model. Also, pooled analysis of 3 studies showed a significantly lower pain score at POD 2 after SILS than after CLS. The weighted mean difference was –1.43 (95% CI: –2.29 to –0.57; p = 0.001), and the included studies showed high heterogeneity (I^2 = 92 %). The analysis was conducted using a random-effects model.

Morphine requirements (mg): Two studies reported postoperative morphine requirements. On POD 1, no significant difference was found between the 2 groups. The weighted mean difference was –0.47 mg (95% CI: –6.34 to 5.39; p = 0.87), and the included studies showed high heterogeneity (I^2 = 90%). The analysis was conducted using the random-effects model. On POD 2, postoperative morphine requirements were similar in the 2 groups. The weighted mean difference was –1.46 mg (95% CI: –6.21 to 3.28; p = 0.55), and the included studies showed high heterogeneity (I^2 = 87%). The analysis was conducted using a random-effects model. On POD 3, the morphine requirement was significantly lower after SILS than CLS. The weighted mean difference was –1.39 mg (95% CI: –2.30 to –0.48; p = 0.003), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using the fixed-effects model.

Time to first bowel movement (days): Only one study reported a significantly shorter time to first bowel movement after SILS; the mean difference was –0.40 days (95% CI: –0.72 to –0.08).

Complications

Figure 5 presents detailed results for pooled analyses of complications.

Intraoperative complications: Pooled analysis of the 6 studies showed no significant difference between the 2 groups. The odds ratio was 0.46 (95% CI: 0.07 to 3.01; p = 0.42), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using the fixed-effects model.

Anastomotic leakage: Pooled analysis of the 6 studies showed no significant difference between the 2 groups. The odds ratio was 0.71 (95% CI: 0.31 to 1.64; p = 0.42), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using the fixed-effects model.

Surgical site infections: Pooled analysis of the 6 studies showed no significant difference between the 2 groups. The odds ratio was 0.85 (95% CI: 0.39 to 1.86; p = 0.68), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using a fixed-effects model.

Gastrointestinal motility dysfunctions: Pooled analysis of the 6 studies showed no significant difference between the 2 groups. The odds ratio was 0.97 (95% CI: 0.27 to 3.47; p = 0.96), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using a fixed-effects model.

Pulmonary complications: Pooled analysis of the 6 studies revealed no significant difference between the 2 groups. The odds ratio was 1.07 (95% CI: 0.31 to 3.72; p = 0.92), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using a fixed-effects model.

Cardiovascular complications: Pooled analysis of the 6 studies showed no significant difference between the 2 groups. The odds ratio was 2.08 (95% CI: 0.49 to 8.90; p = 0.32), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using a fixed-effects model.

Urologic complications: Pooled analysis of the 6 studies showed no significant difference between the 2 groups. The odds ratio was 0.77 (95% CI: 0.27 to 2.24; p = 0.63), and the included studies showed low heterogeneity (I^2 = 5%). The analysis was conducted using a fixed-effects model.

Pathologic outcomes

Figure 6 presents pooled analyses of pathologic outcomes.

Number of harvested lymph nodes: Pooled analysis of the 6 studies showed no significant difference between the 2 groups. The weighted mean difference was –0.26 (95% CI: –1.53 to 1.01; p = 0.68), and the included studies showed moderate heterogeneity (I^2 = 51%). The analysis was conducted using a random-effects model.

Specimen lengths (cm): A pooled analysis of 2 studies showed that specimen lengths were significantly longer in the SILS group than in the CLS group. The weighted mean difference was 3.26 cm (95% CI: 2.01 to 4.52; p < 0.00001), and the included studies showed no heterogeneity (I^2 = 0%). The analysis was conducted using a fixed-effects model.

Lengths of PRMs (cm): Pooled analysis of 2 studies showed no significant difference between the 2 groups. The weighted mean difference was 0.45 cm

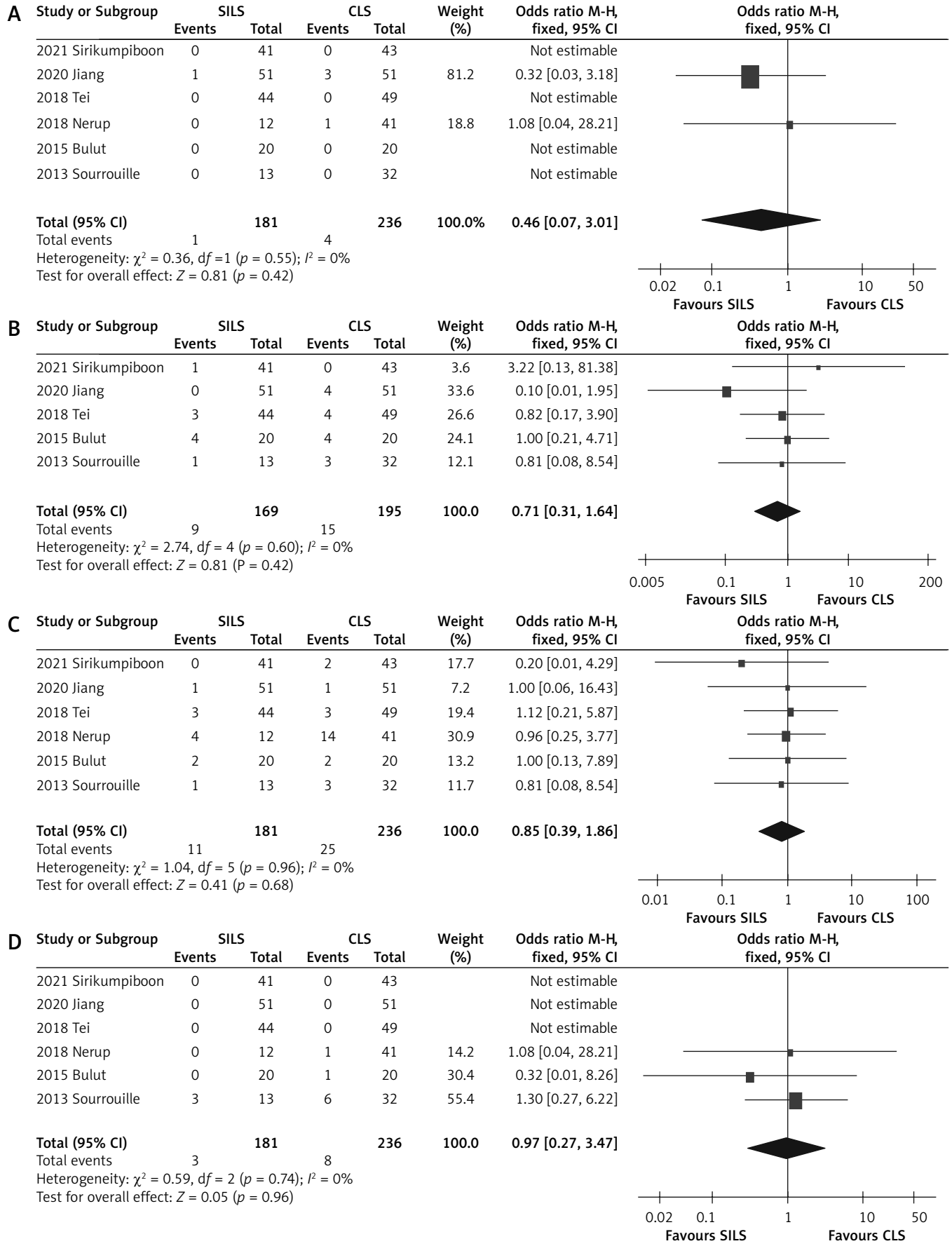


Figure 5. Forest plots comparing complications of single-incision laparoscopic surgery (SILS) vs. conventional laparoscopic surgery (CLS) for rectal cancer. **A** – Intraoperative complications. **B** – Anastomotic leakage. **C** – Surgical site infections. **D** – Gastrointestinal motility dysfunctions

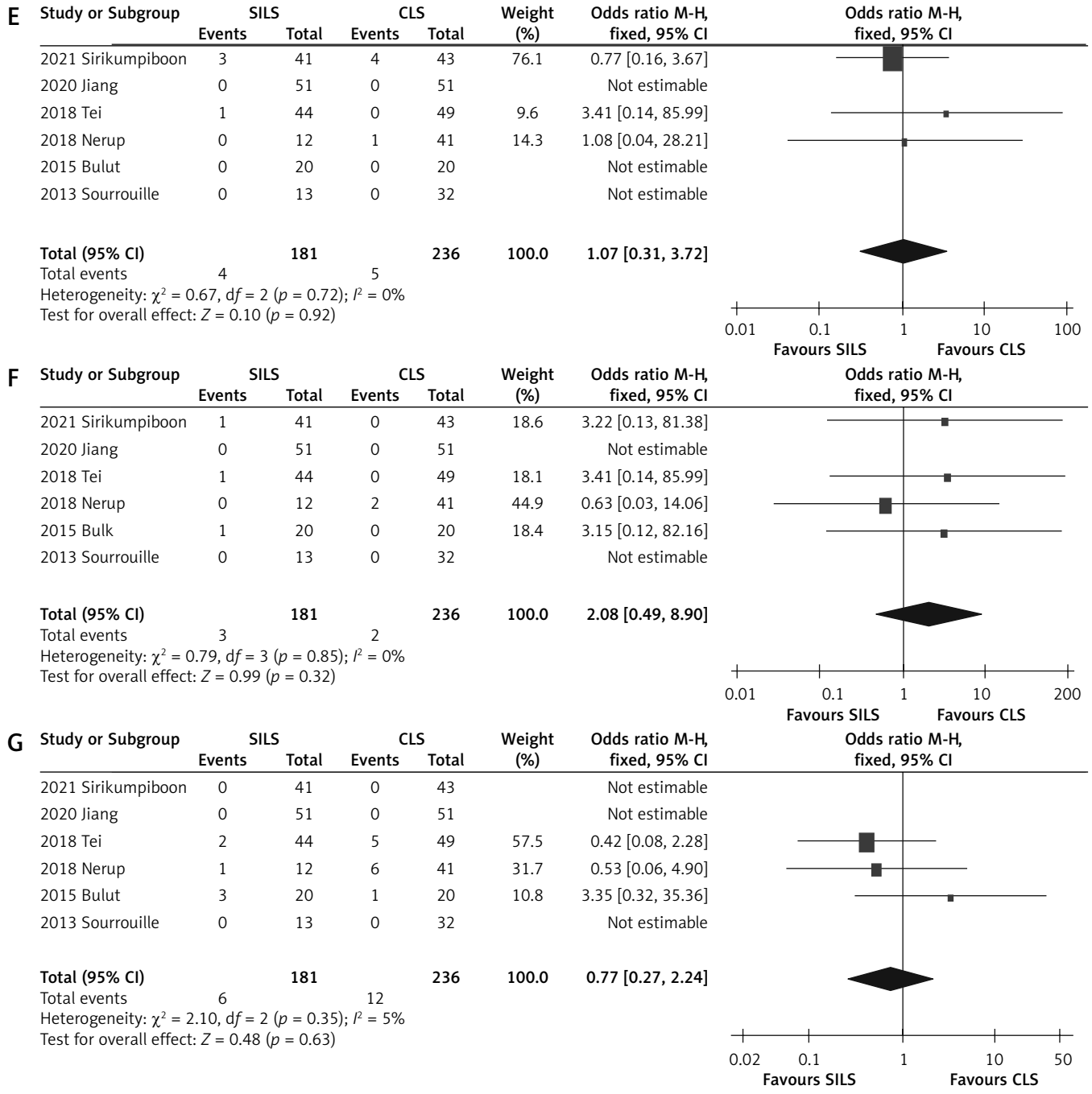


Figure 5. Cont. **E** – Pulmonary complications. **F** – Cardiovascular complications. **G** – Urologic complications

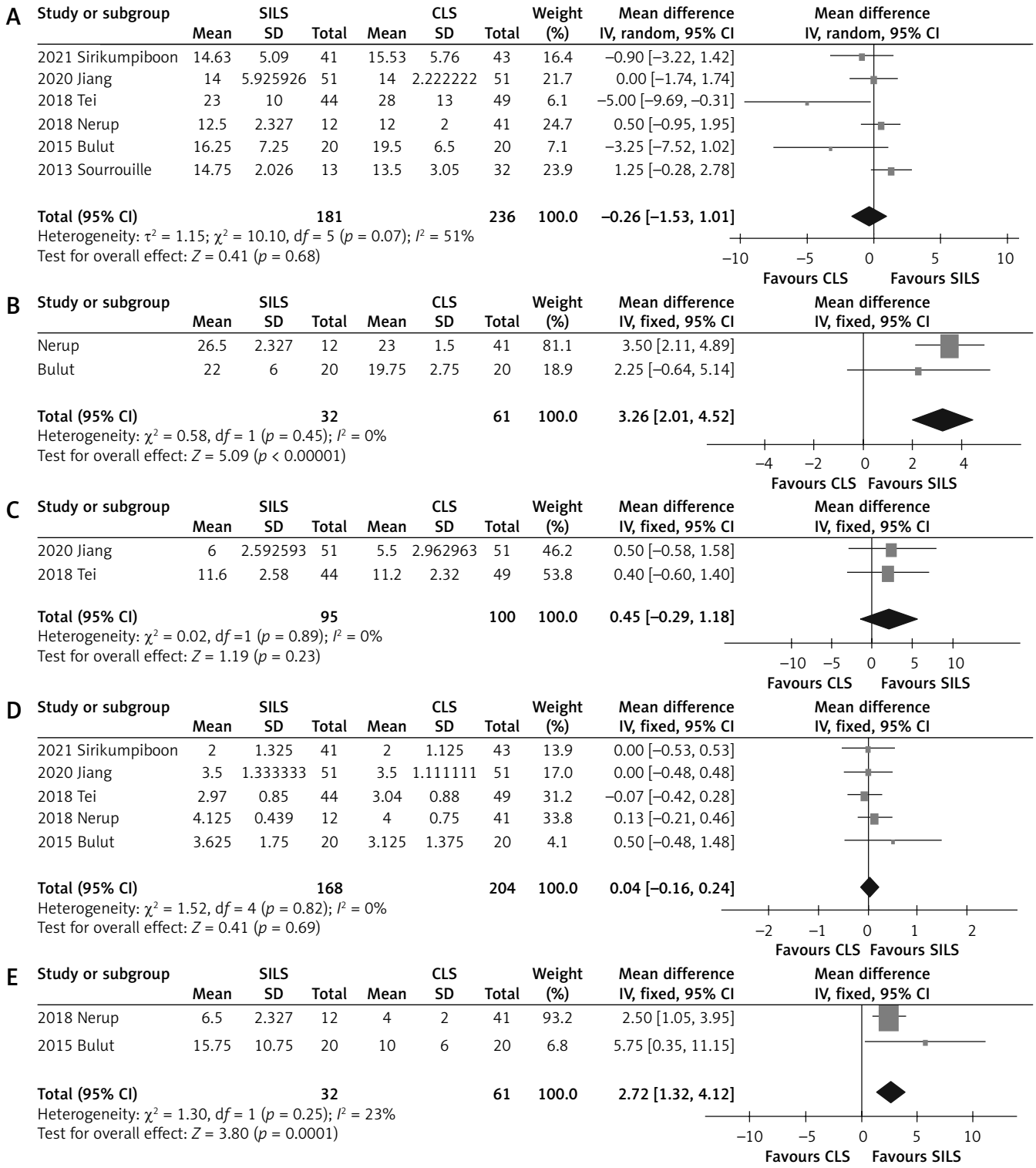


Figure 6. Forest plots comparing pathologic outcomes of single-incision laparoscopic surgery (SILS) vs. conventional laparoscopic surgery (CLS) for rectal cancer. **A** – Number of harvested lymph nodes. **B** – Specimen length (cm). **C** – Length of proximal resection margin (cm). **D** – Length of distal resection margin (cm). **E** – Length of circumferential resection margin (mm)

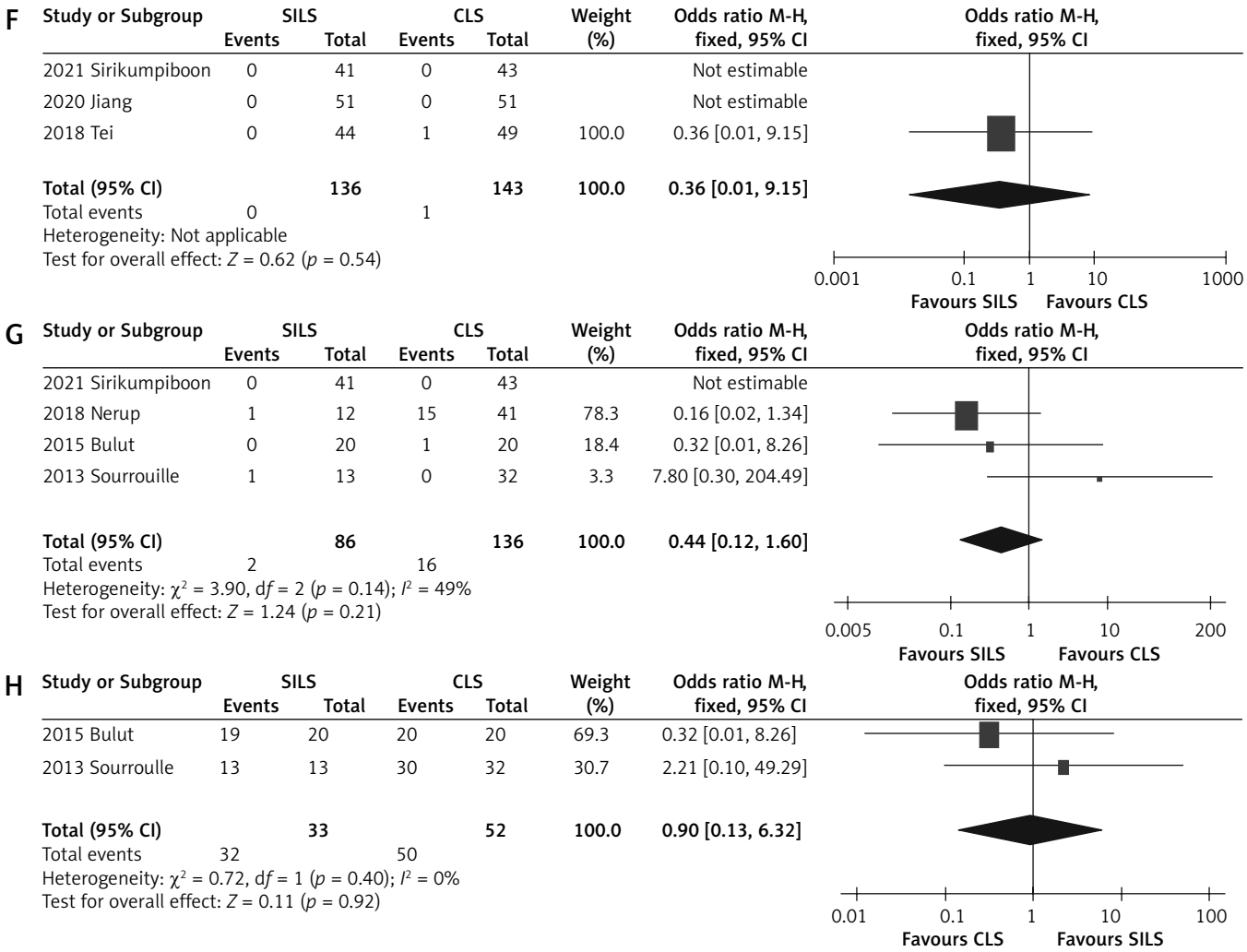


Figure 6. Cont. **F** – Circumferential resection margin involvement. **G** – Incomplete mesorectal grade. **H** – RO resection

(95% CI: –0.29 to 1.18; $p = 0.23$), and the included studies showed no heterogeneity ($I^2 = 0\%$). The analysis was conducted using a fixed-effects model.

Lengths of DRMs (cm): Pooled analysis of 5 studies showed no significant difference between the two groups. The weighted mean difference was 0.04 cm (95% CI: –0.16 to 0.24; $p = 0.69$), and the included studies showed no heterogeneity ($I^2 = 0\%$). The analysis was conducted using a fixed-effects model.

Lengths of CRMs (mm): A pooled analysis of 2 studies showed lengths of CRM was significantly longer in the SILS group. The weighted mean difference was 2.72 mm (95% CI: 1.32 to 4.12; $p = 0.0001$), and the included studies showed low heterogeneity ($I^2 = 23\%$). The analysis was conducted using a fixed-effects model.

CRM involvements: Two studies reported no CRM involvement after SILS or CLS. One study reported CRM involvement in 1 patient in the CLS group and no CRM involvement in the SILS group. The odds ratio was 0.36, and the difference was not statistically significant (95% CI: 0.01 to 9.15).

Incomplete mesorectal grade: Pooled analysis of 4 studies showed no significant difference between the 2 groups. The odds ratio was 0.44 (95% CI: 0.12 to 1.60; $p = 0.21$), and the included studies showed relatively low heterogeneity ($I^2 = 49\%$). The analysis was conducted using a fixed-effects model.

R0 resection rate: Pooled analysis of 2 studies showed no significant difference between the 2 groups. The odds ratio was 0.90 (95% CI: 0.13 to 6.32; $p = 0.92$), and the included studies showed no

heterogeneity (I^2 = 0%). The analysis was conducted using a random-effects model.

Oncologic outcomes

Three studies reported oncologic outcomes [11, 13, 14]. Sirikurnpiboon reported that the 3-year and 5-year survival rate, local recurrence rate, distant metastasis rate, and average times to recurrence and metastasis were not significantly different between the 2 groups [11]. Jiang *et al.* reported that the recurrence rate, 3-year disease-free survival rate, and overall survival rate were not significantly different between the 2 groups [13]. Tei *et al.* found that distant metastasis and local recurrence rates and 3-year overall survival rates were not significantly different in the 2 groups. However, the 3-year relapse-free survival rate was significantly higher for SILS (94.7% in SILS vs. 78.6% in CLS; p = 0.032). The authors attributed this result to different follow-up periods (40 months after SILS vs. 51 months after CLS; p = 0.008) [14]. Pooled analysis was not performed because the included studies did not provide hazard ratios with standard errors or any variable to estimate their values for performing a meta-analysis of time-to-event data.

Discussion

After laparoscopic colectomy was introduced in the 1990s [1–4], in the early 2000s, the safety and feasibility of laparoscopic surgery for colon cancer were demonstrated by several RCTs [25–28]. These studies showed that laparoscopic colectomy had outcomes equivalent or superior to open colectomy, and subsequently, laparoscopic colectomy gained in popularity for colon cancer surgery. As regards rectal cancer, the feasibility of laparoscopic surgery was shown by some comparative studies conducted in the early 2000s [29–31], and later, the CLASICC, the COREAN, and the COLOR II trials confirmed its oncological safety [32–35].

Laparoscopic surgery may produce superior outcomes because it causes less surgical trauma and thus fewer complications and faster recovery than open surgery. In the case of rectal cancer surgery, its superior outcomes are probably due to the magnified view it provides of limited surgical areas in the pelvis, which enable precise dissection along proper surgical planes. Because of these advantages, MIS is being continuously developed to maximize its potential benefits for colorectal surgery.

About 2 decades after the introduction of laparoscopic colectomy, SILS for colon cancer and SILS for rectal cancer were reported by Remzi *et al.* [5] and Bulut and Nielsen [6]. Following clinical studies that compared the outcomes of SILS and CLS for colorectal surgery, some meta-analyses reported promising results, although there were some inconsistencies [36–39]. However, no meta-analysis has addressed the outcomes of SILS specifically for rectal surgery, which is technically more difficult than colon cancer surgery. Because rectal resection is performed in the confined space of the pelvic cavity, the range of motion of the working instruments is limited and traction to maintain a proper surgical plane is difficult. It is a matter of concern whether SILS meets this challenge without compromising surgical outcomes. Questions regarding this topic should be answered by studies on rectal surgery alone.

To the best of our knowledge, this study is the first meta-analysis to compare the outcomes of SILS and CLS in rectal cancer. The key findings of this study are as follows: i) SILS showed superior outcomes in terms of incision length, postoperative pain, and hospital stays; ii) SILS and CLS were similar as regards surgical difficulty-related outcomes; and iii) importantly, the perioperative mortalities, complications, and pathologic qualities of SILS and CLS were comparable.

Incision lengths were significantly shorter for SILS, with a mean difference of 49.58 mm. For rectal surgery, SILS uses only one incision for working port insertion and specimen extraction, whereas CLS usually requires 4 or 5 incisions for port insertion. Thus, the incision length is shorter for SILS, and the present study shows this is a clear advantage of SILS over CLS.

Postoperative pain is related to wound length and site, and because SILS involves one wound only, postoperative pain can be reduced compared with CLS. Our analysis showed that pain scores were significantly lower in the SILS group and that the mean intergroup differences increased from POD 1 (MD = 0.96) to POD 2 (MD = 1.43). When the intergroup difference of postoperative pain score is relatively small, it is probably clinically insignificant, and the morphine requirements are probably the same. It may explain why the group morphine requirements were similar on POD 1 and 2, but on POD 3 they were lower in the SILS group than in the CLS group. Specifically, our study showed that postoperative pain reduced faster in the SILS group. Furthermore,

hospital stay was significantly shorter in the SILS group (mean difference of 1.17 days). The reduced postoperative pain and lower incidence of overall complications can explain the earlier discharges observed in the SILS group.

Operative time, blood loss, and conversion rate to laparotomy are related to surgical difficulty, and these outcomes were similar in the SILS and CLS groups. The technical difficulties of SILS are due to the parallel entry of the laparoscope and working instruments, which makes triangulation restrictive, traction for proper dissection less effective, and limits the surgical view. Also, collisions between the laparoscope and working instruments can occur outside the trocar. Several adaptive methods can be used to minimize these difficulties. First, curved or articulating instruments can overcome the limitations associated with parallel insertion and allow more effective triangulation. Second, a flexible laparoscope can overcome the limited surgical view caused by parallel insertion of the scope and instruments. Third, a 3-dimensional laparoscope can improve depth perception limitations caused by parallel laparoscope and instrument insertion. Fourth, a laparoscope with a right-angled light cord or a bariatric length laparoscope or instruments can prevent external collisions between the operator and assistant. And finally, operators can use the instruments in a cross-hand manner to overcome range of motion limitations [40]. Most of the included studies did not specify the methods to overcome the technical difficulties of SILS, and only 2 studies identified the use of flexible laparoscopes.

In addition to these technical tips, experience also enables surgeons to cope with the surgical difficulties posed by SILS. Some researchers analysed the learning curve for single-incision colon cancer surgery. In a study by Kim *et al.*, the learning period for single-incision laparoscopic anterior resection of sigmoid colon cancer was between 61 and 65 cases with an operation time of 173 min for the 65th case [41], and Kirk *et al.* reported a learning period for single-incision laparoscopic right colectomy of 40 cases with an operation time of 97 min [42]. These studies showed that the operation time was optimized after the learning curve in surgeons with experience. In all studies included in our meta-analysis, expert laparoscopic colorectal surgeons performed the operations. We suppose this contributed to the comparable operative outcomes of SILS to CLS.

Perioperative mortalities, reoperation and readmission rates, and times to first bowel movement were similar in the SILS and CLS groups. Regarding complications, no significant intergroup difference was observed for intraoperative complications, anastomotic leakage, surgical site infection, gastrointestinal motility dysfunction, or pulmonary, cardiovascular, or urologic complications. We suppose that the similar postoperative outcomes of SILS to CLS were in part due to the surgeons' expertise. In a study by Jiang *et al.* the operators had experience of over 100 laparoscopic colorectal surgeries [13]. In a study by Bulut *et al.* the surgeons had long-standing experience of laparoscopic colorectal surgery [17], and in a study by Sourrouille *et al.* a specialized, skilled laparoscopic surgeon performed the operations [24]. Tei *et al.* stated that they conduct SILS as a reasonable alternative to CLS for upper rectal cancer in their department [14]. Sirikurnpiboon stated that more than 500 colorectal cancer surgeries were performed during the study period (2011 to 2014) [11]. Nerup *et al.* concluded that SILS for rectal cancer appears safe and feasible when performed by highly experienced laparoscopic colorectal surgeons [16]. Thus, we believe that surgeons' experience contributes to overcoming the technical issues of SILS and obtaining feasible outcomes for rectal cancer surgery.

In addition, pooled analysis showed that the overall complication incidence was significantly lower for SILS than for CLS (odds ratio = 0.64). We attribute the advantages of SILS over CLS to less surgical trauma, and thus to less systemic inflammatory response, fewer complications, and faster recovery. However, we found little evidence to support the lesser effect of SILS on inflammatory response. Only Bulut *et al.* assessed postoperative levels of immunologic markers, i.e. of C-reactive protein (CRP), interleukin-6 (IL-6), and tissue inhibitor of metalloproteinases-1 (TIMP-1), and reported that postoperative CRP levels at 6 and 24 h after skin incision were significantly lower after SILS than after CLS [17]. In previous studies that compared laparoscopic and open surgery, inflammatory immune response was consistently shown to be attenuated after laparoscopic surgery [43–49]. However, conflicting results were reported for SILS versus CLS [17, 50, 51]. Additional studies are needed to clarify this issue.

One of the advantages of SILS over CLS is that it better preserves abdominal wall integrity, and thus SILS would be expected to reduce the risk of

incisional hernia. This topic was only investigated by Jiang *et al.* [13], who reported one incisional hernia after SILS and none after CLS, which was not a significant difference.

Pathological outcomes of SILS as assessed by numbers of harvested lymph nodes, PRM and DRM length, CRM involvement, the incidence of incomplete mesorectal grade, and R0 resection rate were similar to those of CLS. Oncologically proper resection is a fundamental principle of rectal cancer surgery, and it includes total mesorectal excision (TME) with proper lymph node dissection. TME quality could be assessed by CRM involvement and the integrity of the TME specimen, which is a key determinant for evaluating the safety of laparoscopic rectal cancer surgery [52, 53]. The National Comprehensive Cancer Network (NCCN) guideline recommendations are as follows: to examine a minimum of 12 lymph nodes; to acquire an adequate CRM and an adequate distal margin (1 to 2 cm for distal rectal cancers); and to evaluate the quality of mesorectum for low rectal cancers [54]. All pathologic results presented from the included studies followed the NCCN guidelines, and there was no difference between SILS and CLS.

We summarize the results of this meta-analysis as follows. First, SILS for rectal cancer has clear benefits over CLS in terms of incision length, postoperative pain, and hospital stay. Second, SILS for rectal cancer produced postoperative clinical outcomes comparable to CLS. Third, SILS for rectal cancer produced acceptable pathological outcomes and maintained oncological principles.

Only a decade has passed since SILS was first introduced to treat rectal cancer in 2010. Thus, relatively few clinical studies have been performed, and no long-term follow-up data are available to assess the oncological safety of SILS versus CLS for rectal cancer. It is the first limitation of this study. However, our meta-analysis revealed promising results of SILS for rectal cancer with respect to perioperative and pathologic outcomes. Also, 3 of the studies included in our meta-analysis showed similar short-term oncologic outcomes for SILS and CLS in terms of recurrence, disease-free survival, and overall survival rates. Thus, we consider the results of this study promising and hope they encourage more surgeons to undertake future clinical studies.

The various modalities used to overcome the technical difficulties associated with SILS might affect surgical outcomes. A flexible laparoscope was used for SILS in 2 studies [13, 14], a 5 mm 30° scope in 2 studies [16, 17], and a 0° scope in one study [24], and 3 different types of ports were used for SILS, namely: the SILS™ Port (Covidien, USA) in 3 studies [13, 16, 17], the E-Z access Port (Hakko, Japan) in one [14], and the GelPOINT Port (Applied Medical, Canada) in one [24]. Hence, the heterogeneity of the surgical instruments used is also a limitation. However, no other instrumental or methodological differences were reported in the included studies, and expert laparoscopic colorectal surgeons performed all operations. Thus, we consider that the use of different surgical instruments is unlikely to impact our findings.

Conclusions

This study is the first meta-analysis to compare the outcomes of SILS and CLS for rectal cancer and was conducted using data from the most recent clinical studies. SILS was found to have the following merits over CLS: smaller wounds, less pain, and shorter hospital stay. Furthermore, the study showed that SILS is a safe treatment for rectal cancer that does not compromise clinical or pathological outcomes when performed by experienced laparoscopic colorectal surgeons. Future studies are required to determine the long-term oncologic outcomes of SILS for rectal cancer.

Conflict of interest

The authors declare no conflict of interest.

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