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ORIGINAL SCIENTIFIC REPORT

Systematic Review and Meta-Analysis of Laparoscopic Versus Open Appendicectomy in Adults with Complicated Appendicitis: an Update of the Literature

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Abstract

Aims To review and compare the outcomes of laparoscopic (LA) versus open appendicectomy (OA) in complicated appendicitis in adult patients, eight years after the last literature review.

Methods The PRISMA guidelines were adhered to. Pre-defined inclusion and exclusion criteria were used to search the PubMed, Scopus and Cochrane databases and extract relevant data. Methodological and quality assessment was undertaken with outcome meta-analysis and subgroup analyses of methodological quality, type of study and year of study. Assessment of clinical and statistical heterogeneity and publication bias was conducted.

Results Three randomised control trials (RCTs) (154LA vs 155OA) and 23 case–control trials were included (2034LA vs 2096OA). Methodological quality was low to average but with low statistical heterogeneity. Risk of publication bias was low, and meta-regression indicated shorter length of hospital stay (LOS) in more recent studies, $Q = 7.1$, $P = 0.007$. In the combined analysis LA had significantly less surgical site infections [OR = 0.30 (0.22,0.40); $p < 0.00001$] with reduced time to oral intake [WMD = -0.98 (-1.09,-0.86); $P < 0.00001$] and LOS [WMD = -3.49(-3.70,-3.29); $p < 0.00001$]. There was no significant difference in intra-abdominal abscess rates [OR = 1.11(0.85,1.45); $p = 0.43$]. Operative time was longer during LA [WMD = 10.51 (5.14,15.87); $p = 0.0001$] but did not reach statistical significance ($p = 0.13$) in the RCT subgroup analysis.

Conclusions LA appears to have significant benefits with improved morbidity compared to OA in complicated appendicitis (level of evidence II).

Introduction

Acute appendicitis remains one of the most common emergency pathologies, with a cumulative life time incidence of 9% [1]. Its reported incidence has increased over the last few decades, potentially due to the increased use of CT imaging, with the rate of complicated appendicitis representing a stable 25% of all cases [2]. Over the last three decades with the advent of laparoscopic surgery and the more widespread use of laparoscopy, complicated

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appendicitis (CA) defined as gangrenous or perforated appendicitis with or without peritonitis has been increasingly managed laparoscopically, with up to 67% of cases of CA performed laparoscopically in 2011 in the USA [3]. Laparoscopic practice has been widely adopted by surgeons as they have become more experienced in laparoscopy, in order for patients to benefit from the potential advantages of a minimally invasive procedure, such as reduced wound infection rates and ileus with earlier convalescence and potentially reduced future adhesional complications [4].

Some concerns have been raised in the past though in relation to a potential higher rate of intra-abdominal abscesses (IAA) in the laparoscopic group compared to the open group. A previous systematic review (SR) and meta-analysis (MA) failed to find a difference between the two groups in relation to IAA indicating some benefits in favour of the laparoscopic approach [4]. That evidence though was based on a number of case-controlled (CCTs) studies which were troubled by a number of methodological and external validity problems leading to a low overall level of evidence and recommendation indicating no difference between the two approaches. Since then a number of randomised controlled trials (RCTs), as well as additional CCTs reporting potentially beyond the laparoscopic learning curve, have been published on the subject. Our aim was therefore to perform an update of the previous review and meta-analysis in order to determine whether there is any significant difference between the laparoscopic and open approach in this group of patients in relation to their outcomes and establish the strength and level of existing evidence.

Methods

This study was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[5].

Eligibility criteria

All RCTs and CCTs comparing emergency laparoscopic (LA) versus open appendicectomy (OA) in adult patients (age >16) with CA were included. CA was defined as histologically or intra-operatively diagnosed perforated appendix with or without free or localised pus or gangrenous appendix. Patients with an appendix mass were excluded. Studies were included if reporting on any of the following outcomes: mortality, intra-abdominal abscess (IAA), surgical site infection (SSI), ileus, duration of operation and length of hospital stay (LOS). Additional exclusion criteria included duplicate publications where the most up-to-date and complete publication was included and publications reporting data from large administrative databases without any reporting of baseline characteristic comparison between groups or laparoscopic conversion rates. There were no language restrictions in relation to the database search.

Search and selection strategy

An electronic database search of the Cochrane Library's Controlled Trials Registry and database of systematic reviews, Medline (1980–30 Apr 2016), PubMed, Scopus and Web of Knowledge databases was performed using pre-defined search terms (Supplementary Table 1) by two of the authors. Review of all titles, relevant abstracts and full-paper publications was performed selecting the studies adhering to the eligibility criteria. Back-referencing was also employed, and differences in relation to the inclusion or exclusion of a study were resolved with discussion.

Data abstraction and validity assessment

Data on methodological quality, baseline characteristics and independent variables, intervention characteristics and outcomes were collected on pre-designed data abstraction forms. Methodological assessment was performed using established methods from the Cochrane reviewer's Handbook and risk of bias graded as low, intermediate or high.

Data analysis

Meta-analysis of outcomes was undertaken using the RevMan 5.3 statistical package from the Cochrane collaboration. A pre-requisite for inclusion of a dichotomous outcome in the meta-analysis was the report of sufficient data to form 2×2 contingency tables. Estimates of mean and standard deviation were calculated in studies reporting continuous variables in the form of median and range.

The Mantel–Haenszel statistical method providing OR with 95% CI and the weighted mean difference (WMD) methods were used to analyse dichotomous and continuous data, respectively. A fixed or random effects model was employed depending on the methodological quality, degree of statistical heterogeneity and size of the studies. Chi-square and I^2 statistical tests were employed to assess statistical heterogeneity, and funnel plots graphical representation was performed to assess publication bias. Type of study (RCT vs. CCT), methodological quality (high vs. low) and time period of reported cases in relation to the establishment of laparoscopic surgery subgroup analyses were undertaken. Meta-regression was performed for the outcomes (surgical site infection, intra-abdominal abscess, length of procedure and length of stay) reported

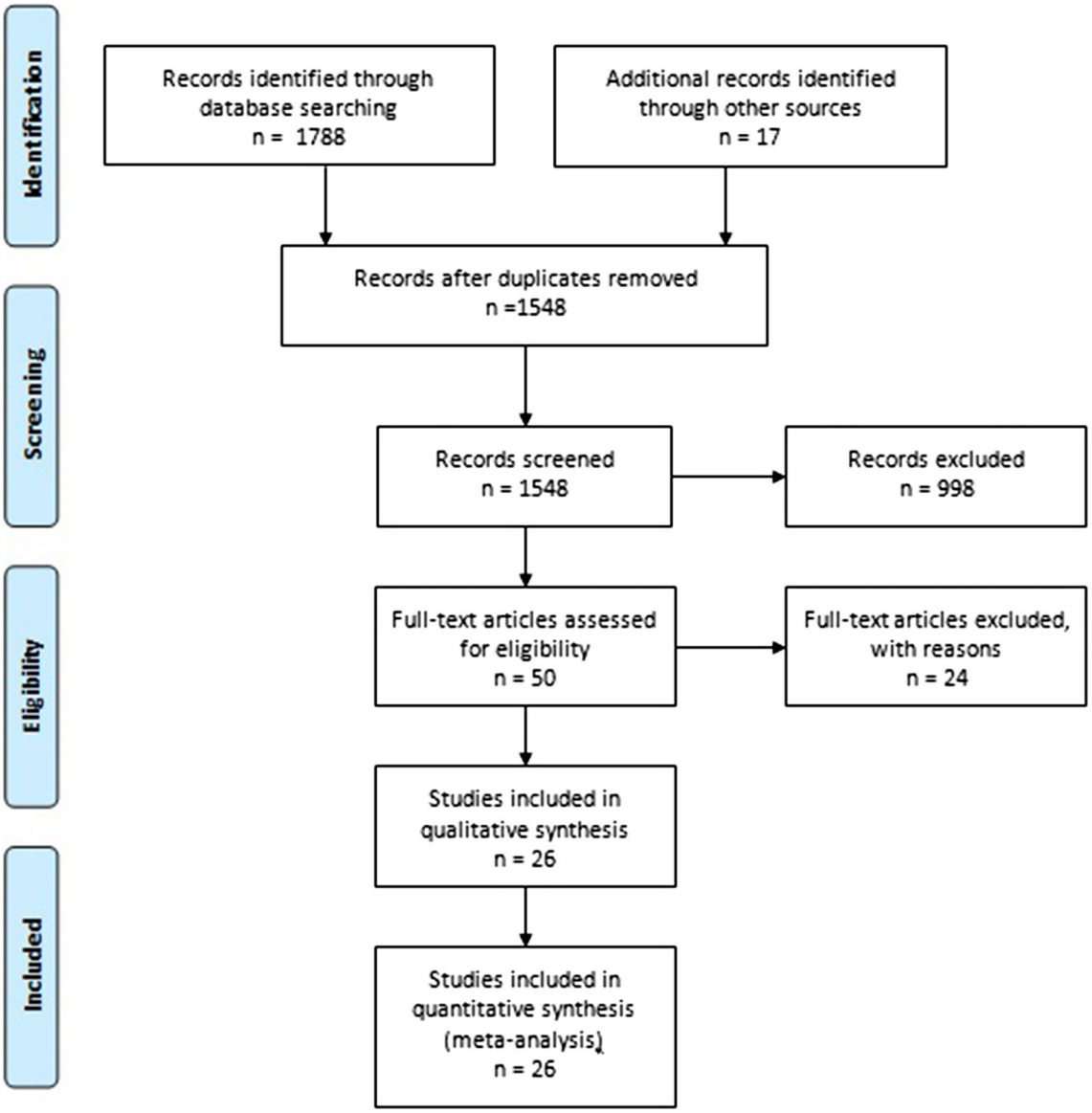

Fig. 1 PRISMA 2009 flowchart—study selection

individually in more than ten studies. The random effects model was used to explore possible causes of heterogeneity such as year of publication, quality of the study (low, intermediate and high) and country of origin (Europe, Asia, America). Finally, the level of evidence and grade of recommendation reported were based on the Oxford Centre of Evidence-Based Medicine guidelines.

Results

The search and selection results are illustrated in Fig. 1. Three RCTs [6–8] (154LA vs 155OA patients) published over the last five years and 23 CCTs (2034LA vs 2096OA patients) published since 1999 were selected (Table 1). All of the RCTs [6–8] and 12 of the CCTs [9–20] have been published since the last SR MA publication in 2010. One of the excluded studies that had been included in the previous meta-analysis was the study by Guller et al. [21] as this was a report from a large national database without reporting of additional independent variables that may significantly affect the outcomes. The great majority of included studies were undertaken in developed/industrialised countries, with the majority of patients having their surgery within the last 10 years (Table 1).

Definition of CA varied slightly among studies in terms of its precise definition, with seven studies mostly

Table 1 Summary of studies

Reference	Type of study	Centre	Inclusion criteria	Exclusion criteria	Sample size	Independent variables	Conversion rate and ITT	Findings
Quezada et al. [6]	CCT	One Chile	Jan 03–Oct 13 Acute appendicitis and peritonitis (intra-abdominal pus)	NR	LA: $n = 97$ OA: $n = 130$	NS: Age, gender, ASA, BMI not reported	13.4% ITT used	SS: LOS in favour of LA, op time shorter OA NS: IAA, SSI, ileus
Taguchi et al. [7]	RCT	One Japan	Oct 08–Aug 14 >19 age, peritonitis or IAA on clinical examination or CT	CA, IBD, previous abdominal surgery, bowel distension, additional procedures, hemodynamic instability	LA: $n = 42$ OA: $n = 39$	NS: Age, gender, ASA, BMI	2.4%, ITT used	SS: Op time shorter in OA NS: IAA, SSI, return to diet, LOS, analgesia
Thompson et al. [8]	RCT	One South Africa	Dec 11–Jun 12 Age >12, peritonitis clinical examination or radiol and histological confirmation	Age <12, pregnant, previous abdo surgery	LA: $n = 39$ OA: $n = 42$	NS: Age, Inflammatory markers, gender NR ASA, BMI	5% ITT used	SS: SSI in favour of LA NS: LOS, IAA, re-operations, op time
Yeom et al. [9]	CCT	One South Korea	Jan 10–Dec 13 radiological diagnosis	Malignancy, additional surgical procedure	LA: $n = 25$ OA: $n = 59$	NS: Age, gender, ASA, BMI	12% ITT used	SS: IAA in favour of OA NS: LOS, SSI, re-operations, op time, return to diet
Dimitriou et al. [10]	CCT	One Germany	Jan 07–Dec 10 pts with acute appendicitis or CA	NR	LA: $n = 84$ OA: $n = 66$	SS: Age NS: Gender NR ASA, BMI	13% ITT used	SS: SSI and LOS in favour of LA NS: IAA, re-operations, op time
Galli et al. [11]	CCT	One Switzerland	Jan 05–Dec 10 age ≥15, perforated appendicitis	Additional pathology, interval appendicectomy	LA: $n = 106$ OA: $n = 63$	S: Age, ASA NS: Gender NR BMI	41% ITT not used	SS: SSI, LOS overall complications in favour of LA NS: IAA, op time
Mohamed et al. [12]	CCT	One Egypt	Sep 06–Sep 09 CA–perforation or abscess	Appendiceal mass, generalised peritonitis, previous abdo surgery, unfit for pneumoperitoneum	LA: $n = 132$ OA: $n = 82$	NS: Age, gender NR ASA, BMI	3% ITT used	SS: SSI, LOS, in favour of LA, op time in favour of OA NS: IAA, post-op ileus, analgesia use
Wilson et al. [13]	CCT	One UK	Apr 09–Oct 12 lap vs open, subgroup analysis IAA and CA	Incidental appendicectomy, SSI	LA: $n = 25$ OA: $n = 25$	NR	NR	NS: IAA
Ferranti et al. [14]	CCT	One Italy	May 04–Jun 09 age ≥15, gangrenous or perforated	NR	LA: $n = 18$ OA: $n = 20$	NS: Age, gender NR ASA, BMI	11% ITT used	SS: SSI in favour of LA NS: IAA, LOS
Schietroma et al. [15]	RCT	One Italy	Nov 05–Feb 11 perforated appendicitis	Recent thromboembolic event, renal, hepatic or vascular disease, pregnancy, malignancy, pt on steroids or drugs affecting immunological response	LA: $n = 73$ OA: $n = 74$	NS: Age, gender, ASA, APACHE score NR BMI	5.4% ITT not used	SS: SSI, IAA, LOS, post-op stress response in favour of LA
Lim et al. [16]	CCT	One Korea	Jul 09–Jan 11 CA: intra-abdominal abscess or peritonitis, gangrenous or perforation confirmed by microscopy	NR	LA: $n = 38$ OA: $n = 22$	NS: Age, gender, ASA NR BMI	NR	SS: IAA and paralytic ileus in the peri-appendiceal abscess group, LOS, TTOI NS: OT, post-op complications
Garg et al. [17]	CCT	One India	Mar 04–Dec 08 CA: intra-operative diagnosis perforated, gangrenous or intra-abdominal pus	Patients with diagnosis other than appendicitis	LA: $n = 49$ OA: $n = 61$	NS: Age, gender, degree of appendicitis NR BMI, ASA	4.1% ITT used	SS: reduced SSI and IAA, shorter LOS, less analgesic use, longer OT in LA NS: Return to oral intake

Table 1 continued

Reference	Type of study	Centre	Inclusion criteria	Exclusion criteria	Sample size	Independent variables	Conversion rate and ITT	Findings
Kehagias et al. [18]	CCT	One Greece	Jan 06–Jan 08 Acute appendicitis, subgroup analysis for complicated appendicitis	pregnancy, hemodynamic instability, chronic medical or psychiatric illness, cirrhosis, coagulation disorders, previous laparotomy, ascites, elective or incidental appendectomy	LA: $n = 38$ OA: $n = 47$	NR	NR	SS: SSI in favour of LA, IAA in favour of OA NS: Respiratory infections, bowel obstruction
Park et al. [19]	CCT	One Korea	2006–2008 Perforated appendicitis ± abscess, Radiological, operative and pathologic diagnosis, age >15	Percutaneous drainage of abscess and antibiotics, ileocolic resection for adhesions or suspected obstruction	without abscess LA: $n = 156$ OA: $n = 318$ With abscess LA: $n = 44$ OA: $n = 69$	NS: Age, gender NR BMI, ASA	Without abscess 2% ITT used with abscess 8% ITT used	SS (without abscess): Longer OT, shorter resumption of diet and LOS for LA NS: IAA and SSI SS (with abscess): Shorter resumption of diet and LOS for LA NS: IAA, SSI, OT
Sleem et al. [20]	CCT	One USA	Jan 05–Jan 08 Perforated appendicectomy confirmed by op note or pathology report	NR	LA: $n = 188$ OA: $n = 59$	NS: Age, gender NR BMI, ASA	15.7% ITT not used	SS: Higher rate of SSI, longer duration of antibiotics and length of stay in OA NS: IAA
Katsuno et al. [34]	CCT	One Japan	May 95–May 07 All pts with CA from hospital records	Pregnancy, dense adhesions	LA: $n = 146$ OA: $n = 84$	NS: Age, gender, NR BMI, ASA	3.4% ITT not used	SS: Lower rate of SSIs, longer OT, analgesic use, TTOI, pLOS in LA group, NS: IAA, other post-op complications
Fukami et al. [26]	CCT	One Japan	Jan 99–Dec 04 All CA OA pts 99-01 and all CA LA pt 02-04	Percutaneous abscess drainage	LA $n = 34$ OA $n = 39$	NS: Age, gender, obesity, co-morbidities	0%–N/A	SS: Lower rate of SSIs, analgesic use, TTOI, duration of drainage, pLOS in LA group NS: OT, IAA, hernia, fistula formation
Kirshtein et al. [23]	CCT	One Israel	Jan 05–Aug 05 All pts with CA from hospital records	NR	LA $n = 50$ OA $n = 98$	S: more females of reproductive age, higher co-morbidity, obese and unknown abdominal pain pts in LA group	16% ITT not used (conversions treated as separate group)	NS: OT, TTOI (solids), pLOS, SSI, IAA
Pokala et al. [28]	CCT	One US	Jan 03–Feb 06 All pts with CA from hospital records	NR	LA $n = 43$ OA $n = 61$	S: more paediatric cases in LA group (separate analysis contacted) NS: Gender, ASA group	18.6% ITT used	SS: longer OT, higher IAA rate in LA group NS: overall complications and SSI
Yau et al. [27]	CCT	One Hong Kong	Jan 99–Jan 04 All pts with CA from hospital records	<14yrs old, generalised peritonitis, co-current operation, medically unfit for LA, CT confirmed appendiceal masses	LA $n = 175$ OA $n = 244$	NS: Age, gender	13.7% ITT used	SS: Shorter OT, LOS and SSI in LA group NS: IAA rates
Lin et al. [32]	CCT	One Taiwan	Jan 01–Dec 03 All pts with CA from hospital records	NR	LA $n = 99$ OA $n = 130$	NS: Age, gender	8% ITT used	SS: Longer OT, shorter antibiotic requirements, shorter TTOI and LOS, lower SSI in LA group NS: post-operative analgesia, re-operation rates, IAA

Table 1 continued

Reference	Type of study	Centre	Inclusion criteria	Exclusion criteria	Sample size	Independent variables	Conversion rate and ITT	Findings
So et al. [22]	CCT	One Singapore	Jan 92–Jun 99 All pts with perforated appendicitis	NR	LA $n = 85$ OA $n = 146$	NS: Age, gender	40% ITT used	SS: Less post-operative analgesia and complications, reduced TTOI and LOS in LA group NS: OT
Piksun et al. [25]	CCT	One Italy	52 prospective pts	NR	LA $n = 28$ OA $n = 24$	Not tested	36% ITT not used, groups tested individually	NS: OT, IAA, SSI, pLOS
Wullstein et al. [31]	CCT	One Germany	Aug 89–Mar 99 for OA 1991–99 LA All pts with CA	Age <14, disease contraindicated in pneumoperitoneum	LA $n = 217$ OA $n = 82$	NR	21% (35–60% in 91–92, 3.4% in 98–99) ITT used	SS: SSI lower in LA NS: IAA
Stoltzing et al. [24]	CCT	One Germany	Jul 91–Jun 99 All pts with perforated appendix		LA $n = 80$ OA $n = 45$	NS: Age, gender, BMI	45% (16% in latter years) ITT not used	SS: SSI lower in LA NS: OT, LOS, IAA
Khalili et al. [30]	CCT	On US	Jan 94–Aug 97 All pts with acute appendicitis		LA $n = 77$ OA $n = 122$	NR	ITT not used	SS: OT shorter in OA NS: LOS, IAA

RCT randomised controlled trial, *CCT* case-controlled trial, *LA* laparoscopic appendicectomy, *OA* open appendicectomy, *CA* complicates appendicitis, *uCA* uncomplicated appendicitis, *Pt* patient, *NR* not reported, *ITT* intention to treat, *SS* statistically significant, *NS* statistically non-significant, *OT* operating time, *TTOI* time to oral intake, *LOS* length of stay in hospital, *pLOS* post-operative length of stay in hospital, *SSI* surgical site infection, *IAA* intra-abdominal abscess

undertaken earlier chronologically including gangrenous CA in addition to perforation and/or purulent peritonitis and/or abscess formation in their diagnosis (Table 2). The diagnosis was performed intra-operatively in most studies, with only 50% of studies confirming the diagnosis histologically. IAA outcome definition was better defined in more recent studies as a radiological or intra-operative diagnosis of a collection and SSI definitions were defined as evidence of wound infection (erythema ± pus) requiring antibiotic or surgical treatment but with no reporting of microbiological wound culture results.

Independent variables such as patients' age and gender were reported in the great majority of studies and statistically compared between groups, while American Society of Anaesthesiology (ASA) scores were only reported in a minority of cases and body mass index (BMI) is reported in only two of the most recent studies. The mean age among groups appears to vary from 23 to 57 years old with standard deviation values extending to a potential younger age of 12 (Ferranti et al.) [14]. Two studies reported a statistically significant younger age for their laparoscopic groups [10, 11] with Galli et al. [11] also reporting statistically higher ASA grades in the OA group.

The laparoscopic surgical experience was not reported in 8 studies, while the remaining studies reported both types of surgery being performed by experienced open and laparoscopic surgeons, even though the degree of experience is not specifically defined in the majority (Table 2). Laparoscopic conversion rates to open surgery varied from 20 to 45% in studies reporting data on patients operated on before 2000, while studies reporting on patients undergoing surgery in the third millennium report conversion rates of 0 to 18%, with the exception of one study that reported a high conversion rate of 41% [11] with no reported laparoscopic surgical experience (Table 1).

The operative procedures themselves are quite homogeneous between studies (Table 2). Various heat sources are used for mesoappendix division, and endoloops are mainly used for appendicular ligation, with retrieval bags employed in the extraction of the surgical specimen from the abdomen. Most open procedures are performed via a McBurney incision or a lower abdominal laparotomy, with only one study reporting on the use of a wound protector [7]. Fourteen of the studies do not report on their wound closure technique, while four studies selectively allow wounds to heal by secondary intention in OA [8, 20, 22, 23]. Clinically appropriate antibiotic regimes appear to be used peri-operatively and post-operatively and continued on the basis of clinical indication. A standardised post-operative care pathway is not reported in any of the studies.

Methodological quality

The methodological quality and risk of bias assessment of the studies is shown in Table 3. The risk of bias within the studies ranged from intermediate to high among studies. This was mainly because of factors such as absence of observer blinding and statistical power calculations in RCTs, inadequate reporting or statistical testing of significant independent variables that may have influenced the outcomes and insufficient reporting of peri-operative care and its standardisation, all potentially influencing internal and external validity.

Diagnosis of CA and peri-operative management of the patients though appeared to be quite homogeneous among studies in regard to surgical techniques and antibiotic prescribing, with reasonable external validity, and thus, a decision was made to proceed with a meta-analysis of outcomes. Unless specifically reported per outcome, there was no evidence of publication bias on visual inspection of funnel plots. Stratification analysis during the meta-analysis did not reveale any differences between the various groups analysed apart from the analysis comparing the RCT against the CCT groups were on some occasions the RCT subgroup found no difference in some outcomes between LA and OA. This difference can potentially be attributed to the small number of patients included in the RCTs compared to the CCTs. Meta-regression analysis showed that part of the heterogeneity in the length of stay could be explained by the year of publication of each study $Q = 7.1$, $P = 0.007$.

Mortality

A great majority of studies [6–12, 14, 17–19, 22–29] report on this outcome. Overall LA was found to have a significantly lower mortality rate compared to OA [OR = 0.14(0.04,0.51); $P = 0.003$], with no statistical heterogeneity ($I^2 = 0\%$). Two studies mainly contributed positive data to the meta-analysis of this outcome reporting high mortality rates in the OA groups, 5% reported by Galli et al.[11] and 11% by Stoltzing et al.[24], versus 0% in the LA group. Both studies had a significantly high laparoscopic conversion rate of over 40% and subsequently failed to use intention to treat analysis; thus, mortality in the LA groups is potentially underreported. Furthermore, one of the studies [11] reported a significantly higher ASA group in the OA group potentially introducing a selection bias in favour of LA. When these two studies are excluded from the MA, there is no difference in mortality between LA and OA.

Intra-abdominal abscess

Twenty-six studies [6–20, 22–28, 30–33] reported on this outcome (Fig. 2). The mean rate of IAA was 8% in the LA

Table 2 Summary of studies' intervention

Study	CA diagnosis	Surgeons	LA			OA	LA and OA		Antibiotic	Histology confirmed
			Procedure	Mesoappendix and appendix resection	Retrieval bag	Procedure	Primary wound closure	Drains used		
Quezada et al. [6]	Intra-op Pus in peritoneal cavity	Multiple staff or fellow under senior supervision	Verres, 3 trocars, 10–5–5 mm	Electrocautery and endoloops	Used	Extended McBurney, med or right paramedian laparotomy	NR	Used-surgeon preference	NR	*NR*
Taguchi et al. [7]	Clinical examination and CT, peritonitis or abscess	6 senior surgeons	3–4 trocars, 10 × 3 5 mm Flex endoscope	Electrocautery and stapler	Used	Midline or pararectal incision + Alexis	Subcuticular	Used	Cefozopran 1 g bd pre-op and post-op as clinically indicated	*NR*
Thompson et al. [8]	Clinical and radiological	? no. of experienced consultants	3 trocars, 10–5–5 mm,	NR	Used	RIF muscle splitting or midline laparotomy	OA: Open or non-absorb suture LA: subcut	Used in 1/3	Co-amoxiclav 1.2 g	*Yes – suppurative appendicitis*
Yeom et al. [9]	Radiological peri-appendiceal abscess	8 experienced surgeons (7 lap trained)	3 trocars, 10–5–5 mm	Electrocautery and endoloops (one stapler)	Used	McBurney	NR	Used	Cephalosporin and metronidazole ± additional	*In all but 4*
Dimitriou et al. [10]	Intra-op perforation, abscess, peritonitis	Experienced lap or open surgeon or attending resident	NR	EndoGIAs	Used	NR	NR	NR	NR	*Yes*
Galli et al. [11]	Intra-op perforation–pus or bowel contents	NR	Hasson tech, 3 trocars, 10–5–12 mm	Electrocautery or clips, stapler (67%), endoloops	Used	McBurney, med laparotomy (92%)	Primary closure	Used-surgeon preference	Cefazolin 2 g and metronidazole 500 mg, post-op co-amoxiclav	*No*
Mohamed et al. [12]	Intra-op and CT, perforation or abscess	NR	Verres needle, 3 trocars	Electrocautery, endoloops	Used	Low midline	NR	Used	Pre-op 3rd gen cephalosporin, post-op cipro or co-amoxiclav + metro	*NR*
Wilson et al. [13]	Histological–necrotic or perforated	Experienced lap surgeons	NR	NR	NR	NR	NR	NR	NR	*Yes*
Ferranti et al. [14]	Intra-op and histological, gangrenous or perforation	NR	Verres needle, 3 trocars	Electrocautery or clips, endoloops, stapler	Used	RF muscle splitting	NR	NR	Pre-op and post-op use as clinically indicated	*Yes*
Schietroma et al. [15]	Intra-op perforation	NR	3 trocars	NR	NR	McBurney or lower midline	NR	NR	Pre-op and post-op cefotaxime and tobramycin	*NR*
Lim et al. [16]	Intra-op abscess or peritonitis and histological gangrene or perforation	Trainees > 20 cases LA and >30 cases OA as first assistant under supervision	10 mm infra-umbilical Left lower quadrant?size	Electrocautery, endoclips, edoloops	Not used	McBurney incision	NR	Discretion of surgeon	Pre-op and post-op 2nd gen cephalosporin iv 3d and PO 4 days + metronidazole for gangrenous	*Yes*

Table 2 continued

Study	CA diagnosis	Surgeons	LA			OA	LA and OA		Antibiotic	Histology confirmed
			Procedure	Mesoappendix and appendix resection	Retrieval bag	Procedure	Primary wound closure	Drains used		
Garg et al. [17]	Intra-op perforated, gangrenous appendix or purulent peritonitis	Lap done by consultants Open by consultants or senior registrars	Veress needle, 10, 10, 5 mm	Electrocautery, endoloop, transfixation of stump if base wide	Used	Right lower paramedian incision	Primary closure	Used	Pre-op antibiotics post-op according to clinical findings	*Yes*
Kehagias et al. [18]	NR	NR	Veress needle 12, 12, 5 mm	Bipolar forceps, two ligating loops if sever inflammation in the appendix base stapler	Used	McBurney muscle splitting incision, double ligation of the stump	OA: wound loosely closed	Discretion of the surgeon	Pre-op antibiotics post-op antibiotics amended according to cultures	*Yes*
Park et al. [19]	Radiological, intra-op and pathologic findings perforated ± abscess	5 qualified surgeons 3 performed open appen -dicectomy 2 used the laparoscopic approach	3 trocars 11–5–5 mm? type of endoscope	Electrocautery, endoloops or stapler	NR	Rocky-Davis or McBurney incision.	NR	Used for generalised peritonitis, abscess, difficult dissection due to adhesions.	Antibiotics on admission until pt afebrile and wbc normal	*Yes*
Sleem et al. [20]	Intra-op or histologically confirmed	None of the surgeons had completed a laparoscopic fellowship	NR	NR	NR	NR	Not standardised some used delayed primary closure	At the discretion of the surgeon	NR	*Yes*
Katsuno et al. 2009	Intra-op gangrenous, purulent peritonitis or abscess	1 experienced surgeon + surgical trainees	3 trocars, 10–5–5 mm,?*type of endoscope*	Coagulation + suture loops or staples	Used	McBurney's or paramedian	Yes	Used when required	Pre-op and post-op use as clinically indicated	*Yes*
Fukami et al. [26]	CT scan, perforation or abscess	6 experienced surgeons for LA, at least 2 other surgeons for OA	3 trocars, 10–10–5 mm, flexible endoscope used	Electrocautery or ultrasound dissector + endolinear cutter	Used	McBurney's or paramedian	Yes	Used when abscess encountered	Pre-op and post-op use as clinically indicated	*Not reported*
Kirshtein et al. [23]	?intra-op Gangrenous, perforated ± abscess	9 surgeons? *experience*	3 trocars, 45 deg endoscope	Coagulation or clips + suture loops or staples	*Used in 67%*	Gridiron or paramedian	Secondary closure in contaminated cases	Used when abscess encountered	Pre-op and post-op use as clinically indicated	Yes

Table 2 continued

Study	CA diagnosis	Surgeons	LA			OA	LA and OA		Antibiotic	Histology confirmed
			Procedure	Mesoappendix and appendix resection	Retrieval bag	Procedure	Primary wound closure	Drains used		
Pokala et al. [28]	Clinical + *CT scan confirmation of CA*	*Not reported*	*Not reported*	*Not reported*	*Not reported*	*Not reported*	*Not reported*	*Not reported*	*Not reported*	*Not reported*
Yau et al. [27]	intra-op gangrenous, perforated ± abscess	Surgical residents–at least 3 years experience	3 trocars, 10–5–5 mm,?*type of endoscope*	Electrocautery or ultrasound dissector + suture loops	Used	Gridiron	*Not given*	Not used	Pre-op and post-op use as clinically indicated	*Not applicable*
Lin et al. [32]	*Intra-abdominal pus*	4 experienced surgeons	3 trocars, 10–3–3 mm,?*endoscope type*	Electrocautery or clips or harmonic scalpel + clips or endoloop	Used	NcBurney's, paramedian or midline	Yes	Used routinely	Pre-op and post-op use as clinically indicated	*Not applicable*
Guller et al. [21]	?intra-op perforation or abscess	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
So et al. [22]	Intra-op perforated–purulent peritonitis	*? number, less experienced surgeons ($n < 20$) associated with higher conversion rates*	3 trocars, 12–5–5 mm,?*endoscope*	Electrocautery, clips or stapler + endoloop or stapler	*Used usually*	Gridiron or midline	Yes but in 4 cases	Used when required	Pre-op and post-op use as clinically indicated	*No*
Piksun et al. [25]	?intra-op perforation	12 surgeons? *experience*	3 trocars, 10–5–12 mm,? *endoscope*	?clips + stapler	Used	*NR*	Yes	Used when abscess encountered	Pre-op and *post-op 5 days* and then as clinically indicated	surgeon or pathologist
Wullstein et al. [31]	?intra-op perforation ± abscess or peritonitis	*?surgeons? experience Learning curve*	3 trocars, 12–5–12 mm,? *endoscope*	Clips or stapler–clips or endoloop	Used	McBurney's	*Not reported*	Used when required	Pre-op and post-op use as clinically indicated	*Not reported*
Stoltzing et al. [24]	Intra-op perforation	*?surgeons? experience Learning curve*	3 trocars, 10–5–12 mm,? *endoscope*	Electrocautery, clips or stapler	Used	Pararectal incision or lower midline laparotomy	*Not reported*	Used routinely	Pre-op and post-op use as clinically indicated	surgeon or pathologist
Khalili et al. [30]	Clinical	*Not reported*	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

CT cross-tomography scan, *LA* laparoscopic appendicectomy, *OA* open appendicectomy, *CA* complicates appendicitis, *uCA* uncomplicated appendicitis, *Pt* patient, pre-op: pre-operative, intra-op: intra-operative, post-op: post-operative, *CIPRO* ciprofloxacin, *METRO* metronidazole

Table 3 Risk of bias assessment

Reference	Selection bias					Performance bias	Attrition bias		Selective reporting bias	Detection bias	Statistical bias		External validity bias	Overall bias
	R	AC	BL	BC	Δ		ID	ITT			SM	PA		
Quezada et al. [6]	NA	NA	NA	LR	LR	HR	LR	LR	LR	HR	LR	NA	UR	IR
Taguchi et al. [7]	LR	UR	HR	LR	LR	LR	LR	LR	UR	LR	LR	HR	HR	HR
Thompson et al. [8]	LR	LR	HR	HR	LR	LR	LR	LR	LR	LR	LR	HR	IR	HR
Yeom et al. [9]	NA	NA	NA	LR	HR	LR	LR	LR	LR	LR	LR	NA	HR	IR
Dimitriou et al. [10]	NA	NA	NA	HR	LR	HR	LR	LR	LR	HR	LR	NA	IR	HR
Galli et al. [11]	NA	NA	NA	HR	IR	HR	LR	HR	LR	HR	LR	NA	IR	HR
Mohamed et al. [12]	NA	NA	NA	IR	LR	LR	LR	LR	LR	LR	IR	NA	LR	IR
Wilson et al. [13]	NA	NA	NA	HR	LR	HR	LR	HR	LR	LR	LR	NA	IR	HR
Ferranti et al. [14]	NA	NA	NA	IR	LR	IR	LR	LR	LR	IR	LR	NA	IR	IR
Schietroma et al. [15]	LR	IR	HR	LR	LR	HR	LR	HR	LR	HR	LR	HR	IR	HR
Lim et al. [16]	NA	NA	NA	LR	LR	LR	NA	NA	LR	LR	LR	NA	IR	IR
Garg et al. [17]	NA	NA	NA	IR	LR	LR	LR	IR	LR	LR	LR	NA	IR	IR
Kehagias et al. [18]	NA	NA	NA	NA	NA	UR	LR	UR	UR	UR	LR	NA	UR	HR
Park et al. [19]	NA	NA	NA	IR	IR	HR	LR	LR	LR	LR	LR	NA	UR	IR
Sleem et al. [20]	NA	NA	NA	HR	LR	HR	LR	HR	LR	LR	LR	NA	HR	HR
Katsuno et al. [33]	NA	NA	NA	LR	LR	UR	LR	IR	LR	UR	LR	HR	UR	IR
Fukami et al. [26]	NA	NA	NA	LR	UR	HR	LR	LR	LR	UR	LR	HR	UR	IR
Kirshtein et al. [23]	NA	NA	NA	HR	LR	HR	LR	HR	LR	UR	LR	HR	LR	HR
Pokala et al. [28]	NA	NA	NA	HR	UR	UR	LR	LR	LR	UR	LR	HR	UR	HR
Yau et al. [27]	NA	NA	NA	UR	UR	UR	LR	LR	LR	UR	LR	HR	UR	IR
Lin et al. [32]	NA	NA	NA	HR	UR	LR	LR	LR	LR	UR	LR	HR	LR	HR
So et al. [22]	NA	NA	NA	UR	UR	HR	LR	LR	LR	UR	LR	HR	LR	IR
Piksun et al. [25]	NA	NA	NA	UR	LR	HR	LR	HR	LR	UR	LR	HR	LR	HR
Wullstein et al. [31]	NA	NA	NA	UR	UR	UR	LR	LR	LR	UR	LR	HR	LR	HR
Stoltzing et al. [24]	NA	NA	NA	LR	HR	HR	LR	HR	LR	IR	LR	HR	HR	HR
Khalili et al. [30]	NA	NA	NA	UR	UR	HR	LR	HR	LR	UR	LR	HR	UR	IR

R randomisation, *AC* allocation concealment, *BL* blinding, *BC* baseline characteristics, Δ diagnosis (histological and outcome definitions), *ID* incomplete data, *ITT* intention to treat analysis, *SM* statistical methods, *PA* power analysis, *NA* not applicable, *LR* low risk, *UR* unclear, *IR* intermediate risk, *HR* high risk

and 6% in the OA group. There was not statistically significant difference between LA and OA in regard to the overall incidence of IAA [OR = 1.11(0.85, 1.45);P = 0.43], with minimal amount of statistical heterogeneity (I^2 = 7%).

Surgical site infection

Three RCTs [7, 8, 15] and 21 CCTs [6, 9–12, 14, 16–20, 22–28, 31–33] reported on this outcome with the smaller number of RCTs finding no significant difference between the two techniques but with a statistically high degree of heterogeneity (I^2 = 77%) (Fig. 3). Overall the incidence of SSI was 6.7 and 17.7% in the LA and OA groups, respectively, with a statistically significant lower rate in the LA group compared to the OA group [OR = 0.30 (0.22,0.40); $P < 0.00001$], with a moderate degree of statistical heterogeneity (I^2 = 37%).

Operative duration

The three RCTs [7, 8, 15] reporting on this outcome found a nearly significant (P = 0.13) longer operative time in the LA group of 12 min with a high degree of statistical heterogeneity (I^2 = 84%) (Fig. 4). Taking into account all types of studies [6, 9–12, 16, 17, 19, 22, 30, 32, 33], the LA procedure lasted an average of 10.5 min longer than the OA [WMD = 10.51(5.14, 15.87);P = 0.0001] with a similarly high degree of statistical heterogeneity (I^2 = 89%).

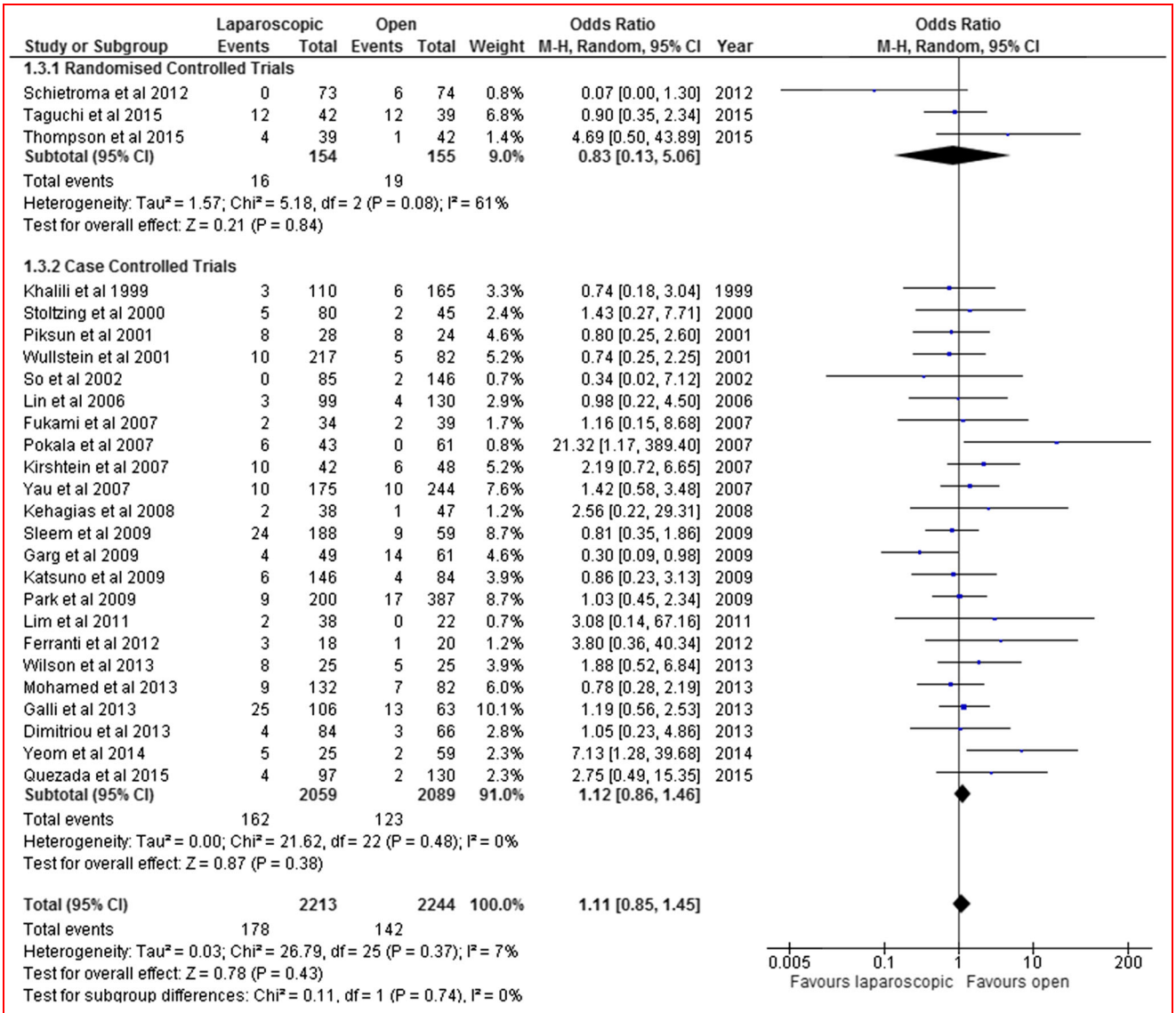

Fig. 2 Forest plot—intra-abdominal abscess

Ileus and time to oral intake

The rate of ileus was only reported by one RCT [7] and 6 CCTs [6, 9, 10, 16, 24, 28], and there was no difference [OR = 0.98(0.51,1.86); $P = 0.94$], between the two groups, with no statistical heterogeneity. Time to oral intake was reported by one RCT and 7 CCTs and was statistically faster [WMD = −0.98(−1.09,−0.86);$P < 0.00001$] in the LA group with no statistical heterogeneity.

Length of stay

All of the RCTs [7, 8, 15] and 12 of the CCTs [6, 9–12, 16, 17, 19, 22, 30, 32, 33] reported on this outcome (Fig. 5). There was no significant difference found among the RCTs ($P = 0.42$), but meta-analysis of all types of studies revealed a significantly shorter hospital stay in favour of the LA group [WMD = −2.27(−3.44,−1.09);$P = 0.0002$]. Both subgroup and overall meta-analyses carried a significant risk of statistical heterogeneity.

Discussion

This systematic review and meta-analysis has been performed 8 years after the last review and meta-analysis on the topic. The number of additional studies performed, including three RCTs, is an indicator of the sustained importance of this topic as well as a positive move towards obtaining higher-quality evidence.

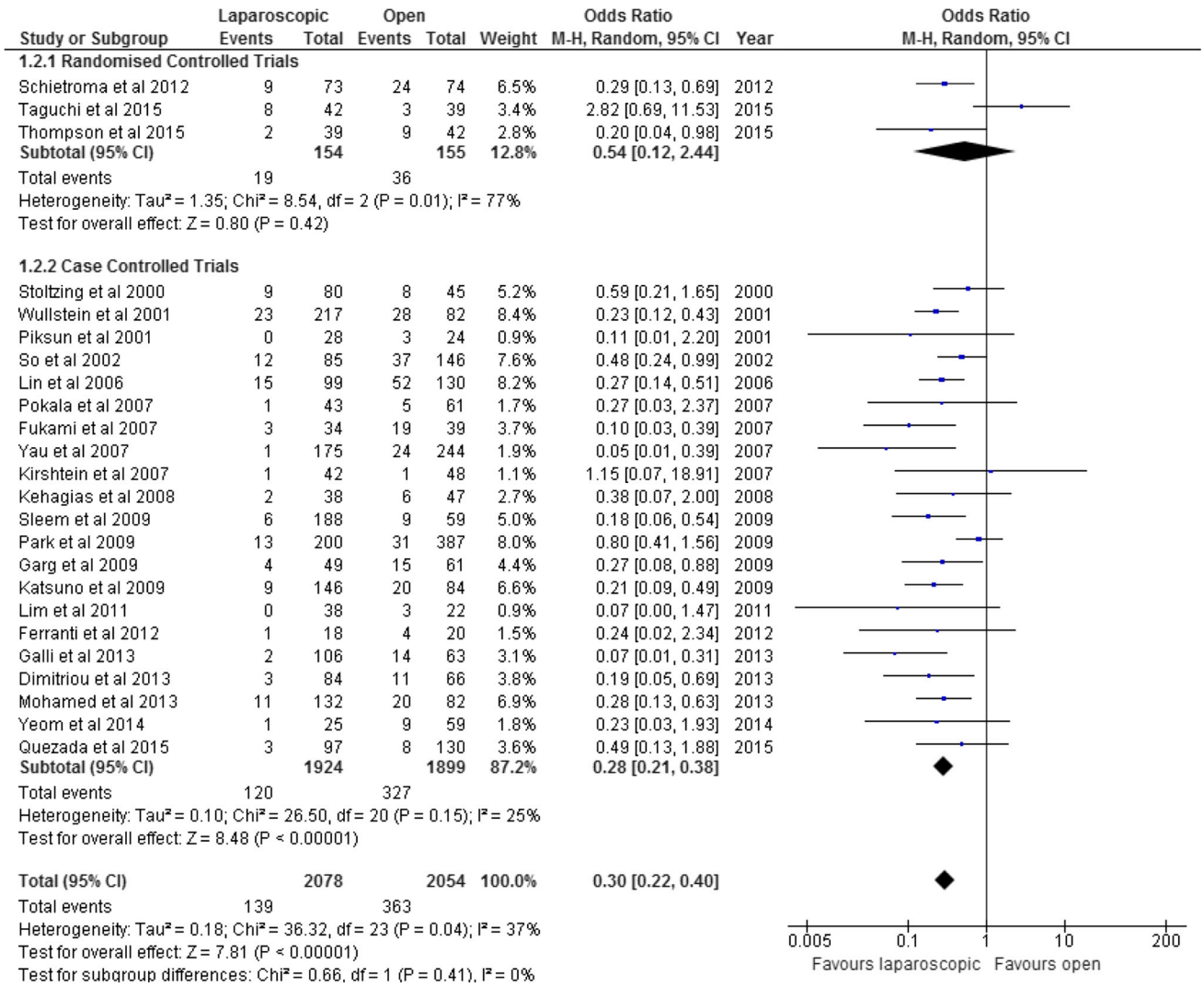

Fig. 3 Forest plot—surgical Site infections

The quality of more recent studies appears to have improved, but findings should still be considered with caution in view of the described methodological deficiencies. These include the lack of use of intention to treat analysis in seven of the included studies, with converted LA cases and their outcomes treated as belonging to the OA group. Current findings reinforce previous results supporting LA as the procedure of choice for CA versus OA, with a reduced rate of SSIs, faster recovery and no difference in the rate of IAA, supported by an increasing number of RCTs and CCTs. The reduction in conversion rates demonstrated in the more recent studies (0–18%) compared to previously published studies (20–45%) is an indirect indicator of the improved laparoscopic skills of surgeons demonstrating an achievement of a laparoscopic learning curve plateau, in agreement with recent literature reports [3, 34, 35].

In terms of individual outcomes, the diagnostic criteria for IAA were fairly well reported in the studies and independent variables that could have affected the incidence of IAA such as the surgical technique and use of antibiotics were well reported. Duration of antibiotic treatment, however, was mainly a clinical decision with no actual parameters provided to guide external validity. Similarly the lack of strict outcome definition for SSI may have influenced the reporting of this outcome explaining some of the degree of statistical heterogeneity observed, even though the reported average difference in the incidence of this complication between the two groups of 6.7% (LA) and 17.7% (OA) is potentially too big to be just attributed to observer bias.

Despite a similar rate of surgical ileus, patients undergoing LA appear to be able to commence oral diet faster, which together with the reduced morbidity

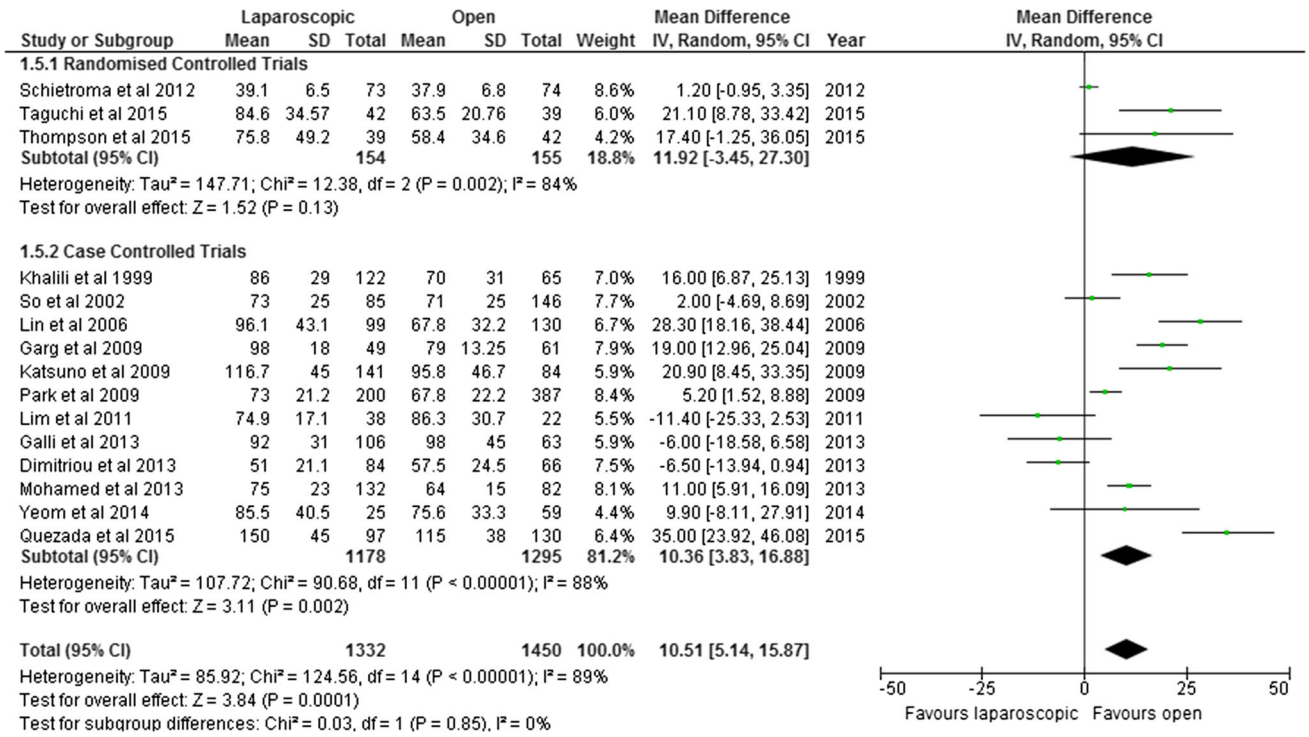

Fig. 4 Forest plot—length of procedure

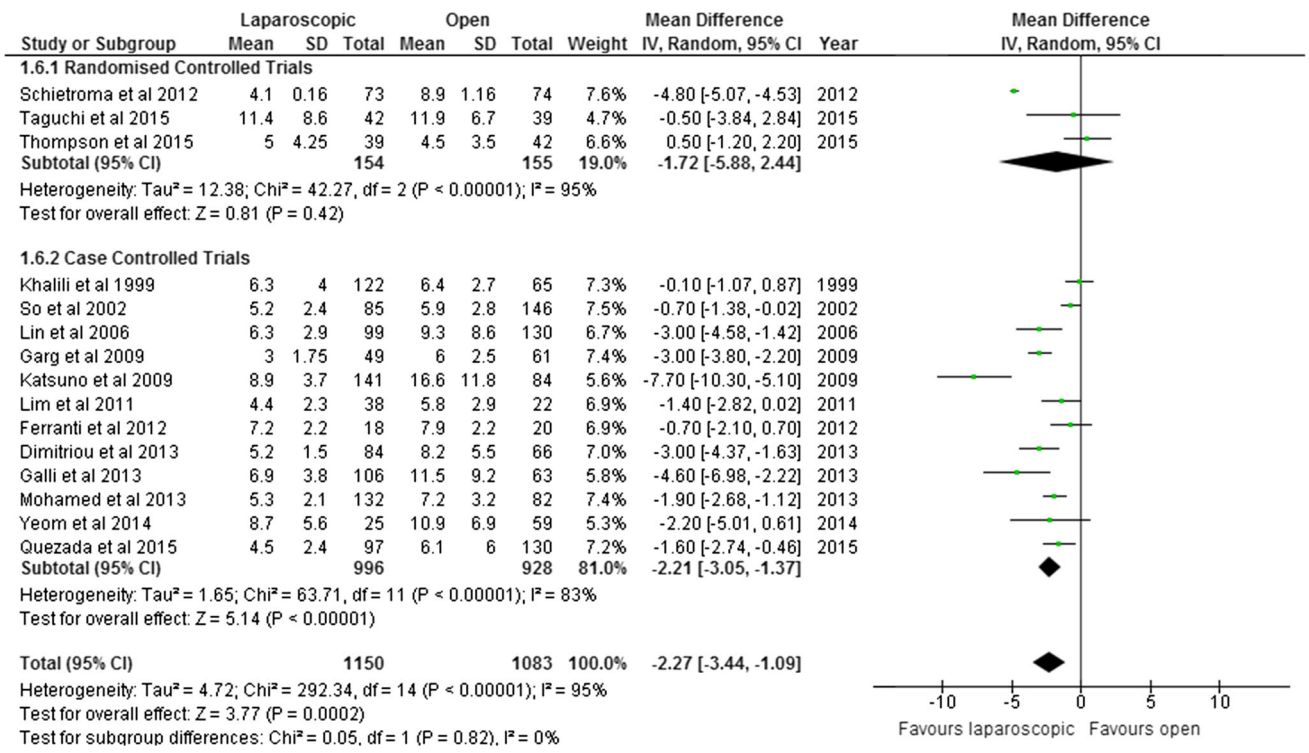

Fig. 5 Forest plot—length of stay

Table 4 Summary of outcomes from large patient database studies

Study	Number of patients		Surgical site infection		Intra-abdominal abscess		Length of stay	
	Open	Lap	Open	Lap	Open	Lap	Open	Lap
Tuggle et al. [39]	730	2060	41 (5.95%)	34 (1.68%)	26 (3.69%)	130 (6.74%)	5.14	3.98
Masoomi et al. [34]	7110	6769	3.54%	1.35%*	4.46%	2.15%*	6.5	4.4*
Tiwari et al. [37]	5323	5212	NR	NR	NR	NR	7.31	4.34*
Yeh et al. [39]	34,895	3976	NR	NR	NR	NR	3.3	2.2*
Masoomi et al. [36]	NR	NR	0.60%	0.16%*	3.59%	1.61%*	6.3	4.5*

* Indicates statistically significant difference

LAP laparoscopic

observed in this group potentially contributes to the finding of a shorter hospital stay. The latter outcome as in the previous MA was not very clearly defined as total or post-operative length of stay. The risk of clinical heterogeneity is therefore plausible, as it may be directly influenced by the pre-operative time to surgery depending on the diagnostic pathways and availability of theatre resources and expertise. One would expect though that in the current age, these independent variables would not differ between the LA and OA group in the healthcare systems of developed countries where most of the included studies have originated from.

A number of studies reporting on data from national or multicentre administrative databases on the reviewed subject were also identified by this review process. These were not included for this meta-analysis because of the potentially high risk of significant methodological bias such as risk of selection bias, performance bias in the absence of technique description, operator experience and peri-operative care description as well as risk of reporting bias. The huge numbers of patients included in these studies though cannot be completely ignored. Their main findings are described in Table 4[3, 34, 36–39], with the great majority supporting the findings of this review and meta-analysis.

The outcomes reported in this review were mainly around the short-term post-operative period. Long-term outcomes such as risk of hernias and the risk of adhesional small bowel obstruction (SBO) have not been investigated in this study. Markar et al. [40] recently contacted a systematic review and meta-analysis to investigate the incidence of SBO following LA and OA defined by the need for re-operation to resolve SBO. Their analysis for patients with CA included 42 thousand patients in a mixture of 14 studies, comprising of RCTs, CCTs as well as big database reports and included both adult and paediatric populations. Despite the inherent risk of bias and lack of methodological assessment of the selected studies, the findings overwhelming suggested that LA has a lower risk of SBO when compared to OA both in the short- and long-term post-operative period.

The benefits of LA in CA may be of even greater benefit in high-risk patient groups. Greater than 90% of patients included in this group of studies though had an ASA score of I and II, when this was reported, with BMI values rarely reported. Masoomi et al. [34] using data on 14 thousand patients derived from a large national database demonstrated through a multivariate regression analysis that LA has significant benefits in obese patients (BMI >30) when compared to OA. A similar finding was reported for patients with ASA scores of III and IV [41], even though this study suffered from some methodological weaknesses affecting its results [42]. Additional potential benefits of LA not captured in this meta-analysis directly linked to the faster convalescence seen in LA are the earlier return to normal daily activities and employment. Furthermore, the significant reduction in morbidity and a shorter length of hospital stay can offset the hospital costs of the laparoscopic equipment and slightly longer operative time [34]. Even though a direct cost-effectiveness analysis has not been undertaken in this review, all of these factors can potentially make LA financially more advantageous than OA in this group of patients. Regardless, the relevant cost-effectiveness of the procedure should be considered within the context of the local healthcare system.

Despite the systematic and statistical measures taken to increase its methodological rigour and improve and measure heterogeneity among included studies, this review and meta-analysis comes with a number of inherent limitations. These are directly linked to the methodological quality of the included studies. As such results should be considered per outcome for external validity as well as assessed against the potential risk of a type I or II error.

Overall, this meta-analysis has shown a higher level of evidence (level II) increasingly supporting LA as the procedure of choice in CA versus OA. LA appears to have a similar rate of IAA to OA, but with lower rates of SSI,

earlier return to oral diet and reduced length of hospital stay.

Compliance with ethical standards

Conflicts of interest There are no conflicts of interest.

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