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REVIEW ARTICLE

Laparoscopic appendicectomy is superior to open surgery for complicated appendicitis

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Abstract

Background Over the last three decades, laparoscopic appendicectomy (LA) has become the routine treatment for uncomplicated acute appendicitis. The role of laparoscopic surgery for complicated appendicitis (gangrenous and/or perforated) remains controversial due to concerns of an increased incidence of post-operative intra-abdominal abscesses (IAA) in LA compared to open appendicectomy (OA). The aim of this study was to compare the outcomes of LA versus OA for complicated appendicitis.

Methods A systematic literature search following PRISMA guidelines was conducted using MEDLINE, EMBASE, PubMed and Cochrane Database for randomised controlled trials (RCT) and case–control studies (CCS) that compared LA with OA for complicated appendicitis.

Results Data from three RCT and 30 CCS on 6428 patients (OA 3,254, LA 3,174) were analysed. There was no significant difference in the rate of IAA (LA = 6.1% vs. OA = 4.6%; OR = 1.02, 95% CI = 0.71–1.47, $p = 0.91$). LA for complicated appendicitis has decreased overall post-operative morbidity (LA = 15.5% vs. OA = 22.7%; OR = 0.43, 95% CI: 0.31–0.59, $p < 0.0001$), wound infection, (LA = 4.7% vs. OA = 12.8%; OR = 0.26, 95% CI: 0.19–0.36, $p < 0.001$), respiratory complications (LA = 1.8% vs. OA = 6.4%; OR = 0.25, 95% CI: 0.13–0.49, $p < 0.001$), post-operative ileus/small bowel obstruction (LA = 3.1% vs. OA = 3.6%; OR = 0.65, 95% CI: 0.42–1.0, $p = 0.048$) and mortality rate (LA = 0% vs. OA = 0.4%; OR = 0.15, 95% CI: 0.04–0.61, $p = 0.008$). LA has a significantly shorter hospital stay (6.4 days vs. 8.9 days, $p = 0.02$) and earlier resumption of solid food (2.7 days vs. 3.7 days, $p = 0.03$).

Conclusion These results clearly demonstrate that LA for complicated appendicitis has the same incidence of IAA but a significantly reduced morbidity, mortality and length of hospital stay compared with OA. The finding of complicated appendicitis at laparoscopy is not an indication for conversion to open surgery. LA should be the preferred treatment for patients with complicated appendicitis.

Keywords Laparoscopic appendicectomy · Open appendicectomy · Complicated appendicitis · Gangrenous appendicitis · Perforated appendicitis · Appendiceal abscess

Acute appendicitis is one of the most common acute general surgical presentations in the world, with the incidence ranging from 100 per 100,000 individuals in North America to 206 per 100,000 individuals in South Korea [1]. Since the introduction of laparoscopic appendectomy (LA) in 1983 by Semm [2], LA has been performed with increasing frequency for treatment of acute appendicitis [3–5]. Although open appendectomy (OA) was the treatment of choice in the early 1990s, LA for uncomplicated appendicitis was gold standard by early 2000s [6, 7]. The advantages of LA include reduced overall post-operative morbidity and wound infection, a shorter length of stay (LOS), less post-operative pain and earlier post-operative recovery [8, 9].

However, the role of LA in complicated appendicitis remains controversial due to reports of a higher incidence of intra-abdominal abscess (IAA) and longer operating time [10, 11]. Three recent meta-analyses comparing LA and OA

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in complicated appendicitis found that LA had reduced surgical site infection with no difference in incidence of IAA, overall morbidity and mortality but significantly longer operating time [12–14]. Nonetheless, because of earlier studies, some surgeons still prefer OA or conversion from LA to OA for complicated acute appendicitis with recent publications continuing to raise concern about the increased risk of IAA associated with LA [15–17]. The aim of this study was to compare LA and OA for the surgical treatment of complicated appendicitis and provide evidence-based guidance to the selection of the most appropriate operative technique.

Methods

Study protocol

A systematic search was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [18]. An institutional ethics approval was not required for this meta-analysis. The following databases were searched for relevant studies: MEDLINE, PubMed (from 1946), EMBASE (from 1949), Cochrane Database, Google Scholar and Google. The search terms "laparoscopic", "laparoscopy", "open", "appendectomy", "appendicitis" and "complicated appendicitis" were used in combinations. The reference lists of selected articles were searched for relevant studies. There were no language restrictions or any other exclusions.

Study selection

All randomised controlled trials (RCT) and case-controlled studies (CCS) that compared LA with OA for complicated appendicitis from 1990 to 2017 were included in this meta-analysis. All other non-comparative studies such as case series and case reports were excluded.

Data extraction

The data were extracted and critically appraised by two independent reviewers (GS and GE). The data were extracted using a standardised data form and included the following: *Patient and operative information*: age, gender, BMI, ASA classification, duration of symptoms, definition of complicated appendicitis and intra-operative techniques. *Primary outcomes*: various types of morbidity, conversion from LA to OA, re-operation rates and mortality. *Secondary outcomes*: mean operating time (OT), LOS, solid food resumption and duration of intravenous (IV) antibiotic administration.

Statistical analysis

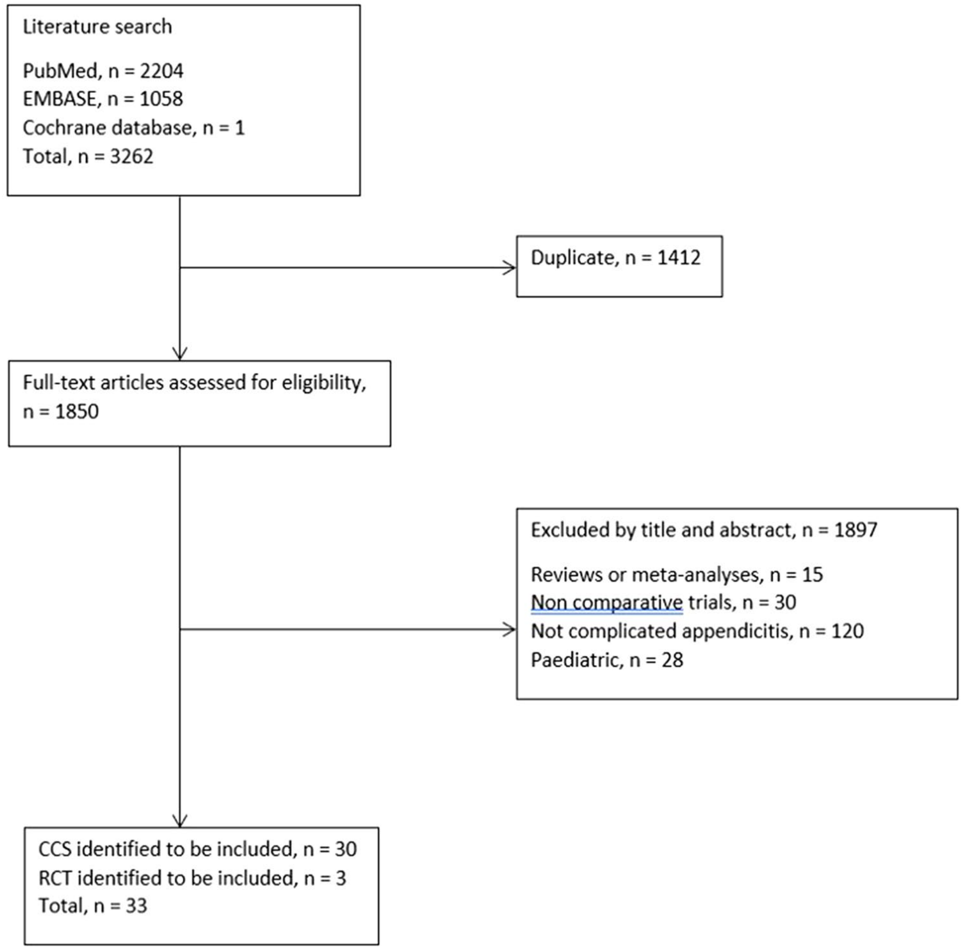
Pooled odds ratios and 95% confidence intervals were calculated for patient outcomes using a random effects model [19]. Weighted mean difference was calculated for continuous variables such as mean OT and total LOS [20]. Relative risk ratio was calculated for dichotomous variables such as post-operative morbidity and mortality [20]. Intention-to-treat analysis was performed where patients were converted from LA to OA or when there were missing data. Yates half correction was used in studies that reported no events for outcomes [20, 21]. Heterogeneity was tested with Cochran's Q statistic, with $p < 0.10$ indicating heterogeneity, and the degree of heterogeneity was quantified using the *I2* statistic, which represents the percentage of the total variability across studies due to heterogeneity [21, 22]. *I2* values of 25, 50 and 75% corresponded to low, moderate and high degrees of heterogeneity [21, 22]. The quality of each RCT was assessed with a Jadad Score [23]. A risk bias assessment was performed for each CCS using the Newcastle–Ottawa Score for non-randomised case–control studies [24].

Results

The literature search generated a total of 3262 articles. Articles were excluded based on titles, abstracts, full texts or a combination of these criteria. A total of three RCT [25–27] and 30 CCS [28–57] were included in this meta-analysis (Fig. 1; Table 1). In these studies, complicated appendicitis was defined as one or more of the following operative findings: perforated appendicitis, generalised peritonitis, presence of frank pus, gangrenous appendicitis or an abscess. Approximately one-fifth of the patients had appendiceal abscess, one-fifth had perforated appendicitis and in one-third, the exact finding was not clearly defined.

There were a total of 6428 patients, with 3254 patients having LA and 3174 patients having OA (Table 1). The quality of the RCT was moderate with a score of two or three (Table 1).The Newcastle–Ottawa Scores were good, ranging from 6 to 8, with the majority (83.%) having a score of seven and only two (6.7%) having a score of six (Table 1).The average age of patients was 39.2 years in LA group and 41 years in OA group ($p = 0.56$). Approximately two-thirds of the patients were female (Table 2). There was no difference in ASA classification between LA and OA groups (Table 2). There were no significant differences between the groups for body mass index (BMI) (average BMI 23.5 for LA vs. 22.7 for OA, $p = 0.3$) and duration of symptoms (average duration LA = 3.1 days vs. 4.0 days, $p = 0.1$) (Table 2).

Fig. 1 PRISMA diagram



Twenty-four studies described the operative technique for appendiceal stump closure (Table 1) [29–32, 34, 37–43, 45–50, 52–57]. For OA, all the patients underwent standard open technique via McBurney's incision with a purse string closure of appendiceal stump. For LA, nine studies used an Endoloop ligation for all cases [37, 40, 43, 45, 46, 53, 54, 56, 57], six studies used either Endoloop or Endostaplers [32, 38, 41, 47, 52, 55], five studies used only Endostaplers [29, 30, 39, 42, 49] and one study each used Endoclip [31], Endosuture [50] and either Endoloop, Endostaplers or Endoclip [48].

Primary outcome

Conversion to open surgery

Twenty-eight studies reported the incidence of conversion from LA to OA [26–34, 36–39, 41, 42, 44–50, 52–57] with 333 patients (11.3%) requiring conversion. The reason for conversion was reported in 193 (57.9%) patients. These included difficulty in dissection and/or friable appendix ($n=50$, 15%), caecal inflammation or a necrotic appendix base ($n=43$, 13%), unable to visualise the appendix base and/or difficult anatomy ($n=36$, 10.8%), extensive peritonitis or pus ($n=33$, 10%), appendiceal mass ($n=15$, 4.5%), lack of space ($n=5$, 1.5%), surgeon's decision ($n=4$, 1.2%), equipment failure ($n=3$, 0.9%), unclear diagnosis ($n=1$), obesity ($n=1$), bowel injury ($n=1$) and bleeding ($n=1$). All patients having conversion to open surgery were included in LA group for analysis on an intention-to-treat basis.

Post-operative morbidity

Thirty-one studies reported the incidence of post-operative morbidity [26–34, 36–57]. In the CCS cohort, the overall morbidity was significantly lower in the LA group ($n=479$, 15.5%) compared with the OA group ($n=671$, 22.7%) (OR = 0.43, 95% CI = 0.31–0.59, $p<0.001$) (Fig. 2; Table 3). Although there was a lower incidence of morbidity for LA (20.8%) compared to OA (32.3%) in the RCT cohort, this was not statistically significant (OR = 0.61, 95% CI = 0.18–2.13, $p=0.44$). The reported types of morbidity included IAA, wound infection, ileus/small bowel obstruction, respiratory complications, incisional hernia, enteric

Table 1 Study demographics

Author	Year	Country	Type	Jadad score	Nos	No. of patients			Intra-operative technique	
						Total	Lap	Open	Lap	Open
Khalili [28]	1999	America	CCS		7	275	110	165	–	–
Stoltzing [29]	2000	Germany	CCS		7	125	80	45	Endo GIA	Purse string suture
Piskun [30]	2001	America	CCS		7	52	28	24	Endo GIA	Purse string suture
Wullstein [31]	2001	Germany	CCS		7	299	217	82	Endoclip	Purse string suture
So [32]	2002	Singapore	CCS		7	231	85	146	Endoloop/stapler	Purse string suture
Kouwenhoven [33]	2005	Netherlands	CCS		8	55	34	21	–	–
Lin [34]	2006	Taiwan	CCS		8	229	99	130	Endoloop/endoclip	Purse string suture
Towfigh [35]	2006	America	CCS		6	85	19	66	–	–
Pokala [36]	2007	America	CCS		7	104	43	61	–	–
Yau [37]	2007	Hong Kong	CCS		7	244	175	69	Endoloop	Purse string suture
Kirshtein [38]	2007	Israel	CCS		7	98	50	48	Endoloop/stapler	Purse string suture
Fukami [39]	2007	Japan	CCS		7	73	39	34	Endolinear cutter	Purse string suture
Kehagias [40]	2008	Greece	CCS		7	85	38	47	Endoloop	Purse string suture
Park [41]	2009	Korea	CCS		7	587	200	387	Endoloop/endo GIA	Purse string suture
Katsuno [42]	2009	Japan	CCS		7	230	146	84	Endo stapler	Purse string suture
Garg [43]	2009	India	CCS		8	110	49	61	Endoloop	Purse string suture
Sleem [44]	2009	America	CCS		6	247	223	24	–	–
Khiria [45]	2011	India	CCS		7	117	106	11	Endoloop	Purse string suture
Lim [46]	2011	Korea	CCS		7	60	38	22	Endoloop	Purse string suture
Ferranti [47]	2012	Italy	CCS		7	38	18	20	Endoloop/stapler	Purse string suture
Schietroma [25]	2012	Italy	RCT	2		147	73	74	–	–
Galli [48]	2013	Switzerland	CCS		7	169	106	63	Endoloop/endoclip/stapler	Purse string suture
Dimitriou [49]	2013	Germany	CCS		7	150	84	66	Endo GIA	Purse string suture
Mohamed [50]	2013	Egypt	CCS		7	214	132	82	Endosuture	Purse string suture
Wilson [51]	2013	UK	CCS		7	50	25	25	–	–
Yeom [52]	2014	Korea	CCS		7	84	25	59	Endoloop/endo GIA	Purse string suture
Quezada [53]	2015	Chile	CCS		7	227	97	130	Endoloop	Purse string suture
Thomson [26]	2015	South Africa	RCT	3		81	39	42	–	–
Kim [54]	2016	Korea	CCS		7	207	169	38	Endoloop	Purse string suture
Horvath [55]	2016	Germany	CCS		7	1516	590	926	Endoloop/endo GIA	Purse string suture
Taguchi [27]	2016	Japan	RCT	3		81	42	39		
Wu [56]	2017	China	CCS		7	115	56	59	Endoloop	Purse string suture
Yang [57]	2017	China	CCS		7	43	19	24	Endoloop	Purse string suture
Total						6428	3254	3174		

NOS = Newcastle–Ottawa Scale

fistula, appendiceal stump leakage, abdominal wall haematoma, bleeding and retained appendix (Table 3).

Thirty-one studies reported the incidence of IAA [26–34, 36–57]. In the CCS cohort, there was no significant difference in IAA incidence between the LA and OA groups [LA = 189 (6.1%) patients compared to OA 135 (4.6%) patients; OR = 1.02, 95% CI = 0.71–1.47, $p = 0.91$] (Fig. 3; Table 3). There was evidence of statistical heterogeneity ($I^2 = 43.86\%$, $p = 0.01$). Similarly, there was no difference in IAA rate in the RCT group [LA = 13 patients (8.4%) vs. OA = 14 patients (9.0%): OR = 0.93, 95% CI = 0.19–4.56, $p = 0.93$]. The mode of treatment of the IAA was reported in 212 (60.4%) patients. There was no difference in the incidence of different treatment modalities between LA and OA: 123 (38.4%) patients underwent radiology-guided aspiration or drainage (LA 35.8% vs. OA = 41.8%, OR = 1.00, 95% CI = 0.61–1.65, $p = 0.998$), 48 (15%) patients were treated with IV antibiotics (LA 17.3% vs. OA = 12.1%, OR = 1.71, 95% CI = 0.91–3.23, $p = 0.095$) and 41 (12.8%) patients required re-operation (LA 12.8% vs. OA = 12.8%, OR = 1.00, 95% CI = 0.52–1.93, $p = 0.999$).

Thirty studies reported the incidence of wound infection [26, 27, 29–34, 36–50, 52–57]. In the CCS group, the wound infection rate was significantly lower in the

Table 2 Patient co-morbidities and operative findings for combined RCT and CCS data

	LA	OA	*p* value
Age (years)	39.2 ± 11.9	41.0 ± 13.2	0.56
Male, *n* (%)	1256 (38.6)	1569 (49.4)	0.06
ASA 1, *n* (%)	496 (15.2)	400 (12.6)	0.48
ASA 2, *n* (%)	167 (5.1)	161 (5.1)	0.66
ASA 3, *n* (%)	48 (1.5)	50 (1.6)	0.1
ASA 4, *n* (%)	1 (0)	2 (0)	0.56
ASA 5, *n* (%)	0 (0)	0 (0)	N/A
ASA = not defined, *n* (%)	2542 (78.2)	2561 (80.7)	N/A
BMI	23.5	22.7	0.3
Duration of symptoms (days)	3.1	4.0	0.1
Perforated appendix, *n* (%)	886 (27.2)	848 (26.7)	N/A
Peritonitis, *n* (%)	6 (0.2)	9 (0.3)	N/A
Suppurative, *n* (%)	75 (2.3)	58 (1.8)	N/A
Gangrenous, *n* (%)	161 (4.9)	121 (3.8)	N/A
Abscess, *n* (%)	653 (20.1)	910 (28.7)	N/A
Unclassified, *n* (%)	1473 (45.3)	1228 (38.7)	N/A

LA group (*n* = 137, 4.7%) compared with the OA group (*n* = 354, 12.8%) (OR = 0.26, 95% CI = 0.19–0.36, $p < 0.001$) (Table 3). There was evidence of statistical heterogeneity ($I^2 = 41.33\%$, $p = 0.01$). Although there was a lower incidence in the RCT group, it was not statistically significant [LA = 19 patients (12.3%) and OA = 36 patients (23.2%); OR = 0.54, 95% CI = 0.12–2.44, $p = 0.42$].

Seventeen studies reported the incidence of post-operative ileus/small bowel obstruction [27, 29, 30, 37, 40–43, 46, 48–50, 52–56]. The post-operative ileus/small bowel obstruction rate was significantly lower of in the LA group (*n* = 59, 3.1%) compared with the OA group (*n* = 79, 3.6%) (OR = 0.65, 95% CI = 0.42–1.00, $p = 0.048$) (Table 3). Although there was some evidence of statistical heterogeneity, it was not significant ($I^2 = 10.5\%$, $p = 0.33$).

Nine studies reported the incidence of respiratory complications [36, 38, 40, 42, 43, 45, 48, 50, 56]. There was a significantly lower incidence in the LA group (1.8%) patients compared to the OA group (6.4%) (OR = 0.25, 95% CI = 0.13–0.49, $p < 0.0001$) (Table 3). There was no evidence of statistical heterogeneity ($I^2 = 0\%$, $p = 0.74$).

Five studies reported the incidence of subsequent incisional hernia [39, 50, 53–55]. The incidence was similar with four (0.4%) patients in the LA group compared to 13 (1.1%)

Study name	Odds ratio	Lower limit	Upper limit	p-Value
	Statistics for each study			
Khalili 1999	1.00	0.28	3.63	1.000
Stoltzing 2000	1.25	0.54	2.87	0.604
Piskun 2001	0.79	0.21	2.91	0.723
Wullstein 2001	0.36	0.18	0.70	0.003
So 2002	0.47	0.23	0.95	0.037
Kouwenhoven 2005	0.58	0.11	3.19	0.531
Lin 2006	0.41	0.22	0.75	0.004
Pokala 2007	1.25	0.56	2.79	0.594
Yau 2007	0.40	0.16	0.98	0.045
Kirshtein 2007	0.95	0.31	2.96	0.934
Fukami 2007	0.11	0.04	0.34	0.000
Kehagias 2008	0.60	0.23	1.57	0.299
Park 2009	0.85	0.50	1.46	0.559
Katsuno 2009	0.15	0.07	0.32	0.000
Garg 2009	0.23	0.10	0.52	0.000
Sleem 2009	0.05	0.02	0.14	0.000
Khiria 2011	0.02	0.00	0.17	0.000
Lim 2011	0.50	0.14	1.80	0.289
Ferranti 2012	0.86	0.19	3.85	0.841
Galli 2013	0.43	0.23	0.81	0.010
Dimitriou 2013	0.63	0.28	1.40	0.252
Mohamed 2013	0.33	0.18	0.62	0.001
Wilson 2013	1.88	0.52	6.84	0.337
Yeom 2014	1.16	0.42	3.20	0.770
Quezada 2015	0.56	0.26	1.22	0.145
Kim 2016	0.30	0.14	0.63	0.002
Horvath 2016	0.44	0.24	0.82	0.010
Wu 2017	0.02	0.00	0.08	0.000
Yang 2017	1.29	0.17	10.15	0.806
	0.43	0.31	0.59	0.000

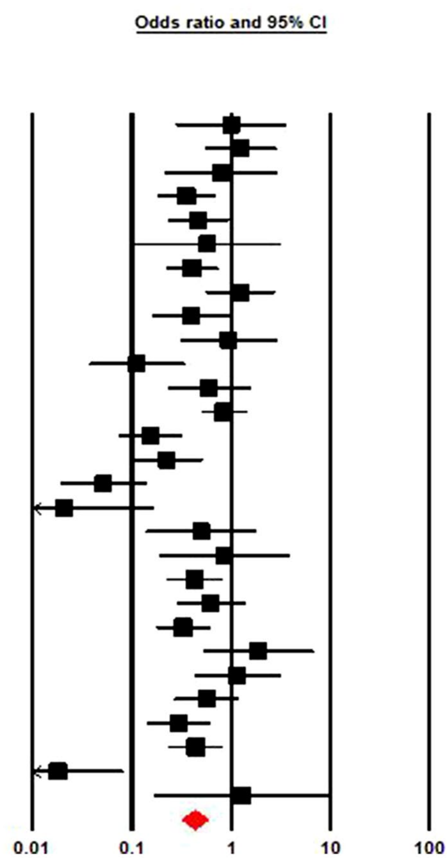


Fig. 2 Forest plot for overall post-operative morbidity in the CCS group. This favours LA with OR = 0.43 (95% Cl = 0.31–0.59, $p < 0.001$)

Table 3 Primary outcomes for the RCT and CCS groups

Morbidity	Type	# of studies	LA (%)	OA (%)	OR	95% CI	*p* value
Overall post-operative morbidity	RCT	3	20.8	32.3	0.61	0.18–2.13	0.441
Overall post-operative morbidity	CCS	29	15.5	22.7	0.43	0.31–0.59	< 0.001
IAA	RCT	3	8.4	9.0	0.93	0.19–4.56	0.929
IAA	CCS	29	6.1	4.6	1.02	0.71–1.47	0.912
IAA radiology-guided drainage	CCS	15	35.8	41.8	1.0	0.61–1.65	0.998
IAA IV antibiotics	CCS	11	17.3	12.1	1.71	0.91–3.23	0.095
IAA re-operation	CCS	8	12.8	12.8	1.0	0.52–1.93	0.999
Wound complications	RCT	3	12.3	23.2	0.54	0.12–2.44	0.421
Wound complications	CCS	27	4.7	12.8	0.26	0.19–0.36	< 0.001
Post-operative ileus/SBO	CCS	17	3.1	3.6	0.65	0.42–1.00	0.048
Respiratory complications	CCS	9	1.8	6.4	0.25	0.13–0.49	< 0.001
Incisional hernia	CCS	5	0.4	1.1	0.49	0.06–3.87	0.497
Enteric fistula	CCS	4	0.5	1.9	0.28	0.06–1.31	0.106
Stump leakage	CCS	1	4	1.7	N/A	N/A	N/A
Abdominal wall haematoma	CCS	2	0.5	1.2	N/A	N/A	N/A
Bleeding	CCS	2	1.1	0	N/A	N/A	N/A
Retained appendix	CCS	2	0.4	0	N/A	N/A	N/A
Unclassified	CCS	7	2.5	4.4	N/A	N/A	N/A
Reoperations	CCS	11	2.6	2.2	0.78	0.45–1.34	0.366
Mortality	RCT	3	0	0	N/A	N/A	N/A
Mortality	CCS	25	0	0.4	0.15	0.04–0.61	0.008

Study name	Odds ratio	Lower limit	Upper limit	p-Value
	Statistics for each study			
Khalili 1999	1.00	0.28	3.63	1.000
Stoltzing 2000	2.06	0.41	10.38	0.380
Piskun 2001	1.35	0.42	4.35	0.616
Wullstein 2001	0.75	0.22	2.55	0.641
So 2002	0.34	0.02	7.12	0.486
Kouwenhoven 2005	0.59	0.08	4.57	0.617
Lin 2006	0.98	0.22	4.50	0.984
Pokala 2007	21.32	1.17	389.40	0.039
Yau 2007	1.33	0.36	5.00	0.670
Kirshtein 2007	1.30	0.28	6.16	0.737
Fukami 2007	0.88	0.12	6.50	0.888
Kehagias 2008	2.56	0.22	29.31	0.451
Park 2009	1.03	0.45	2.34	0.952
Katsuno 2009	0.56	0.14	2.31	0.426
Garg 2009	0.30	0.09	0.98	0.045
Sleem 2009	0.20	0.08	0.51	0.001
Khiria 2011	0.12	0.03	0.53	0.005
Lim 2011	3.08	0.14	67.16	0.474
Ferranti 2012	3.80	0.36	40.34	0.268
Galli 2013	1.19	0.56	2.53	0.657
Dimitriou 2013	1.05	0.23	4.86	0.950
Mohamed 2013	0.78	0.28	2.19	0.643
Wilson 2013	1.88	0.52	6.84	0.337
Yeom 2014	7.13	1.28	39.68	0.025
Quezada 2015	2.75	0.49	15.35	0.248
Kim 2016	1.13	0.13	9.94	0.914
Horvath 2016	7.97	1.74	36.48	0.008
Wu 2017	0.46	0.17	1.24	0.125
Yang 2017	1.28	0.07	21.86	0.866
	1.02	0.71	1.47	0.912

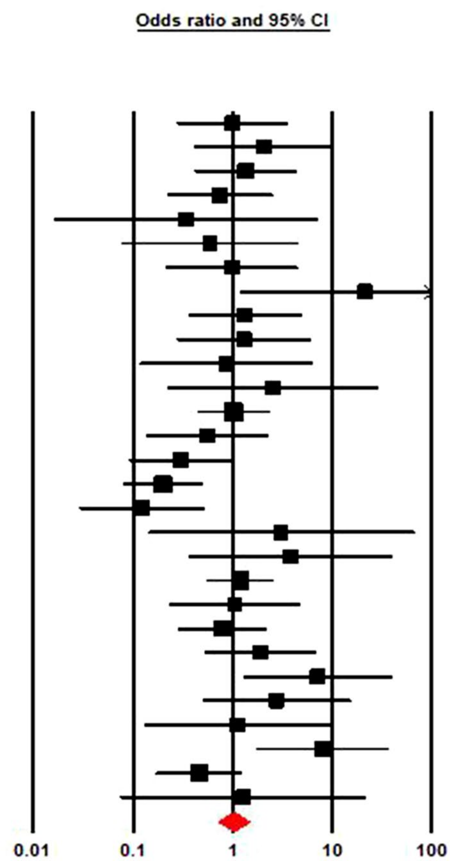


Fig. 3 Forest plot for IAA in the CCS group. There is no difference in both groups with OR = 1.02 (95% CI = 0.71–1.47, $p = 0.91$)

patients in the OA group (OR = 0.49, 95% CI = 0.06–3.87, $p = 0.497$). There was evidence of statistical heterogeneity ($I^2 = 62.44\%$, $p = 0.03$).

Four studies reported the incidence of enteric fistula [34, 39, 45, 50]. The incidence between LA and OA was similar with two (0.5%) patients in the LA group and five (1.9%) patients in the OA group (OR = 0.28, 95% CI = 0.06–1.31, $p = 0.106$). There was no evidence of statistical heterogeneity ($I^2 = 0\%$, $p = 0.96$).

Eleven studies reported the incidence of re-operation [27, 29, 30, 32, 34, 36, 39, 41, 48, 49, 55]. The re-operation rate was similar in both groups (LA = 36, 2.6% vs. OA = 42, 2.2%; OR = 1.0, 95% C = 0.52–1.93, $p = 0.999$). There was no evidence of statistical heterogeneity ($I^2 = 0\%$, $p = 0.59$). The indications for re-operation included the following: IAA (51.3%), wound dehiscence (21.1%), unresolved small bowel obstruction (1.3%) and no indication provided (26.3%).

Mortality

Twenty-eight studies reported mortality [26–29, 32–34, 37–50, 52–57]. There was no mortality in the LA group compared 13 (0.4%) deaths in the OA group (OR = 0.15, 95% CI = 0.04–0.61, $p = 0.008$). There was no evidence of statistical heterogeneity ($I^2 = 0\%$, $p = 0.82$). The reported causes of mortality were multi-organ failure, respiratory, cardiac and renal complications.

Secondary outcomes

Twenty-five studies reported the operative duration (OT) [26–30, 32, 34, 36–39, 42–46, 48–50, 52–57] which was similar (LA group 74.6 min ± 19.6 and OA group 82.2 min ± 24.7, $p = 0.19$) (Table 4). Thirty studies reported the average LOS [26–30, 32–34, 36–39, 42–57] which was significantly shorter for the LA group (6.4 ± 2.8 days) compared to the OA group (8.9 ± 4.8 days) ($p = 0.02$) (Table 4). Twelve studies reported the average time to resume normal diet [26–30, 32–34, 36–39, 42–57] which was significantly shorter for the LA group (2.7 ± 0.9 days) compared with the OA group (3.7 ± 1.1 days) ($p = 0.03$) (Table 4). Eight studies reported the duration of IV antibiotics and there was no significant difference between LA and OA ($p = 0.49$) (Table 4).

Discussion

The results of this meta-analysis clearly demonstrate a significant benefit in performing LA in complicated appendicitis compared with OA. There was no difference in the incidence of IAA, but a significant reduction in the overall mortality with LA. The incidence post-operative wound infection, respiratory complications and ileus/SBO were also significantly lower in the LA group compared to the OA group. There was a significant reduction in LOS and time for resumption of solid food in the LA group. As expected, the mortality in both groups was low; nonetheless, the mortality was significantly higher in the OA group.

Previous RCT and meta-analyses have failed to reveal this clear benefit for LA in complicated appendicitis. A major contributor to this is the relatively low case numbers within the RCT. The use of CCS resulted in an over twentyfold increase in cases for comparison, allowing for a clear distinction to be demonstrated between LA and OA. Our research group has reported a similar phenomenon when comparing early laparoscopic cholecystectomy (LC) with delayed LC in patients presenting with acute cholecystitis [58, 59]. Using only RCT, there was no significant difference in overall morbidity, common bile duct injury (CBDI) and bile leak [58]. Performing a meta-analysis using CCS resulted in a twenty-fivefold increase in patient numbers and demonstrated a 50% reduction in overall morbidity, CBDI, bile leaks and mortality when an early LC is performed for acute cholecystitis [60].

As the majority of the studies used in the present study were CCS, there may be some risks of bias of some form that may favours better outcomes in the LA group. One potential selection bias is the patient co-morbidities resulting in bias that may favour either LA or OA. As the patient characteristics in both groups including sex, gender, BMI and ASA scores were similar, a selection bias based on co-morbidities is most unlikely. Another potential bias is the nature or extent of disease may be different due to a selection bias that may favour one approach. Although there was a range of definitions for complicated appendicitis across the various studies, there was no significant difference in the distribution of disease between the LA and OA groups. Similarly, there was no significant difference in the duration of symptoms between LA and OA. The

Table 4 Secondary outcomes for combined RCT and CSS data

	# of studies	LA	OA	*p* value
Mean length of hospital stay (days)	30	6.4 ± 2.8	8.9 ± 4.8	0.02
Mean OT (min)	25	82.2 ± 24.7	74.6 ± 19.6	0.19
Solid food resumption (days)	12	2.7 ± 0.9	3.7 ± 1.1	0.03
IV Abx (day)	8	5.5 ± 1.8	6.3 ± 3.2	0.49

duration of symptoms is important, as it is one of the main determinants for the presence of complicated appendicitis [61–63]. Therefore, the lack of randomisation in the CCS appears unlikely to have created a selection bias between the two groups. In order to demonstrate significant differences in outcomes for complicated appendicitis, a RCT involving 511 patients in each group would be required to demonstrate a 30% reduction in overall mortality, 204 patients in each group to show a 40% reduction in wound infection rate and 4161 to demonstrate a 33% difference in IAA. Until a large RCT or multiple RCT to allow large meta-analysis to be performed is reported, the current study provides the best available evidence of the benefits of LA in complicated appendicitis.

Although the mortality for OA was low, there was no mortality in the LA group. The significantly lower mortality for LA in complicated appendicitis is comparable with comparisons of laparoscopic with open surgery for other indications such as cholecystectomy [64, 65] and colectomy [66, 67]. Some reasons for the lower mortality rate for LA is the reduced incidence of respiratory complications, a reduced incidence of ileus, which may lead to aspiration pneumonia and reduced multi-organ failure in the LA group. Underlying medical co-morbidities including chronic obstructive pulmonary disease, renal insufficiency and diabetes mellitus have been associated with increased mortality in appendectomy [68–70] were unable to be due to insufficient data. Three previous meta-analyses failed to demonstrate a difference in mortality due to insufficient numbers of cases [12–14]. Our study has additional seven studies, with almost 2000 additional patients that allowed the difference in mortality to be demonstrated.

Complicated appendicitis is known to be associated with a higher risk of IAA [16, 61], with some studies reporting an incidence up to 26% [10, 71]. A previous major concern for LA in complicated appendicitis was the reported increased incidence of IAA associated with LA [16, 17]. In laparoscopic surgery for complicated appendicitis and other causes of peritonitis, there were concerns that the intraperitoneal bacterial contamination may be compounded by the pneumoperitoneum [71, 72]. However, studies assessing laparoscopic surgery in generalised peritonitis have demonstrated there is no increased risk of bacteraemia associated with the pneumoperitoneum and increased intra-abdominal pressure [73, 74]. Other factors that may influence the rate of IAA include the duration of antibiotic treatment and operative laparoscopic techniques such as extensive peritoneal lavage [71, 72]. Unfortunately, these were not defined or reported in most of the studies. Two previous meta-analyses did not show a significant difference between IAA rate in LA and OA groups [13, 14]. The reported IAA rate in our study (LA = 6.2% and OA = 4.8%) was lower than previously reported (LA = 8% and OA = 6%) [14], which may be explained by improved laparoscopic techniques, improved equipment and increased surgical expertise.

LA for complicated appendicitis has a reduced incidence of wound infection that has also been reported in cholecystectomy [65, 75] and colectomy [66, 76]. The major factor contributing to reduction in wound infection is the reduced wound contamination with use of laparoscopic ports and specimen retrieval bags preventing the contamination of the surgical wound [77]. Another factor may be the preservation of immune function during the post-operative period in laparoscopic compared to open surgery [78, 79].

Elective laparoscopic gastrointestinal surgery is associated with lower rate of post-operative respiratory complications compared to open surgery [80–82]. This study is the first to demonstrate a significantly lower incidence of post-operative respiratory complications following LA for complicated appendicitis. The most common factor leading to reduced post-operative respiratory complications in laparoscopic surgery is less severe post-operative pain [80, 82]. However, these findings are where the open surgery used either a right subcostal wound [80] or a midline laparotomy [83]. An open appendicectomy wound is much smaller and in the lower abdomen. Although post-operative pain is significantly less for LA [12, 13], this does not necessarily fully explain the reduced incidence of respiratory complication in LA. Furthermore, a reduced OT does not explain it, as this is similar. There are likely to be other factors that are not currently clear to explain the reduced incidence of respiratory complications.

Decreased post-operative ileus is another benefit of laparoscopic gastrointestinal surgery, such as LC and laparoscopic colectomy [84, 85]. Previous studies comparing LA to OA for suspected acute appendicitis have not demonstrated a difference in the incidence of post-operative ileus [13, 14]. Likewise, a recent meta-analysis was unable to demonstrate a reduced incidence of ileus in LA for complicated appendicitis [14]. The addition of 10 extra studies has confirmed that there is a significant reduction in post-operative ileus in LA for complicated appendicitis. Although post-operative ileus is complex and multi-factorial, one explanation may be the reduced manipulation of the small bowel and the abdominal wall in laparoscopic surgery [84, 85]. Another contributing factor may be the earlier resumption of solid food that has also been associated with less post-operative ileus [85, 86].

The incidence of incisional hernia following either LA or OA for complicated appendicitis is low and showed no significant difference. This may be correct, although it may be due to inadequate numbers as most studies failed to report on this or have an adequate follow-up duration to allow for the occurrence of incisional hernia.

A significantly lower LOS is almost universal in all comparisons of laparoscopic and open gastrointestinal surgery [65–67] including LA for complicated appendicitis [15].

The factors contributing to this include reduced pain, earlier return of gut function and reduced post-operative morbidity. Nonetheless, the LOS following LA is still almost 1 week. This may be due to the use of prolonged intravenous antibiotics and ongoing patient monitoring to ensure no complications related to intra-abdominal sepsis occur. A recent study demonstrated that following early laparoscopic washout for intra-abdominal sepsis post LA the resolution of Systemic Inflammatory Response Syndrome within 48 h was associated with no further occurrence of intra-abdominal infection [87]. Further studies are needed to confirm this finding after LA for complicated appendicitis may result in earlier, safe discharge policies. Another possible reduction in LOS may occur with earlier transfer from intravenous to oral antibiotics; once again this requires further research studies.

A consistent criticism of LA in complicated appendicitis has been a longer average OT [12–14]. Certainly, in two previous meta-analyses, the average OT was significantly longer in the LA group [13, 14]. In our study, there was a no significant difference in OT. When the average OT was further subcategorised as before and after 2010, there was a trend towards reduction in average OT after 2010 in the LA group (86.4 min) compared with before 2010 (78.9 min). This may reflect the increasing use and expertise in laparoscopic techniques.

Conclusion

Our meta-analysis provides clear evidence that LA is a safe method for treating complicated appendicitis compared with OA. LA for complicated appendicitis is associated with a reduced mortality, total morbidity, wound infection, respiratory complications and ileus without a higher incidence of IAA. LA should now be considered the routine approach for patients presenting with complicated appendicitis. There is no evidence to support conversion from LA to OA when complicated appendicitis is found at laparoscopy.

Compliance with ethical standards

Disclosures Gaik S. Quah, Guy D. Eslick and Michael R. Cox have no conflict of interest or financial disclosures to declare.

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