ΜΕΤΑΠΤΥΧΙΑΚΗ ΕΡΓΑΣΙΑ

ΑΠΟΛΙΝΩΣΗ ΚΟΛΟΒΩΜΑΤΟΣ ΣΚΩΛΗΚΟΕΙΔΟΥΣ ΑΠΟΦΥΣΗΣ ΣΤΗ ΛΑΠΑΡΟΣΚΟΠΙΚΗ ΣΚΩΛΗΚΟΕΙΔΕΚΤΟΜΗ: ΜΕΤΑ-ΑΝΑΛΥΣΗ ΔΙΚΤΥΟΥ ΑΠΟ ΤΟ MINIMALLY INVASIVE SURGERY SYNTHESIS OF INTERVENTIONS AND OUTCOMES NETWORK (MISSION)

ΣΤΑΥΡΟΥ ΑΘΑΝΑΣΙΟΥ ΑΝΤΩΝΙΟΥ

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Optimal stump management in laparoscopic appendectomy: A network meta-analysis by the Minimally Invasive Surgery Synthesis of Interventions and Outcomes Network (MISSION)

Ηράκλειο Κρήτης, 2017

POSTGRADUATE DISSERTATION

OPTIMAL STUMP MANAGEMENT IN LAPAROSCOPIC APPENDECTOMY: A NETWORK META-ANALYSIS BY THE MINIMALLY INVASIVE SURGERY SYNTHESIS OF INTERVENTIONS AND OUTCOMES NETWORK (MISSION)

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Postgraduate study course

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Heraklion Crete, 2017

Μακάριος ἀνήρ, ὃς οὐκ ἐπορεύθη
ἐν βουλῇ ἀσεβῶν καὶ ἐν ὁδῷ
ἁμαρτωλῶν οὐκ ἔστη καὶ ἐπὶ
καθέδρᾳ λοιμῶν οὐκ ἐκάθισεν.

ἀλλ᾽ ἢ ἐν τῷ νόμῳ Κυρίου τὸ
θέλημα αὐτοῦ, καὶ ἐν τῷ νόμῳ
αὐτοῦ μελετήσει ἡμέρας καὶ
νυκτός.

καὶ ἔσται ὡς τὸ ξύλον τὸ
πεφυτευμένον παρὰ τὰς διεξόδους
τῶν ὑδάτων, ὃ τὸν καρπὸν αὐτοῦ
δώσει ἐν καιρῷ αὐτοῦ, καὶ τὸ
φύλλον αὐτοῦ οὐκ ἀποῤῥυήσεται·
καὶ πάντα, ὅσα ἂν ποιῇ,
κατευοδωθήσεται.

Ψαλμοί, α′ 1 – 3

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PREFACE

The idea behind this research work was born upon the observation of a higher incidence of organ/space infection (intra-abdominal abscess) following laparoscopic compared to open appendectomy. The expert panel of the European Association for Endoscopic Surgery (EAES), a member of which was the author of this work, has considered its lower risk for wound infection, the shorter convalescence and the decreased opertive pain and has favored it over conventional open surgery, which was the mainstay of treatment for over a century. However, the panel has noted a lack of evidence on the effect of different methods of ligation of the appendix stump on perioperative outcomes. This study aims to assist surgeons, clinical practice guidelines committees and policymakers in making evidence-based decisions in the respective fields. Strengths and limitations of the body of evidence and of the network geometry and specific study characteristics were specifically addressed.

ACKNOWLEDGMENTS

The present dissertation is the results of a collaborative work. The author had the idea, designed the protocol, collected the data, synthesized the evidence, interpreted the results and wrote the study. Prof. Dimitrios Mavridis performed the statistical analyses and assisted in the interpretation of the results. Prof. Anastas E. Philalithis AKC MBBS PhD MRCP MSc was the supervisor and Mr. George F. Fragiadakis PhD BSc MSc MHBA was co-supervisor of this work. Mr. Shahab Hajibandeh MD MBChB, Mr. Shahin Hajibandeh MD MBChB, Dr. Ramon Gorter MD and Dr. Mark Tenhagen MD cross-checked the data. Mr. George A. Antoniou MD PhD MSc FEBVS, Dr. Christos Koutras MD PhD MPH, Prof. Rudolph Pointer MD PhD, Prof. George E. Chalkiadakis MD PhD, Prof. Frank-Alexander Granderath MD PhD, and Hendrik Jaap Bonjer MD PhD FRCSC all made substantial comments on the content of this study.

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ΠΕΡΙΛΗΨΗ

Εισαγωγή

Η λαπαροσκοπική σκωληκοειδεκτομή είναι η κύρια μέθοδος αντιμετώπισης της οξείας σκωληκοειδίτιδας. Δεν υπάρχουν αρκετές βιβλιογραφικές ενδείξεις αναφορικά με την αποτελεσματικότερη μεθόδο απολίνωσης της σκωληκοειδούς απόφυσης. Σκοπός της παρούσης μελέτης ήταν η διερεύνηση της σχετικής αποτελεσματικότητας και η διαμόρφωση ενός πίνακα κατάταξης των μεθόδων απολίνωσης του κολοβώματος της σκωληκοειδούς απόφυσης.

Μέθοδοι

Αναζητήθηκαν ηλεκτρονικές πηγές βάσεων δεδομένων για τον εντοπισμό τυχαιοποιημένων ελεγχόμενων δοκιμών (randomized controlled trials–RCTs) που συγκρίνουν μεθόδους απολίνωσης της σκωληκοειδούς απόφυσης. Τα πρωταρχικά μέτρα έκβασης ήταν η λοίμωξη οργάνου/θέσης (organ/space infection) και η επιπολής λοίμωξη χειρουργικής θέσης (superficial surgical site infection). Πραγματοποιήσαμε μετα-ανάλυση δικτύου και εκτιμήσαμε τη σχετική κατά ζεύγη επίδραση της θεραπείας υπολογίζοντας την αναλογία πιθανοφάνειας (odds ratio–OR) και το αντίστοιχο διάστημα εμπιστοσύνης 95% (confidence interval–CI). Ιεραρχήσαμε τις ανταγωνιζόμενες μεθόδους χρησιμοποιώντας διαγράμματα κατάταξης (rankograms) και την επιφάνεια κάτωθεν της αθροιστικής καμπύλης κατάταξης (surface under the cumulative ranking curve–SUCRA).

Αποτελέσματα

Σαράντα τρεις τυχαιοποιημένες μελέτες πληρούσαν τα κριτήρια συμπερίληψης και παρείχαν δεδομένα για περισσότερους των 5000 ασθενών. Η απολίνωση με ράμμα φαινόταν να αποτελεί την πλέον αποτελεσματική μέθοδο θεραπείας, όσον αφορά τόσο στο λοίμωξη οργάνου/θέσης, όσο και στην επιπολής λοίμωξη χειρουργικής θέσης. Στατιστική σημαντικότητα παρατηρήθηκε στις συγκρίσεις αγκτήρα (clip) έναντι ενδοσκοπικού βρόγχου (endoloop) (OR 0.56, 95% CI 0.32 έως 0.96) για τη λοίμωξη οργάνου/θέσης, και ράμματος έναντι αγκτήρα (OR 0.20, 95% CI 0.08 έως 0.55), καθώς και αγκτήρα έναντι ενδοσκοπικού βρόγχου (OR 2.22, 95% CI 1.56 έως 3.13) για την επιπολής λοίμωξη χειρουργικής θέσης. Το δίκτυο ενημερώθηκε κατά κύριο λόγο από

έμμεσες συγκρίσεις θεραπειών.

Συμπεράσματα

Η χρήση απολίνωσης της σκωληκοειδούς απόφυσης στη λαπαροσκοπική σκωληκοειδεκτομή φαίνεται να υπερτερεί των λοιπών μεθόδων στο συνδυασμό παραμέτρων λοίμωξης οργάνου/θέσης και επιπολής λοίμωξης χειρουργικής θέσης.

ABSTRACT

Background

Laparoscopic appendectomy is the predominant method of treatment of acute appendicitis. There is insufficient evidence on the most effective management of the appendix stump. Aim of this study was to investigate the relative effectiveness and provide a treatment ranking of different options for securing the appendix stump.

Methods

Electronic databases were searched to identify randomized controlled trials (RCTs) comparing ligation methods of the appendix. The primary outcomes were organ/space infection and superficial surgical site infection. We performed a network meta-analysis and we estimated the pairwise relative treatment effects of the competing interventions using the odds ratio (OR) and its 95% confidence interval (CI). We obtained a hierarchy of the competing interventions using rankograms and the surface under the cumulative ranking curve (SUCRA).

Results

Forty-three RCTs were eligible and provided data for more than 5000 patients. Suture ligation appeared to be the most effective treatment strategy, in terms of both organ/space infection and superficial surgical site infection. Statistical significance was reached for the comparisons of clip versus endoloop (OR 0.56, 95% CI 0.32 to 0.96) for organ/space infection; and suture versus clip (OR 0.20, 95% CI 0.08 to 0.55) and clip versus endoloop (OR 2.22, 95% CI 1.56 to 3.13) for superficial surgical site infection. The network was informed primarily by indirect treatment comparisons.

Conclusions

The use of suture ligation of the appendix in laparoscopic appendectomy seems to be superior to other methods for the composite parameters of organ/space and superficial surgical site infection.

INTRODUCTION

Acute appendicitis affects approximately 0.11% of the Western population [1]. Surgical resection of the inflamed appendix is the most common intervention, whereas antibiotic therapy has been proposed as a treatment option in selected cases. Laparoscopic appendectomy is an effective alternative to open appendectomy and is performed with an increasing trend in Europe and the United States [2–5]. A recent Consensus Statement of the European Association for Endoscopic Surgery has suggested laparoscopic appendectomy be the treatment of choice for acute appendicitis [6].

There is, however, insufficient evidence on the most effective management of the appendix stump, because high quality direct comparative evidence is lacking. The four prominent management options are endoloops, sutures, endoclips and endoscopic staplers. Each of these options has been applied in randomized comparisons between laparoscopic and conventional (i.e. open), single-incision or needlescopic appendectomy, and conservative treatment. Comparative treatment effect estimates may be obtained using statistical methods applying indirect treatment comparisons such as network meta-analysis [7,8].

Aim of the present study was to comparatively assess the safety and efficiency of management options of the appendix stump in patients subjected to laparoscopic appendectomy and to provide an evidence-based treatment ranking via applying network meta-analysis methods on the outcomes of available randomized controlled trials (RCTs).

MATERIALS AND METHODS

Protocol and registration

The protocol of this systematic review and network meta-analysis was registered at the publicly available registry of the University of York (http://www.crd.york.ac.uk/PROSPERO/; registration number: CRD42016032730). Our review complied with the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions [9].

Outcome measures

The outcomes of interest were organ/space infection and superficial surgical site infection, as defined by the Centers for Disease Control and Prevention [10].

Eligibility criteria

Patients with acute appendicitis of any stage (acute focal, purulent, gangrenous, perforated) were included. Individuals of any age and gender were considered. The working diagnosis should have been established with any or a combination of physical examination, ultrasonography, computed tomography, or magnetic resonance imaging. Studies reporting on patients subjected to diagnostic laparoscopy without preoperative establishment of diagnosis were included, provided laparoscopic appendectomy was the only procedure undertaken. We included RCTs comparing methods of ligation of the appendix, including endoloop, laparoscopic suture, endoclip and endoscopic stapler, to open appendectomy, single-incision appendectomy, needlescopic appendectomy, and conservative treatment, or to each other. Non-randomized studies were excluded, because significant selection bias was expected to challenge the

transitivity within the network context [11]. Transitivity refers to the ability to learn about the relative effectiveness between treatments indirectly.

Information sources, search and study selection

The electronic databases of MEDLINE (Pubmed); EMBASE, AMED, CINAHL (OpenAthens); and CENTRAL (Wiley Online) were searched. The grey literature was interrogated using OpenGrey (Exalead). No date, language, or article type restrictions were applied. Titles and abstracts were screened by the primary review author and cross-checked by another two independent review authors (SH, SH) against our eligibility criteria. The full texts of records considered to be relevant were retrieved and assessed. Articles satisfying our inclusion criteria were included in qualitative and quantitative synthesis. The reference lists of selected articles were also screened. The last search was run in February 2016 and the cross-check was performed in March 2016.

Data items and collection process

Data of interest were collected from each article. We contacted the authors of selected articles via e-mail, requesting to cross-check the extracted data and complete missing information, if there was any. Data abstraction was performed by the primary review author. The data were cross-checked by two independent review authors (RG, MT). Discrepancies were resolved by discussion; an independent review author (GA) acted as an arbitrator. An electronic datasheet based on the Cochrane Consumers and Communication Review Group's data extraction template was constructed and pilot-tested on the three most recent studies and refined accordingly in liaison with the biostatistician of the group (DM).

Risk of bias within studies

The primary review author and another two review authors (RG, MT) independently evaluated the risk of bias of each study using the Cochrane Collaboration's Tool [12]. Disagreements were resolved by discussion, and a third review author acted as an arbitrator (GA). More specifically, the following criteria were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. An industry-sponsored study was conventionally considered of high risk of bias; if the source of funding was not reported or the authors did not disclose conflicts of interest, no judgment was made (unclear risk of bias). Risk of bias assessment was summarized using Review Manager 5.3 (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Statistical analysis

Detailed information on methods of analysis is available in the appendix. We first conducted pairwise meta-analyses for each pair of interventions using a random-effects model in Stata/SE (StataCorp. Stata Statistical Software. College Station, TX: StataCorp LP; 2013). We estimated the pairwise relative treatment effects of the competing interventions using the odds ratio (OR) and 95% confidence interval (CI). Summary results were produced for all outcomes.

We performed a network meta-analysis in Stata using the *network* command and self-programmed Stata routines [13–15]. We used the restricted maximum likelihood method to estimate heterogeneity assuming a common estimate for the heterogeneity variance across the different comparisons. Differences between direct and indirect evidence were explored by

computing the inconsistency factor within each closed loop of evidence. We also employed the node-splitting approach, which separates evidence on a particular comparison into ‘direct’ and ‘indirect’ [16].

To check the assumption of consistency in the entire network, we used the ‘design-by-treatment’ model [17,18]. We estimated the contribution of each direct comparison to each of the summary estimates using the contribution plot, as has been previously described [19]. We estimated the ranking probabilities for all treatments of being at each possible rank for each intervention. We obtained a hierarchy of the competing interventions using rankograms and the surface under the cumulative ranking curve (SUCRA) and mean ranks [20]. We produced the relevant plots using the suite of Stata commands by Chaimani et al [21].

RESULTS

Study selection

After exclusion of duplicate records, 152 out of 1504 articles were selected for full text review, and 43 articles provided data suitable for quantitative synthesis [22–64]. The study selection process is outlined in **Fig. 1**. Detailed information on study selection and reasons for exclusion is available upon request. The network geometry of studies reporting on organ/space infection and superficial surgical site infection is illustrated using network plots in **Fig. 2**.

Network characteristics

Data on 5171 patients were available for the outcome measure organ/space infection and data on 5853 patients were available for superficial surgical site infection. With regard to the primary outcome measures, most trials compared laparoscopic appendectomy using endoloops versus conventional appendectomy (n=21), followed by stapled laparoscopic versus conventional appendectomy (n=7), and sutured laparoscopic versus conventional appendectomy (n=4). There were two three-arm studies [26,63]. Direct head-to-head comparisons were available only for

closure with sutures versus clips (n=2) and endoloops versus clips (n=1). Due to the complexity of the network, there were multiple pathways to inform indirect treatment comparisons and to assess the presence of inconsistency between direct and indirect evidence, including different routes of indirect evidence.

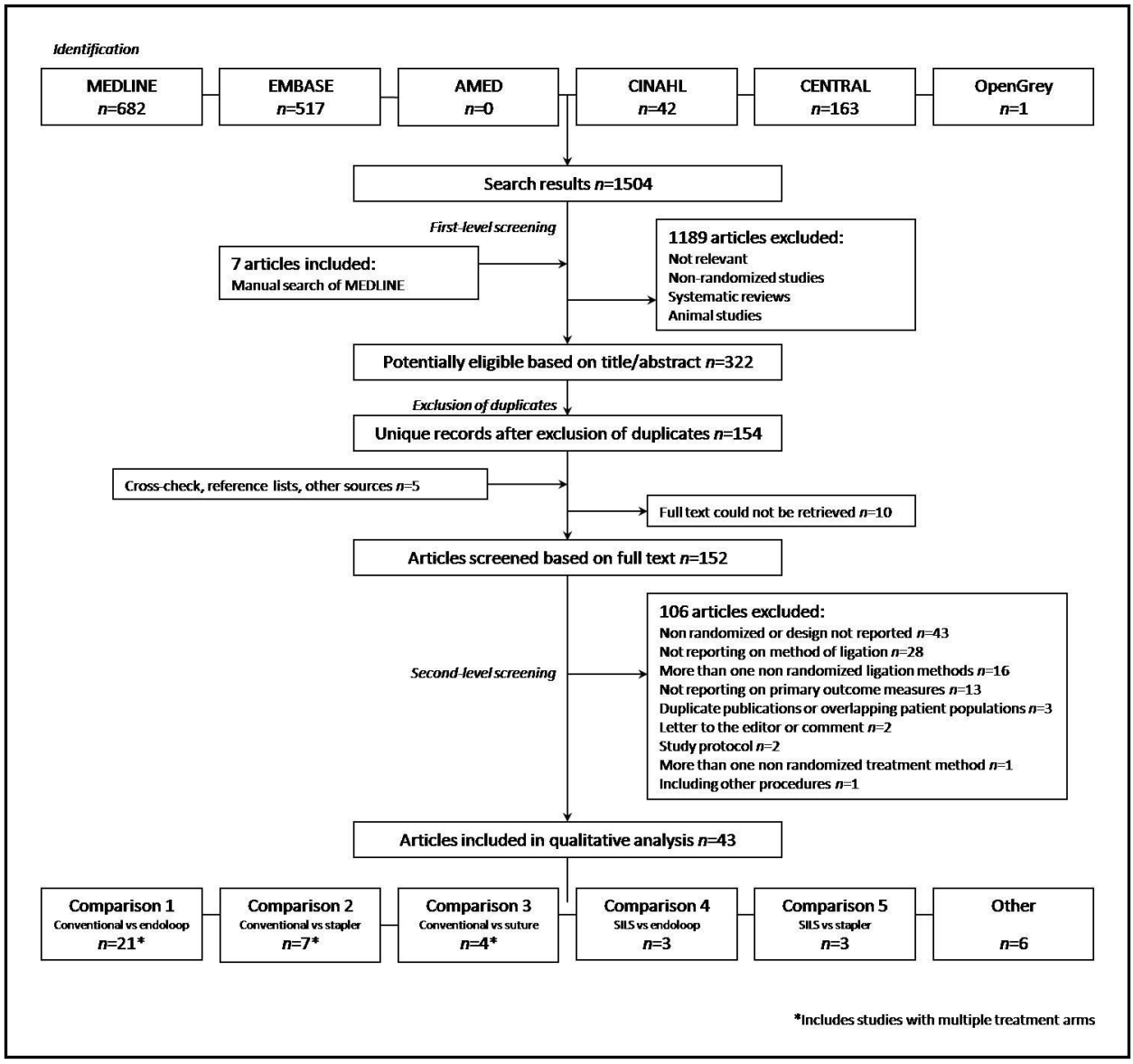

Fig. 1 *Flow chart of search and study selection history.*

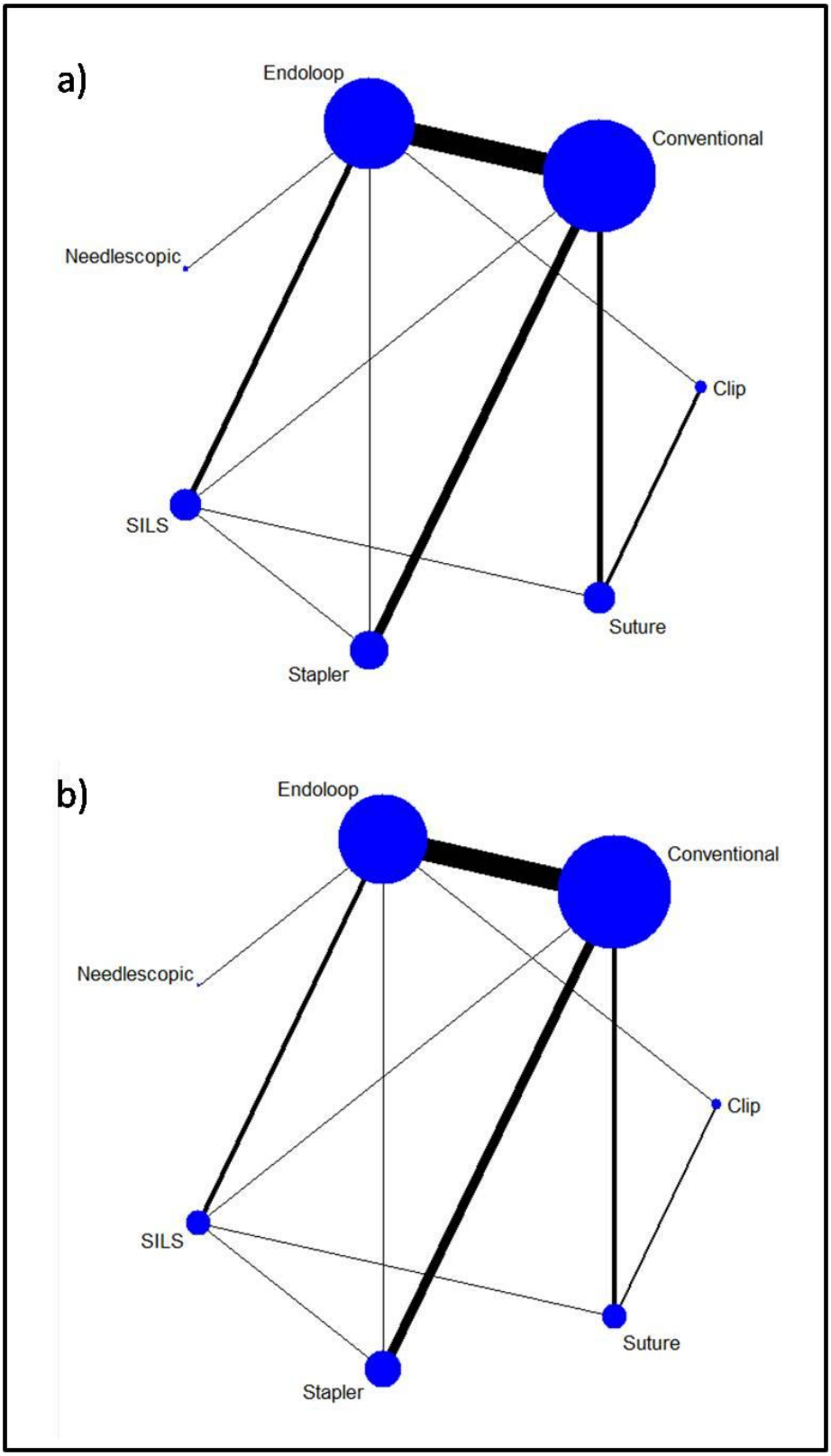

Fig. 2 *Network plots for the outcomes a) organ/space infection and b) superficial surgical site infection. The size of nodes is proportional to the number of trials reporting the relevant treatment. Edges are weighted according to the inverse variance of the direct treatment effect estimates for the respective comparisons.*

Study characteristics

Study characteristics are summarized in **Table 1** and detailed in the appendix. Most studies were conducted in one or two centers, whereas in one study there were 10 participating centers [26]. There was generally no significant variation of inclusion and exclusion criteria, although several studies enrolled patients with complicated or uncomplicated appendicitis confirmed with diagnostic imaging, whereas other studies considered patients with clinical suspicion of appendicitis. Furthermore, three studies included only pediatric patients [33,49,58], one study included only females [51], two studies included only males [29,41], and one study included military patients, predominantly males [38]. Risk of bias assessment is summarized in **Fig. 3** and detailed in the appendix. The main findings were poor reporting of allocation concealment, blinding and conflicts of interest. Individual study outcomes are provided in the appendix.

Synthesis of results

We did a random-effects network meta-analysis to evaluate the relative effectiveness between the competing treatments and provide a hierarchy of ranking. Suture ligation of the appendix stump appeared to be the most effective treatment strategy, in terms of both organ/space infection and superficial surgical site infection, according to the estimated relative effects and SUCRA values. However, the estimates for the relative effectiveness of suture ligation versus other competing treatments were wide, because most trials had a small number of events. Furthermore, statistical significance was reached only for the comparisons of clip versus endoloop (OR 1.80, 95% CI 1.04 to 3.14) and clip versus needlescopic (OR 4.69, 95% CI 1.03 to 21.25) for organ/space infection; and suture versus clip (4.90, 95% CI 1.81 to 13.23) and clip versus endoloop (0.45, 95% CI 0.32 to 0.64) for superficial surgical site infection. **Tables 2 and**

	Year	Intervention(s)/control	Intervention(s) control (*n*)
Endoloop			
Attwood et al[22]	1992	Endoloop vs conventional	30/32
Tate et al[23]	1993	Endoloop vs conventional	46/42
Kum et al[24]	1993	Endoloop vs conventional	52/57
Hebebrand et al[25]	1994	Endoloop vs conventional	25/23
Ortega et al[26]	1995	Endoloop vs stapler vs conventional	89/78/86
Hansen et al[27]	1996	Endoloop vs conventional	79/72
Mutter et al[28]	1996	Endoloop vs conventional	50/50
Cox et al[29]	1996	Endoloop vs conventional	33/31
Hart et al[30]	1996	Endoloop vs conventional	44/37
Reiertsen et al[31]	1997	Endoloop vs conventional	42/42
Pedersen et al[32]	2001	Endoloop vs conventional	282/301
Little et al[33]	2002	Endoloop vs conventional	44/44
Al-Mulhim et al[34]	2002	Endoloop vs conventional	30/30
Lintula et al[35]	2002	Endoloop vs conventional	48/54
Milewczyk et al[36]	2003	Endoloop vs conventional	96/104
Lau et al[37]	2005	Endoloop v sneedlescopic	189/174
Ricca et al[38]	2007	Endoloop vs conventional	27/24
Shaikh et al[39]	2009	Endoloop vs conventional	48/52
Wei et al[40]	2010	Endoloop vs conventional	112/108
Tzovaras et al[41]	2010	Endoloop vs conventional	75/72
Khalil et al[42]	2011	Endoloop vs conventional	72/75
Goudar et al[43]	2011	Endoloop vs conventional	114/120
Park et al[44]	2012	Endoloop vs SILS	62/42
Teoh et al[45]	2012	Clip vs SILS	97/98
Colac et al[46]	2013	Endoloop vs clip	26/27
Kye et al[47]	2013	Endoloop vs SILS	52/52
Cipe et al[48]	2014	Endoloop vs conventional	121/120
Wu et al[49]	2015	Endoloop vs SILS	30/30
Stapler			
Ortega et al[26]	1995	Stapler vs endoloop vs conventional	78/89/86
Martin et al[50]	1995	Stapler vs conventional	81/88
Laine et al[51]	1997	Stapler vs conventional	25/25
Klingler et al[52]	1998	Stapler vs conventional	87/82
Bauwens et al[53]	1998	Stapler vs conventional	26/28
Katkhouda et al[54]	2005	Stapler vs conventional	113/134
Moberg et al[55]	2005	Stapler vs conventional	81/82
Simon et al[56]	2009	Stapler vs conventional	20/20
Frutos et al[57]	2013	Stapler vs SILS	91/93
Perez et al[58]	2013	Stapler vs SILS	25/25
Suture			
Olmi et al[59]	2005	Suture vs conventional	150/138
Kaplan et al[60]	2009	Suture vs conventional	50/50
Ates et al[61]	2012	Suture vs clip	31/30

Gonenc et al[62]	2012	Suture vs clip	46/61
Sozutek et al[63]	2013	Suture vs conventional vs SILS	25/25/25
Kocatas et al[64]	2013	Suture vs conventional	50/46
Clip			
Ates et al[61]	2012	Clip vs suture	30/31
Gonenc et al[62]	2012	Clip vs suture	61/46
Colac et al[46]	2013	Clip vs endoloop	26/27

SILS: single-incision laparoscopic surgery

Table 1. *Randomized trials, comparisons and number of patients included in the network meta-analysis*

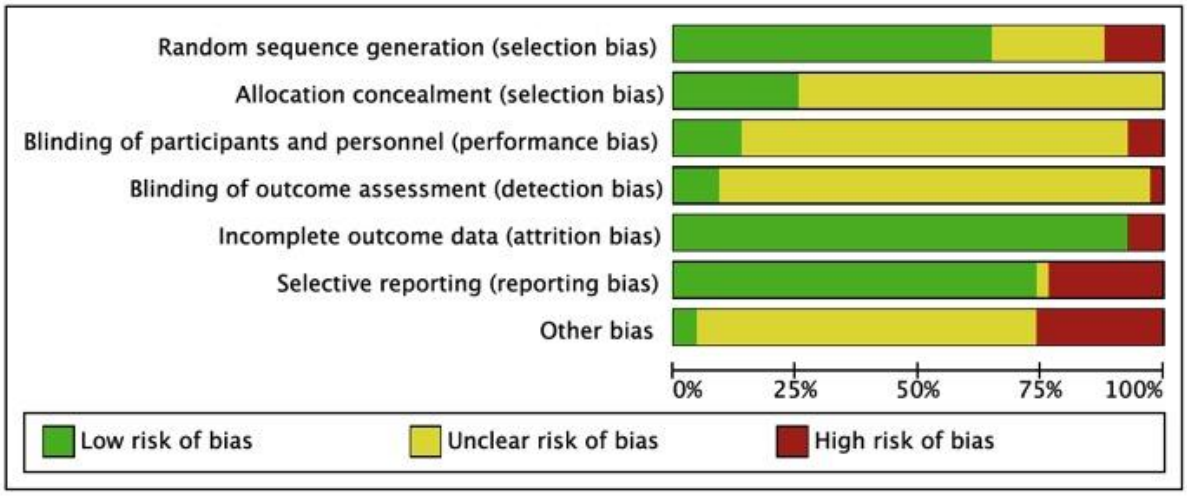

Fig. 3 *Review authors' judgments of risk of bias presented as percentages across all included studies.*

3 list ORs and interval estimations for all direct and mixed comparisons. The rankograms illustrating the probability of each treatment ranking are presented in **Fig. 4**. The scatter plot of **Fig. 5** demonstrates the composite SUCRA values for organ/space infection and superficial surgical site infection of each treatment strategy. The bar charts of study limitations provided in

	Suture	Conventional	Stapler	Clip	SILS	Endoloop	Needlescopic
Suture	*86.6 (57.8)*	0.52 (0.08, 3.57)	0.49 (0.12,2.04)	0.61 (0.18, 2.08)	0.32 (0.06, 1.64)	0.34 (0.09, 1.25)	**0.13 (0.02, 0.89)**
Conventional	0.63 (0.17, 2.33)	*72.3 (10.5)*	0.94 (0.11, 8.33)	1.18 (0.15, 9.09)	0.62 (0.06, 6.25)	0.65 (0.08, 5.26)	0.25 (0.02, 3.13)
Stapler	-	0.75 (0.34, 1.66)	*57.6 (7.5)*	1.25 (0.59, 2.63)	0.65 (0.18, 2.44)	0.69 (0.30, 1.61)	0.27 (0.05, 1.37)
Clip	0.37 (0.04, 3.57)	-	-	*56.5 (20.3)*	0.52 (0.16, 1.70)	**0.56 (0.32, 0.96)**	**0.21 (0.05, 0.97)**
SILS	1.00 (0.02, 52.63)	1.00 (0.02,52.36)	1.00 (0.02,52.63)	-	*35.5 (3.3)*	1.05 (0.36, 3.13)	0.41 (0.07, 2.38)
Endoloop	-	0.54* (0.29, 1.01)	0.62 (0.13, 3.03)	0.33 (0.01, 8.33)	1.22 (0.39, 3.85)	*34.6 (0.0)*	0.39 (0.09, 1.56)
Needlescopic	-	-	-	-	-	0.39 (0.10, 1.52)	*6.9 (0.6)*

Estimates are presented as OR with 95% CI in parentheses.
ORs above 1 suggest that the treatment listed in the upper row is superior; ORs below 1 suggest that the treatment listed in the left column is superior. Surface under the cumulative ranking curve values (SUCRAs) are given in the diagonal and the probability of being the best treatment in parentheses. Statistically significant values are given in bold.
SILS: Single-incision laparoscopic surgery
*τ^2=0.1243; τ^2 values for each other direct meta-analysis of at least two RCTs are equal to 0.0000

Table 2. *League table demonstrating the relative effectiveness for each pair of comparison for organ/space infection. The upper right half lists mixed network meta-analysis outcomes; the right lower half lists direct meta-analysis outcomes.*

the appendix suggest that indirect comparisons were mainly informed by studies with unclear risk of bias, which limits our confidence on the mixed effects estimates. We did not find evidence of inconsistency between direct and indirect evidence by comparing direct and indirect estimates using the inconsistency factor and the node-splitting method, as shown in the appendix. This finding could be genuine, or it can be caused by the small number of events in most trials, which results in wide CIs for most relative effects and may mask inconsistency.

	Needlescopic	Suture	Clip	Endoloop	Stapler	SILS	Conventional
Needlescopic	*82.0 (64.1)*	0.47 (0.02, 12.50)	0.10 (0.01, 2.08)	0.22 (0.01, 4.55)	0.16 (0.01, 3.57)	0.16 (0.01, 3.70)	0.35 (0.01, 11.10)
Suture	-	*80.1 (19.5)*	**0.20 (0.08, 0.55)**	0.45 (0.16, 1.27)	0.34 (0.11, 1.06)	0.34 (0.10, 1.22)	0.74 (0.14, 3.85)
Clip	-	1.89 (0.23, 16.67)	*64.5 (15.8)*	**2.22 (1.56, 3.13)**	1.67 (0.92, 2.94)	1.64 (0.69, 4.00)	3.57 (0.65, 20.00)
Endoloop	0.22 (0.01, 4.55)	-	2.17 (0.19, 25.00)	*50.9 (0.3)*	0.75 (0.38, 1.47)	0.75 (0.33, 1.72)	1.64 (0.30, 9.09)
Stapler	-	-	-	8.33 (0.44, 100.00)	*33.8 (0.0)*	1.00 (0.36, 2.78)	2.17 (0.35, 14.29)
SILS	-	1.00 (0.06, 16.67)	-	0.65 (0.26, 1.64)	1.02 (0.02, 50.00)	*33.8 (0.3)*	2.17 (0.33, 14.29)
Conventional	-	**0.16 (0.05, 0.44)**	-	**0.47 (0.33, 0.66)**	0.60 (0.33, 1.09)	0.31 (0.03, 3.13)	*5.0 (0.0)*

Estimates are presented as OR with 95% CI in parentheses.
ORs above 1 suggest that the treatment listed in the upper row is superior; ORs below 1 suggest that the treatment listed in the left column is superior. Surface under the cumulative ranking curve values (SUCRAs) are given in the diagonal and the probability of being the best treatment in parentheses. Statistically significant values are given in bold.
SILS: Single-incision laparoscopic surgery
τ^2 values for each direct meta-analysis of at least two RCTs are equal to 0.0000

Table 3. *League table demonstrating the relative effectiveness for each pair of comparison for surgical site infection. The upper right half lists mixed network meta-analysis outcomes; the right lower half lists direct meta-analysis outcomes.*

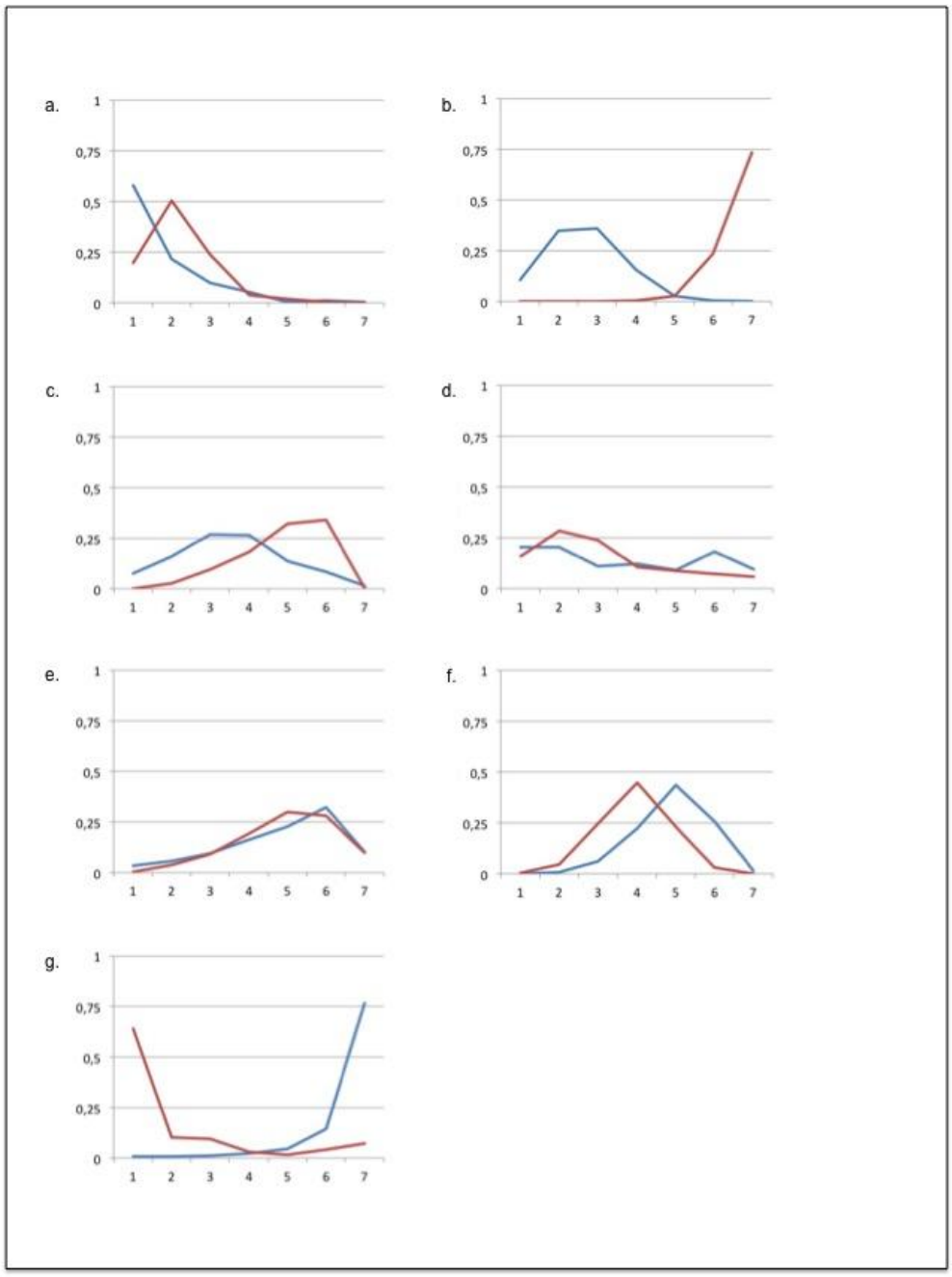

Fig. 4 *Rankogram of treatment strategies for securing the appendix stump for organ/space infection and superficial surgical site infection. The red line represents the probability (vertical line) of each treatment to rank first, second, third etc. (horizontal line). a: Suture; b: Conventional; c: Stapler; d: Clip; e: SILS; f: Endoloop; g: Needlescopic.*

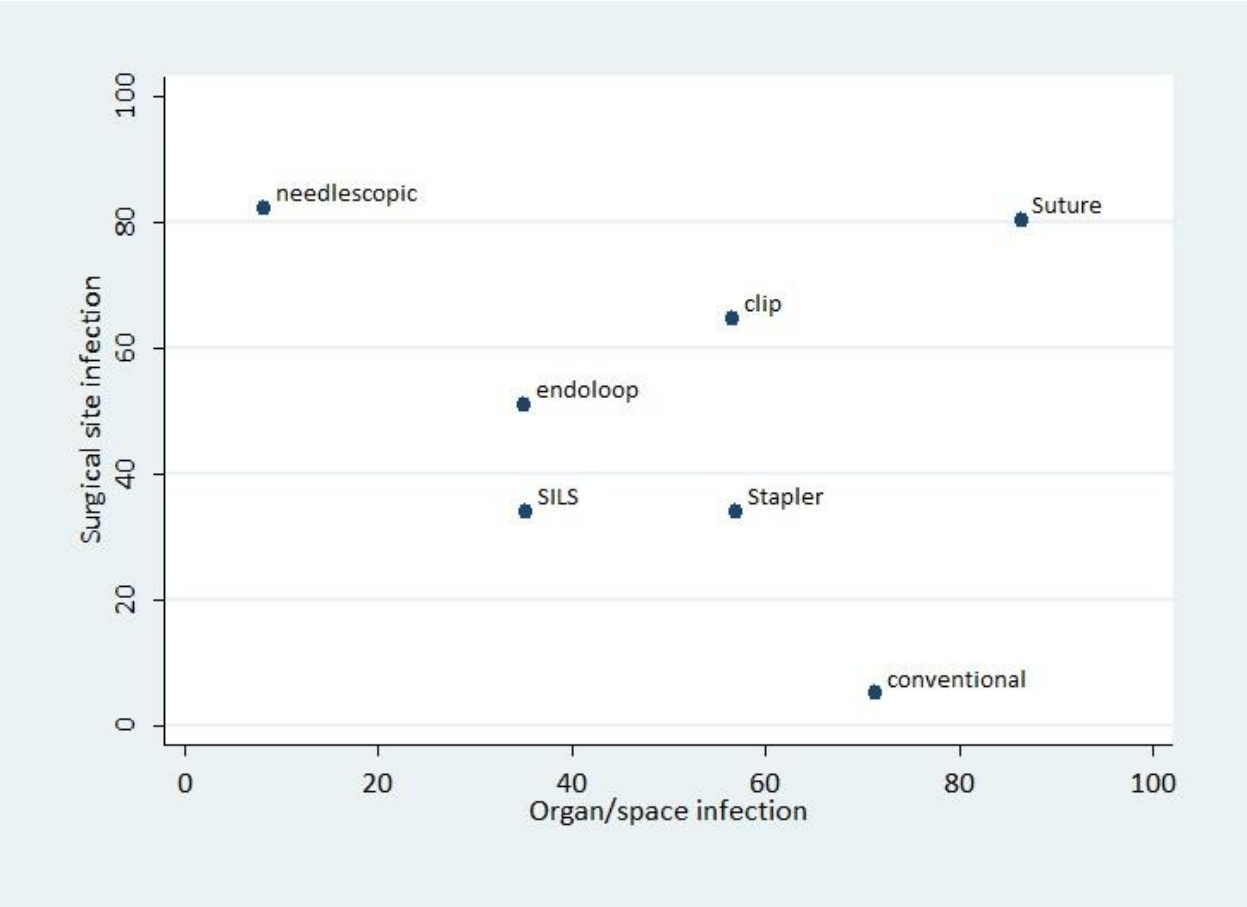

Fig. 5 *Scatter plot of surface under the cumulative ranking curve values of treatment strategies against organ/space infection and superficial surgical site infection. Items at the top right corner correspond to the least harmful combined effect, whereas items at the bottom left corner demonstrate the more harmful combined effect.*

DISCUSSION

This is the first meta-synthesis of evidence addressing the relative treatment effects of different methods of securing the appendix stump in laparoscopic appendectomy. The network was sparse for both primary outcomes and the statistical power was low to detect significant differences. Most CIs were wide, reflecting the uncertainty around relative effect estimates, not only because of the small number of trials for some comparisons, but also because most trials had a low number of events. Only five randomized trials have directly compared ligation methods of the appendix [26,44,46,61,62], and therefore estimation of the relative treatment effects using conventional direct meta-analysis methods is associated with uncertainty. Current guidelines do not favor one method over another, due to lack of robust comparative evidence. Network meta-analysis synthesizes both direct and indirect evidence providing more powerful estimates and allowing comparisons of relative effectiveness between interventions that have never been compared head to head.

Suture ligation was the most effective strategy with regard to the key endpoint of organ/space infection, as it achieved a larger SUCRA and had greater possibility of being more effective treatment than conventional appendectomy. This is of specific importance, considering that postoperative abscess remains a concern in laparoscopic appendectomy [65]. Indeed, conventional appendectomy was ranked higher than other laparoscopic ligation methods in terms of postoperative abscess, albeit without reaching statistical significance. Laparoscopic appendectomy with suture ligation of the appendix had a 5.5-fold probability of being a better treatment strategy compared to conventional appendectomy, which merits further investigation.

The second key finding of this analysis refers to the ranking of the suture closure technique as the best method associated with the least comparative risk of superficial surgical site infection, whereas stapler ligation appears to be the least efficacious in terms of reducing the risk of superficial surgical site infection. This may be related to the fact that conventional stapling devices require changing of the working port to a 12mm or a 15mm trocar, resulting in greater tissue damage. Needlescopic appendectomy was most effective treatment with regard to this outcome parameter, however it was ranked last in terms of organ/space infection, which makes it a less favorable treatment approach for this reason. Clip ligation had an approximately 5-fold risk of superficial surgical site infection compared to suture ligation, albeit with a wide interval estimate. None of the other treatment strategies were significantly inferior to suture ligation, however the possibilities of being the best treatments were virtually zero. In an attempt to combine the two outcome endpoints of organ/space infection and superficial surgical site infection, we plotted each treatment's SUCRA values on a two-dimensional table with the two axes corresponding to the two outcomes **(Fig. 4)**. Suture ligation seemed to be the most effective treatment when considering both outcome endpoints.

Compared to endoloops, staplers and clips, sutures are without doubt the least expensive material. Nevertheless, operation time and the associated costs need to be taken into account. Mastering of laparoscopic suturing techniques may allow for a low cost appendectomy, while providing optimal postoperative outcomes. Available trials do not provide adequate data to perform a cost analysis. Several observational studies suggest a cost advantage of endoloop and clip ligation over stapler ligation [66–74]. There is a lack of data comparing the cost of suture ligation with other methods of securing the appendix stump. Future trials need to focus on the

cost effectiveness of suture ligation, taking into account the operative time and other resource utilization parameters, such as hospital length of stay, days taken off work for the treated patients etc. Although suture ligation in laparoscopic appendectomy appears to be a suitable method for uncomplicated appendicitis, it can be hypothesized that acute appendicitis with inflammatory infiltration of the appendix base may be best treated by stapler ligation or open surgery.

Another interesting finding of this analysis is the comparative risk of needlescopic appendectomy for organ/space infection, where ORs ranged between 0.13 and 0.39. Statistical significance was not reached in any of the comparison due to wide estimate intervals, as a result of the fact that only one study encompassing 363 patients contributed to the network [37]. Since it is rather unlikely that further adequately powered randomized trials will assess the risk of organ/space infection, it seems reasonable to suggest that needlescopic appendectomy be avoided, because of a high level of suspicion of this method being associated with a higher risk of postoperative abscess.

Evaluation of the confidence in treatment ranking, using the procedure proposed by Salanti et al. [75], suggests making a weak recommendation based on moderate level of evidence, as outlined below.

Domain	Risk of bias	Downgrading
Study limitations	serious	yes (-)
Indirectness (Joint consideration of indirectness and intransitivity)	not serious	no
Inconsistency (Joint consideration of statistical heterogeneity and statistical inconsistency)	not serious	no

(continued)		
Imprecision	very serious	yes (yes -/-)
Publication bias	not serious	no

Table 4. *Evaluation of confidence in treatment ranking*

This consideration needs to be taken into account by surgeons making clinical decisions and health institution administrators deciding on institutional guidelines. The latter will need to undertake a SWOT analysis on an individual basis, considering the following:

Strengths: The presence of laparoscopic equipment, the availability of an operating room suitable for laparoscopic procedures and the level of surgical competency in laparoscopic procedures.

Weaknesses: The incidence of complications in laparoscopic procedures, their long duration and the lack of training of operating room staff in laparoscopic procedures.

Opportunities: Young-aged surgical staff may be more flexible in the incorporation of new surgical modalities. The availability or the opportunity to obtain quality laparoscopic equipment needs also to be taken into account. Considerations associated to direct and indirect costs, such as the lack of adequate resources to purchase endoscopic staplers or the temporary lack of endoloops may not justify precluding the performance of laparoscopic appendectomies in a specific institution. Research grants may be an optimal opportunity to implement a clinical trial investigating the clinical effectiveness and the cost-benefit association including operative time of suture ligation laparoscopic and conventional appendectomy.

Threats: Lack of compliance with changes in surgical practice may represent the main threat.

The results of this analysis need to be considered under the prism of several limitations. Events were generally rare for both outcome measures. Meta analysis is known to give misleading results for rare events. This is expected, as meta-analytical methods rely on asymptotic statistical theory. An increase in sample size will not certainly solve the problem because, although events would increase, the control probabilities would remain unchanged. Rare events may cause biased estimates or wide confidence intervals with subsequent low power to detect statistical significant differences. Furthermore, inspection of the interval plot suggests that, although statistical significance was observed in several comparisons, the ranges of predictive intervals for these comparisons include the value 1. This means that further trials may change the summary estimates of this analysis.

Indirect treatment effects estimates were largely informed by RCTs of unclear risk of bias, therefore downgrade of the provided evidence may be reasonable. Furthermore, large CIs may mask inconsistency and prevent identifying differences between direct and indirect evidence. Although no inconsistency was found, this was expected because most studies had a low number of events and this led to much uncertainty. Another limitation is that directs comparisons of treatment methods contribute 20.9% and 16.5% to the entire network, for the outcomes superficial surgical site infection and organ/space infection, respectively. Furthermore, RCTs comparing SILS with clip, stapler and suture ligation were of high methodological quality; however their contribution to the network was only 5.7% and 5.8%, respectively.

Due to inadequate reporting, it was not possible to employ subgroup analyses for the grade of appendicitis and the presence of inflammation of the appendix base. This would provide further insight into the comparative risk of postoperative abscess and superficial surgical site

infection and would allow treatment ranking based on the extent and the level of inflammation. Treatment effects on specific patient groups, such as children, patients with diabetes or those under chemotherapy could not be assessed with sensitivity analyses, due to poor reporting. Individual patient meta-analysis may shed light into the hypothesis that immunomodulated patients may benefit from conventional surgery. Furthermore, cost analysis could not be undertaken, because of the scarcity of data. Similarly, valuable information would be provided by comparative analyses of resource utilization, such as hospital or high dependency/intensive care unit length of stay. Also, quality of life, recovery time, time off work, pain scores etc. do not seem to have been investigated and might constitute implications for future research. Operative experience of participating surgeons was inconsistently reported, which limits the external validity of the reported results.

This systematic review generates new hypotheses and identifies areas for future research. A well-designed and adequately powered randomized trial is needed to draw solid conclusions on the comparative efficacy of suture ligation laparoscopic appendectomy and conventional appendectomy with regard to organ/space infection. Confirmation of the null hypothesis would address any doubts with regard to the safety of the laparoscopic procedure. Future trials need to further report on operative times of suture ligation laparoscopic appendectomy.

CONCLUSION

This network meta-analysis suggests that the use of suture ligation of the appendix in laparoscopic appendectomy may be superior to other methods of appendix stump closure.

Needlescopic appendectomy seems to be inferior to other treatment options with regard to postoperative abscess, whereas conventional appendectomy carries the highest risk of superficial surgical site infection.

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DISCLOSURES

Stavros A. Antoniou was member of the expert panel for the development of the 2015 European Association for Endoscopic Surgery Consensus Conference Guidelines for the treatment of acute appendicitis. Ramon Gorter and Mark Tenhagen were members of the research team for the development of the 2015 European Association for Endoscopic Surgery Consensus Conference Guidelines for the treatment of acute appendicitis. Hendrik Jaap Bonjer was head of the expert panel for the development of the 2015 European Association for Endoscopic Surgery Consensus Conference Guidelines for the treatment of acute appendicitis and reports consultancy for Olympus, Medtronic and Ethicon EndoSurgery, has received educational grant from Stryker and research grants from Medtronic, Applied Medical and Ethicon EndoSurgery, all outside the submitted work. Dimitrios Mavridis, Shahab Hajibandeh, Shahin Hajibandeh, George A. Antoniou, Christos Koutras, Rudolph Pointer, George E. Chalkiadakis, Frank-Alexander Granderath, George F. Fragiadakis and Anastas E. Philalithis have no conflict of interest or financial ties to disclose.

APPENDIX

Optimal stump management in laparoscopic appendectomy: a network meta-analysis by the Minimally Invasive Surgery Synthesis of Interventions and Outcomes Network (MISSION)

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1. Search syntax for electronic databases

a. MEDLINE via Pubmed

Search No	Search strategy
#1	MeSH descriptor: [laparoscopy] explode all trees
#2	laparoscop*: TI,AB,KW
#3	#1 OR #2
#4	MeSH descriptor: [appendectomy] explode all trees
#5	appendectomy: TI,AB,KW
#6	appendicectomy: TI,AB,KW
#7	#4 OR #5 OR #6
#8	laparoscop* near2 appendectomy: TI,AB,KW
#9	laparoscop* near2 appendicectomy: TI,AB,KW
#10	#3 OR #7 OR #8 OR #9
#11	MeSH descriptor: [surgical procedures, operative] explode all trees
#12	surgical* and procedure* and operat*: TI,AB,KW
#13	MeSH descriptor: [general surgery] explode all trees
#14	surgery: TI,AB,KW
#15	general near2 surgery: TI,AB,KW
#16	#11 OR #12 OR #13 OR #14 OR #15
#17	MeSH descriptor: [clinical trials, randomized] explode all trees
#18	random* and control* and trial* TI,AB,KW
#19	random* near2 trial*: TI,AB,KW
#20	random*: TI,AB,KW
#21	trial*: TI,AB,KW
#22	MeSH descriptor: [placebos] explode all trees
#23	placebo*: TI,AB,KW
#24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	#10 AND #16 AND #24

b. EMBASE, AMED and CINAHL via OpenAthens

Search No	Search strategy
#1	laparoscopy: AF
#2	appendectomy: AF
#3	appendicectomy: AF
#4	#2 OR #3
#5	surgery: AF
#6	randomized: TI,AB
#7	placebo: TI,AB
#8	randomly: TI,AB
#9	trial: TI,AB
#10	groups: TI,AB
#11	#6 OR #7 OR #8 OR #9 OR #10
#12	#1 AND #4 AND #11

c. CENTRAL via Wiley Online Library

Search No	Search strategy
#1	MeSH descriptor: [laparoscopy] explode all trees
#2	laparoscop*: TI,AB,KW
#3	#1 OR #2
#4	MeSH descriptor: [appendectomy] explode all trees
#5	appendectomy: TI,AB,KW
#6	appendicectomy: TI,AB,KW
#7	#4 OR #5 OR #6
#8	MeSH descriptor: [surgical procedures, operative] explode all trees
#9	surgical* and procedure* and operat*: TI,AB,KW
#10	MeSH descriptor: [general surgery] explode all trees
#11	surgery: TI,AB,KW
#12	#8 OR #9 OR #10 OR #11
#13	#3 AND #7 AND #12

d. OpenGrey via Exalead

Search No	Search strategy
#1	laparoscop*
#2	appendectomy
#3	appendicectomy
#4	#2 OR #3
#5	#1 AND #4

2. Extracted data items

I. Study-related data
primary author
year of publication
journal of publication
primary institution
country (or countries) where the study was conducted
number of participating institutions
inclusion and exclusion criteria
perioperative antibiotics administration (type of antibiotic, dosage, duration of antibiotic treatment)
treatment method of study group(s) and the reference group
method of stump management in the study group(s) and the reference group

II. Disease severity data
complicated/uncomplicated, acute focal, purulent, gangrenous, perforated appendicitis, macroscopic inflammation of the appendix base

III. Treatment outcome data
organ/space infection and superficial surgical site infection in the study group(s) and the reference group
method and definition of diagnosis
cost of treatment in the study group(s) and the reference group

3. Methods of analysis

Relative treatment effects

First, we conducted a pairwise meta-analysis for each pair of interventions using a random-effects model in Stata/SE (StataCorp/LP, TX, USA). A random-effects model assumes that different studies assessed different yet related treatment effects. We estimated the pairwise relative treatment effects of the competing interventions using odds ratios (OR) for the primary dichotomous outcomes (organ/space infection and superficial surgical site infection). We planned to estimate mean differences for continuous variables of secondary outcome measures. If studies would use different scales, we planned to use standardized mean differences. We produced summary results for all outcomes and gave 95% confidence intervals. We used restricted maximum likelihood to estimate heterogeneity. If there would be studies reporting the median and interquartile range (IQR), we planned to include these studies in a sensitivity analysis assuming that they come from a normal distribution (mean=median, standard deviation=IQR/1.35), recognizing the fact that most probably normality would not hold in these studies. If studies would report the median and range, we planned to use the methodology developed by Hozo et al to compute mean and standard deviations.[1] If studies would not report the standard deviation we planned to estimate it from the 95% confidence interval, the p-value, the standard error or other information, which allows estimation of the standard deviation.[2] If studies would not report the standard deviation, we would impute it in a sensitivity analysis by borrowing it from other studies and more specifically from that with the largest estimated standard deviation.[3]

Methods for indirect and mixed comparisons

The network was expected to provide also indirect evidence for the relative effectiveness/safety of any pair of interventions, if these interventions are compared in studies sharing a common comparator. For example, if there are studies comparing needlescopic appendectomy to open appendectomy and studies comparing single-incision laparoscopic appendectomy to open appendectomy, these two sets of studies provide indirect evidence for the relative effectiveness/safety between needlescopic appendectomy and single-incision laparoscopic appendectomy. Network meta-analysis (NMA) synthesizes direct and indirect evidence and allows estimation of the relative effectiveness between any pair of interventions, even if these have not been compared head-to-head in any of the included trials. We performed network meta-analysis in Stata using the mvmeta command,[4] and self-programmed Stata routines available at http://www.mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis and published by Chaimani et al.[5] We used the restricted maximum likelihood method to estimate heterogeneity assuming a common estimate for the heterogeneity variance across the different comparisons. A key assumption of NMA is that of transitivity, suggesting that the distribution of effect modifiers is the same across treatment comparisons.[6] We would explore, if there would be sufficient number of studies per comparison, the distribution of age, publication year, sample size, proportion of pediatric, proportion of immunocompromized patients, proportion of patients with inflammation of the appendix base and proportion of patients with no macroscopic signs of inflammation per treatment comparison. Transitivity may manifest itself statistically in differences between direct and indirect evidence. This is known as the consistency assumption. We explored for differences between direct and indirect evidence by comparing direct and indirect estimates by computing the inconsistency factor within each closed loop of evidence. We also employed the node-splitting approach by Dias et al, which separates evidence on a particular comparison into 'direct' and 'indirect'.[7] To check the assumption of consistency in the entire network, we used the 'design-by-treatment' model as described by Higgins and colleagues.[8] This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials vs. three-arm trials) give different results as well as disagreement between direct and indirect evidence. We planned to explore for small-study effects within each treatment comparison that is compared in at least 10 studies using funnel plot and Egger's regression test.[9] We also planned to use contour enhanced funnel plots to disentangle the effects of publication bias and small study effects and a selection model to estimate the correlation between probability of publication and magnitude of effect.[10–12] We estimated the contribution of each direct comparison to each of the summary estimates using the contribution plot and methodology presented by Krahn et at and the Stata commands presented by Chaimani et al.[4,13] We estimated the ranking probabilities for all treatments of being at each possible rank for each intervention using the mvmeta command in Stata. We obtained a hierarchy of the competing interventions using rankograms. We obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks.[14] We produced the relevant plots using the suite of Stata commands by Chaimani et al.[4] We planned to conduct the following subgroup analyses, if there would be a sufficient number (at least five) of trials per group considered: i. Patients with vs. without macroscopic inflammation of the base

of the appendix. ii. No macroscopic inflammation of the appendix vs. acute focal/purulent/gangrenous/and perforated appendicitis. iii. Paediatric vs. adult patients. iv. Immunocompromized patients (patients undergoing chemotherapy, patients under steroid medication, diabetics and HIV positive patients) vs. non-immunocompromized patients. We planned to use meta-regression to explore the impact of publication year on treatment outcomes, given that there are at least ten studies in the analysis. Sensitivity analyses for the primary outcome measures would consider trials in which the outcome assessors are blinded to treatment allocation, in order to alleviate the risk of detection bias. We also planned to include trials that did not report (or allow estimation of) the standard deviation and trials with skewed outcomes as a sensitivity analysis. We would be cautious in the interpretation of the results from subgroup analyses and meta-regressions because these analyses are observational by nature (study characteristics are not randomized but observed) and with many analyses there is an inflation of the type I error rate.

4. Study and publication data

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	Journal	Country	No. of institutions	Inclusion criteria	Exclusion criteria
Endoloop					
Attwood et al[15]	Surgery	Ireland	1	Suspected acute appendicitis	not reported
Tate et al[16]	Lancet	China	1	1. Clinical diagnosis of acute appendicitis 2. “Patients suitable for laparoscopy” 3. “Patients suitable for grid-iron incision in the right iliac fossa”	"Need for elective, interval appendectomy"
Kum et al[17]	Br J Surg	Singapore	1	1. Age >12y 2. Diagnosis of acute appendicitis	not reported
Hebebrand et al[18]	Chirurg	Germany	1	1. Diagnosis of acute appendicitis	not reported
Ortega et al[19]	Am J Surg	USA	10	1. Clinical diagnosis of acute, perforated or chronic appendicitis 2. Right lower-quadrant pain 3. “Suitable candidates for laparoscopy and laparotomy”	1. Pregnancy 2. Minors 3. Prisoners 4. Patients incapable of providing informed consent
Hansen et al[20]	World J Surg	Australia	1	1. Diagnosis of acute appendicitis 2. Age >12y	Pregnancy
Mutter et al[21]	Surgery	France	2	1. Male gender 2. Age >15y 3. Suspected acute appendicitis	1. Generalized peritonitis 2. Uncertain diagnosis
Cox et al[22]	World J Surg	Australia	1	1. Male gender 2. Age >18y 3. Clinical diagnosis of acute appendicitis	not reported
Hart et al[23]	Can J Surg	Canada	1	Clinical diagnosis of acute appendicitis	1. Generalized peritonitis 2. Multiple previous operations 3. Over 24 weeks gestation
Reiertsen et al[24]	Br J Surg	Norway	1	1. Suspected appendicitis 2. Age 18-60y	1. Pregnancy 2. Severe cardiopulmonary disease 3. Previous history of peritonitis 4. Previous history of major abdominal surgery
Pedersen et al[25]	Br J Surg	Denmark	2	Clinical diagnosis of acute appendicitis	1. “Contraindication to pneumoperitoneum”
Little et al[26]	J Pediatr Surg	USA	1	1. Diagnosis of acute appendicitis 2. Pediatric patients	2. Need for interval appendectomy
Al-Mulhim et al[27]	Saudi Med J	Saudi Arabia	1	1. Female gender 2. Clinical diagnosis of acute appendicitis 3. “Patients suitable for laparoscopy” 4. “Patients suitable for a right iliac fossa muscle-splitting approach”	1. Pregnancy
Lintula et al[28]	J Pediatr Surg	Finland	2	1. ASA I-II 2. Age 4-15y 3. Weight 15-75kg 4. “Decision to operate for suspected acute appendicitis”	1. History of pain of more than one week duration 2. History of previous abdominal operation 3. Bleeding diathesis 4. Renal failure 5. Liver failure 6. Neurologic disease
Milewczyk et al[29]	Surg Endosc	Poland	1	“Suspected appendicitis”	1. Diffuse peritonitis 2. History of multiple laparotomies 3. “Cardiorespiratory insufficiency“ 4. Did not approve the random treatment
Lau et al[30]	Surg Laparosc Endosc Percutan Tech	China	1	1. Age 12-65y 2. Clinical diagnosis of acute appendicitis	1. History of major lower abdominal surgery 2. Mentally incapacitated or physically handicapped patients 3. Patients who did not provide consent
Ricca et al[31]	JSLS	USA	2	1. Clinical diagnosis of acute appendicitis 2. BMI >24.9kg/m^2	not reported
Shaikh et al[32]	JSLS	Pakistan	1	1. Age 15-60y 2. Clinical diagnosis of acute appendicitis	1. Palpable mass in the right lower quadrant 2. Patients who did not provide consent
Wei et al[33]	Surg Endosc	China	1	1. Age >14y 2. Clinical diagnosis of acute appendicitis	1. Pregnancy 2. Inability to provide consent
Tzovaras et al[34]	Surg Endosc	Greece	1	1. Male gender 2. Age >15y 3. Suspected acute appendicitis	1. ASA III-IV 2. Previous lower abdominal surgery 3. Contraindication to pneumoperitoneum
Khalil et al[35]	Saudi J Gastroenterol	Pakistan	1	1. Clinical diagnosis of appendicitis 2. Age 12-60y 3. ASA I	1. Previous abdominal surgery 2. Large ventral hernias 3. Mass in the right iliac fossa 4. Symptom duration more than 5 days
Goudar et al[36]	J Clin Diagn Res	India	2	1. Age 12-48y 2. Clinical diagnosis of acute appendicitis	1. Appendicular mass 2. Peritonitis 3. Abscess 4. Previous abdominal hernia 5. Large ventral hernia
Park et al[37]	J Laparoendosc Adv Surg Tech	Korea	1	Computed tomography diagnosis of suppurative appendicitis	1. Computed tomography diagnosis of perforated appendicitis or generalized peritonitis 2. History of previous abdominal surgery 3. BMI >30kg/m^2
Teoh et al[38]	Ann Surg	China	2	1. History of right lower quadrant pain or periumbilical pain migrating to the right lower quadrant 2. Presence of right lower quadrant guarding 2. Tenderness upon physical examination 3. Fever of more than 38°C and/or WBC >10.000/µl	1. “Clinically doubtful diagnosis” 2. Duration of symptoms more than 5 days 3. Palpable mass in the right lower quadrant 4. History of cirrhosis 5. History of coagulation disorders 6. Generalized peritonitis 7. Shock upon admission 8. Previous abdominal surgery 9. Ascites 10. Suspected or proven malignancy 11. Contraindication to general anesthesia 12. Inability to give informed consent 13. Pregnancy

	Journal	Country	No. of institutions	Inclusion criteria	Exclusion criteria
Colac et al[39]	Surg Laparosc Endosc Percut Tech	Turkey	1	not reported	1. Age < 16y 2. Previous major abdominal surgery 3. Pregnancy 4. Refusal to consent 5. Conversion to open surgery
Kye et al[40]	J Laparoendosc Adv Surg Tech	Korea	1	not reported	not reported
Cipe et al[41]	Chirurgia	Turkey	1	not reported	1. Pregnancy 2. History of lower abdominal surgery
Wu et al[42]	Pediatr Surg Int	China	1	1. Diagnosis of appendicitis 2. Age 5-12y 3. Weight 20-45 4. Disease duration < 48h 5. WBC< 25.000/µl	1. Appendiceal abscess 2. Prior history of surgery 3. ASA >III
Stapler					
Ortega et al[19]	Am J Surg	USA	10	1. Clinical diagnosis of acute, perforated or chronic appendicitis 2. Right lower-quadrant pain 3. "Suitable candidates for laparoscopy and laparotomy"	1. Pregnancy 2. Minors 3. Prisoners 4. Patients incapable of providing informed consent
Martin et al[43]	Ann Surg	USA	1	1. Age >14y 2. "Presumptive diagnosis of acute appendicitis"	not reported
Laine et al[44]	Surg Endosc	Finland	1	1. Female gender 2. Suspected acute appendicitis 3. Age 16-40y	not reported
Klingler et al[45]	Am J Surg	Austria	2	1. Age 14-70y 2. ASA I-III	1. Refusal to participate 2. Pregnancy
Bauwens et al[46]	Chirurg	Germany	1	1. Diagnosis of acute appendicitis 2. Working patients	1. Age < 18y 2. Pregnancy 3. Follow up not possible
Katkhouda et al[47]	Ann Surg	USA	1	1. Right lower quadrant pain or migrating periumbilical pain 2. Nausea and /or vomiting 3. Fever >38°C and/or WBC>10.000/µl 4. Right lower quadrant guarding and tenderness	1. Symptoms more than 5 days and/or palpable mass in the right lower quadrant 2. History of cirrhosis 3. History of coagulation disorders 4. Generalized peritonitis 5. Shock on admission 6. Large ventral hernia, history of laparotomies for small bowel obstruction, ascites with abdominal distention 7. Severe cardiac or pulmonary disease 8. Mental disability 9. Pregnancy
Moberg et al[48]	Br J Surg	Sweden	1	1. Clinical suspicion of acute appendicitis	1. Pregnancy 2. ASA III-IV 3. Foreign language speaking 4. Living in another district or abroad 5. Drug abuse 6. Psychiatric disorder 7. Lack of availability of an authorized surgeon 8. " Patient not willing or not informed about the study"
Simon et al[49]	J Laparoendosc Adv Surg Tech	Germany	1	1. Age 7-16 2. ASA I-II	1. Immunologic disease
Frutos et al[50]	Ann Surg	Spain	1	1. Right lower quadrant pain or migrating periumbilical pain 2. Signs of peritoneal irritation and abdominal defence 3. Age >11y	1. Cirrhosis 2. Coagulation disorders 3. Clinical or radiological suspicion of abscess or diffuse peritonitis 4. Septic shock 5. Contraindication to laparoscopic surgery 6. Contraindication to general anesthesia 7. Pregnancy 8. Mental disorder
Perez et al[51]	Surg Endosc	USA	1	1. Diagnosis of appendicitis 2. Symptom duration < 2 days	not reported
Suture					
Olmi et al[52]	Surg Endosc	Italy	1	not reported	not reported
Kaplan et al[53]	Acta Chir Belg	Turkey	1	1. History of right lower quadrant pain or migrating periumbilical pain with nausea and/or vomiting 2. Temperature >38°C and/or WBC >10.000/µl 3. Right lower quadrant guarding and tenderness 4. "Positive radiological findings in ultrasonography or computed tomography"	1. Inflammatory bowel disease 2. Mental disorders 3. Pregnancy 4. Coagulation disorders 5. Alcoholism 6. Large ventral hernia 7. History of laparotomies for small bowel obstructions 8. Ascites with abdominal distention 9. Drug abuse 10. Psychiatric disorders 11. Symptoms >5 days 12. Palpable mass in the right lower quadrant
Ates et al[54]	Surg Laparosc Endosc Percutan Tech	Turkey	1	1. "Clinical suspicion of acute appendicitis"	not reported
Gonenc et al[55]	J Laparoendosc Adv Surg Tech	Turkey	1	"Clinical and radiological diagnosis of acute appendicitis"	1. Refusal to participate 2. Mental disability 3. Age < 15y 4. Pregnancy 5. Severe sepsis or septic shock on admission 6. Medical or technical contraindication to laparoscopy 7. ASA III-IV 8. Intraoperative diagnosis of complicated appendicitis 9. Conversion 10. Absence of inflammation at histopathological examination
Sozutek et al[56]	Surg Laparosc Endosc Percutan Tech	Turkey	1	not reported	1. Age <18y 2. ASA>III 3. Pregnancy 4. Anticoagulant therapy 5. Intraoperative diagnosis other than appendicitis

	Journal	Country	No. of institutions	Inclusion criteria	Exclusion criteria
Kocatas et al[57]	Turk J Trauma Emerg Surg	Turkey	1	"Preoperative diagnosis of acute appendicitis"	1. Refusal to participate 2. Mental disability 3. Age <15y 4. Pregnancy 5. Severe sepsis 6. Contraindication to laparoscopy 7. ASA III or IV 8. Conversion to open surgery 9. Complicated appendicitis
Clip					
Ates et al[54]	Surg Laparosc Endosc Percutan Tech	Turkey	1	"Clinical suspicion of acute appendicitis"	not reported
Gonenc et al[55]	J Laparoendosc Adv Surg Tech	Turkey	1	"Clinical and radiological diagnosis of acute appendicitis"	1. Refusal to participate 2. Mental disability 3. Age < 15y 4. Pregnancy 5. Severe sepsis or septic shock on admission 6. Medical or technical contraindication to laparoscopy 7. ASA III-IV 8. Intraoperative diagnosis of complicated appendicitis 9. Conversion 10. Absence of inflammation at histopathological examination
Colac et al[39]	Surg Laparosc Endosc Percut Tech	Turkey	1	not reported	1. Age <16y 2. Previous major abdominal surgery 3. Pregnancy 4. Refusal to consent 5. Conversion to open surgery

y: years
ASA: American Society of Anesthesiologists score
BMI: body mass index
WBC: white blood cell count

5. Stump management data

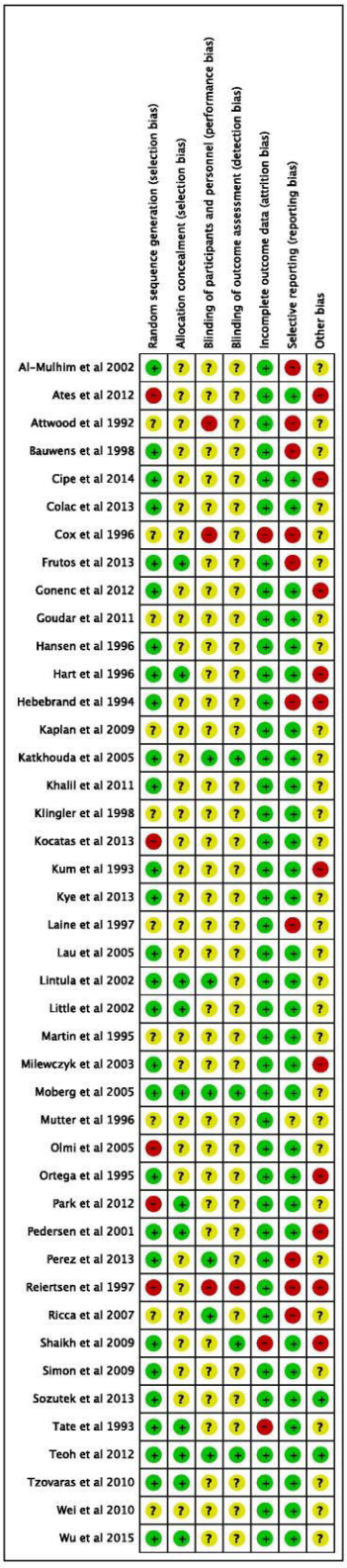
see next page

	Interventions	Stump management in intervention group*	Stump management in control group**
Endoloop			
Attwood et al[15]	Endoloop vs conventional	2 proximal and one distal catgut endoloop	Inversion purse string catgut suture
Tate et al[16]	Endoloop vs conventional	Catgut endoloop	Not reported
Kum et al[17]	Endoloop vs conventional	1 endoloop ligature	Not reported
Hebebrand et al[18]	Endoloop vs conventional	2 proximal and 1 distal Roeder loops	Z-wise sutures
Ortega et al[19]	Endoloop vs stapler vs conventional	Cat gut endoloops	Not reported
Hansen et al[20]	Endoloop vs conventional	1 endoloop ligature	Ligation, not buried
Mutter et al[21]	Endoloop vs conventional	2 endoloop ligatures	Ligation, not specified with what
Cox et al[22]	Endoloop vs conventional	1 proximal and 1 distal endoloop	Vicryl ligature
Hart et al[23]	Endoloop vs conventional	2 endoloop ligatures	Ligation, not further specified
Reiertsen et al[24]	Endoloop vs conventional	2 Roeder loops	Simple ligation
Pedersen et al[25]	Endoloop vs conventional	2 proximal and one distal endoloop	Not reported
Little et al[26]	Endoloop vs conventional	Endoloop	Suture ligation
Al-Mulhim et al[27]	Endoloop vs conventional	2 endoloop ligatures proximally, clip on the distal stump	Inversion and ligation with Vicryl ligatures
Lintula et al[28]	Endoloop vs conventional	2 endoloop ligatures	Not reported
Milewczyk et al[29]	Endoloop vs conventional	2 endoloop ligatures	Inversion and ligation
Lau et al[30]	Endoloop vs needlescopic	2 catgut endoloop ligatures	Not reported
Ricca et al[31]	Endoloop vs conventional	Endoloop, not further specified	Not reported
Shaikh et al[32]	Endoloop vs conventional	2 endoloop ligatures	Not reported
Wei et al[33]	Endoloop vs conventional	2 proximal and one distal endoloop	Not reported
Tzovaras et al[34]	Endoloop vs conventional	Endoloop, not further specified	Not reported
Khalil et al[35]	Endoloop vs conventional	Vicryl No. 1 endoloop	Not reported
Goudar et al[36]	Endoloop vs conventional	1 proximal and 1 distal endoloop	Not reported
Park et al[37]	Endoloop vs SILS	1 endoloop ligature	1 endoloop ligature
Teoh et al[38]	Clip vs SILS	2 PDS endoloop ligatures	2 PDS endoloop ligatures
Colac et al[39]	Endoloop vs clip	2 endoloop ligatures	2 XL size hem-o-lock clip
Kye et al[40]	Endoloop vs SILS	1 endoloop ligature	1 endoloop ligature
Cipe et al[41]	Endoloop vs conventional	2 endoloop ligatures	Not reported
Wu et al[42]	Endoloop vs SILS	1 endoloop	1 endoloop
Stapler			
Ortega et al[19]	Stapler vs endoloop vs conventional[†]	Not reported	Cat gut endoloops
Martin et al[43]	Stapler vs conventional	Endo-GIA 30mm	Not reported
Laine et al[44]	Stapler vs conventional	Stapler	Inversion purestring suture
Klingler et al[45]	Stapler vs conventional	Endo-GIA	Not reported
Bauwens et al[46]	Stapler vs conventional	Endo-GIA 30mm	Inversion and ligation
Katkhouda et al[47]	Stapler vs conventional	Endolinear cutter 45 with blue staples	Double ligation with absorbable suture
Moberg et al[48]	Stapler vs conventional	"linear cutting device"	Ligation
Simon et al[49]	Stapler vs conventional	Endo-GIA	Inversion and ligation
Frutos et al[50]	Stapler vs SILS	Endo-GIA blue load	Endo-GIA
Perez et al[51]	Stapler vs SILS	Stapler	Stapler
Suture			
Olmi et al[52]	Suture vs conventional	Not reported	Not reported
Kaplan et al[53]	Suture vs conventional	2 proximal and 1 distal Vicryl sutures (extracorporal knotting)	Not reported
Ates et al[54]	Suture vs clip	3 2/0 polyglactin 920 sutures	2 proximal 9mm or 11mm titanium clips
Gonenc et al[55]	Suture vs clip	1 or 2 intracorporeal knots with 2/0 silk, one distal titanium endoclip	2 proximal, one distal titanium endoclips
Sozutek et al[56]	Suture vs conventional vs SILS[‡]	1 2/0 polypropylene suture	Not reported
Kocatas et al[57]	Suture vs conventional	1 or 2 2/0 silk, clip on the distal stump	2/0 silk

	Interventions	Stump management in intervention group*	Stump management in control group**
Clip			
Ates et al[54]	Clip vs suture	2 proximal 9- or 11mm titanium clips	3 2/0 polyglactin 920 sutures
Gonenc et al[55]	Clip vs suture	2 proximal, one distal titanium endoclips	1 or 2 intracorporeal knots using 2/0 silk, one distal titanium endoclip
Colac et al[39]	Clip vs endoloop	2 XL size hem-o-lock clip	2 endoloop ligatures

SILS: Single-incision laparoscopic surgery
* Refers to the first mentioned group in the Interventions method.
** Refers to the first mentioned group in the Interventions method.
† Endo-GIA 30mm in the conventional group
‡One 2/0 polypropylene suture in SILS group

6. Review authors' summarized judgments on risk of bias for each included study



7.1 Review authors' detailed judgments on risk of bias for each included study

see next page

Author	Year	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
Al-Mulhim et al[27]	2002	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	high risk of bias (incidence of postoperative abscess not reported)	unclear risk of bias (unknown whether registered, conflicts not disclosed)
Ates et al[54]	2012	high risk of bias (randomization according to admission number)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	high risk of bias (post-randomization exclusion of patients)
Attwood et al[15]	1992	unclear risk of bias (randomization method not reported)	unclear risk of bias	unclear risk of bias	high risk of bias	unclear risk of bias	low risk of bias	high risk of bias (incidence of postoperative abscess not reported)	unclear risk of bias (unknown whether registered, conflicts not disclosed, source of funding not reported)
Bauwens et al[46]	1998	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	high risk of bias (incidence of postoperative abscess not reported)	unclear risk of bias (unknown whether registered, unknown source of funding, conflicts not disclosed)
Cipe et al[41]	2014	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	high risk of bias (unknown whether registered, post-randomization exclusion of converted cases, significantly different rate of normal vs inflammed appendices between groups)
Colac et al[39]	2013	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown if registered)
Cox et al[22]	1996	unclear risk of bias (randomization method not reported)	unclear risk of bias	high risk of bias	unclear risk of bias	unclear risk of bias	high risk of bias (high attrition rate)	high risk of bias (incidence of postoperative abscess not reported)	unclear risk of bias (unknown whether registered, conflicts not disclosed)
Frutos et al[50]	2013	low risk of bias	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	high risk of bias (incidence of postoperative abscess not reported)	unclear risk of bias (funding source not reported)
Gonenc et al[55]	2012	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	high risk of bias (postrandomization exclusion of converted cases and patients with no histological evidence of appendicitis, source of funding not reported)
Goudar et al[36]	2011	unclear risk of bias (randomization method not reported)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, 6 patients excluded post-randomization)
Hansen et al[20]	1996	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, conflicts not disclosed, post-randomization exclusion of converted cases)
Hart et al[23]	1996	low risk of bias	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	high risk of bias (postrandomization exclusion of converted cases, unknown whether registered, source of funding not reported, conflicts not disclosed)
Hebebrand et al[18]	1994	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	high risk of bias (incidence of postoperative abscess not reported)	high risk of bias (postrandomization exclusion of converted cases, unknown whether registered, source of funding not reported, conflicts not disclosed)

Author	Year	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
Kaplan et al[53]	2009	unclear risk of bias (randomization method not reported)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, conflicts not disclosed, unknown source of funding)
Katkhouda et al[47]	2005	low risk of bias	unclear risk of bias	low risk of bias	low risk of bias	low risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, conflicts not disclosed)
Khalil et al[35]	2011	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered)
Klingler et al[45]	1998	unclear risk of bias (randomization method not reported)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, conflicts of interest not disclosed, one patient excluded post-randomization)
Kocatas et al[57]	2013	high risk of bias (highly different male-to-female ratio between groups)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered)
Kum et al[17]	1993	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	high risk of bias (postrandomization exclusion of patients with perforation or absence of inflammation, unknown whether registered, unknown source of funding, conflicts not disclosed)
Kye et al[40]	2013	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown conflict of interest)
Laine et al[44]	1997	unclear risk of bias (randomization method not reported)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	high risk of bias (incidence of postoperative abscess not reported)	unclear risk of bias (unknown whether registered, conflicts of interest not disclosed)
Lau et al[30]	2005	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown if registered, conflicts not disclosed)
Lintula et al[28]	2002	low risk of bias	low risk of bias	low risk of bias	low risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, conflicts not disclosed)
Little et al[26]	2002	low risk of bias	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, conflicts of interest not disclosed)
Martin et al[43]	1995	unclear risk of bias (randomization method not reported)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, conflicts not disclosed)
Milewczyk et al[29]	2003	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	high risk of bias (post-randomization exclusion of patients without signs of appendicitis, post-randomization exclusion of patients who did not agree with randomized treatment, unknown conflict of interest)
Moberg et al[48]	2005	low risk of bias	low risk of bias	low risk of bias	low risk of bias	low risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, conflicts not disclosed)
Mutter et al[21]	1996	unclear risk of bias (randomization method not reported)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	unclear risk of bias (outcome measures not clearly defined)	unclear risk of bias (unknown whether registered, conflicts not disclosed)

Author	Year	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other sources of bias
Olmi et al[52]	2005	high risk of bias (randomization according to admission number)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, conflicts not disclosed)
Ortega et al[19]	1995	low risk of bias	unclear risk of bias	low risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	high risk of bias (unknown whether registered, industry-sponsored)
Park et al[37]	2012	high risk of bias (significantly different male-to-female ratio between groups)			unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, source of funding not reported)
Pedersen et al[25]	2001	low risk of bias	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	high risk of bias (unknown whether registered, significantly different rate of gangrenous or perforated appendices between groups)
Perez et al[51]	2013	low risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias	low risk of bias	high risk of bias (incidence of wound infection not reported)	unclear risk of bias (unknown whether registered, source of funding not reported)
Reiertsen et al[24]	1997	high risk of bias (significantly different male-to-female ratio between groups)	unclear risk of bias	high risk of bias	high risk of bias	high risk of bias	low risk of bias	high risk of bias (incidence of wound infection not reported)	high risk of bias (postrandomization exclusion of patients without appendicitis, unknown whether registered, funding not reported, conflicts not disclosed)
Ricca et al[31]	2007	unclear risk of bias (randomization method not reported)	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias	low risk of bias	high risk of bias (incidence of postoperative abscess not reported)	unclear risk of bias (unknown whether registered)
Shaikh et al[32]	2009	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	high risk of bias (high attrition rate)	low risk of bias	high risk of bias (post-randomization exclusion of patients converted to open appendectomy, unknown conflict of interest)
Simon et al[49]	2009	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered)
Sozutek et al[56]	2013	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	low risk of bias
Tate et al[16]	1993	low risk of bias	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	high risk of bias (high attrition rate)	low risk of bias	unclear risk of bias (unknown whether registered, conflicts not disclosed)
Teoh et al[38]	2012	low risk of bias	low risk of bias	low risk of bias	low risk of bias	low risk of bias	low risk of bias	low risk of bias	low risk of bias
Tzovaras et al[34]	2010	low risk of bias	low risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered)
Wei et al[33]	2010	unclear risk of bias (randomization method not reported)	unclear risk of bias	unclear risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered)
Wu et al[42]	2015	low risk of bias	low risk of bias	low risk of bias	unclear risk of bias	unclear risk of bias	low risk of bias	low risk of bias	unclear risk of bias (unknown whether registered, unknown source of funding)

8. Outcome data

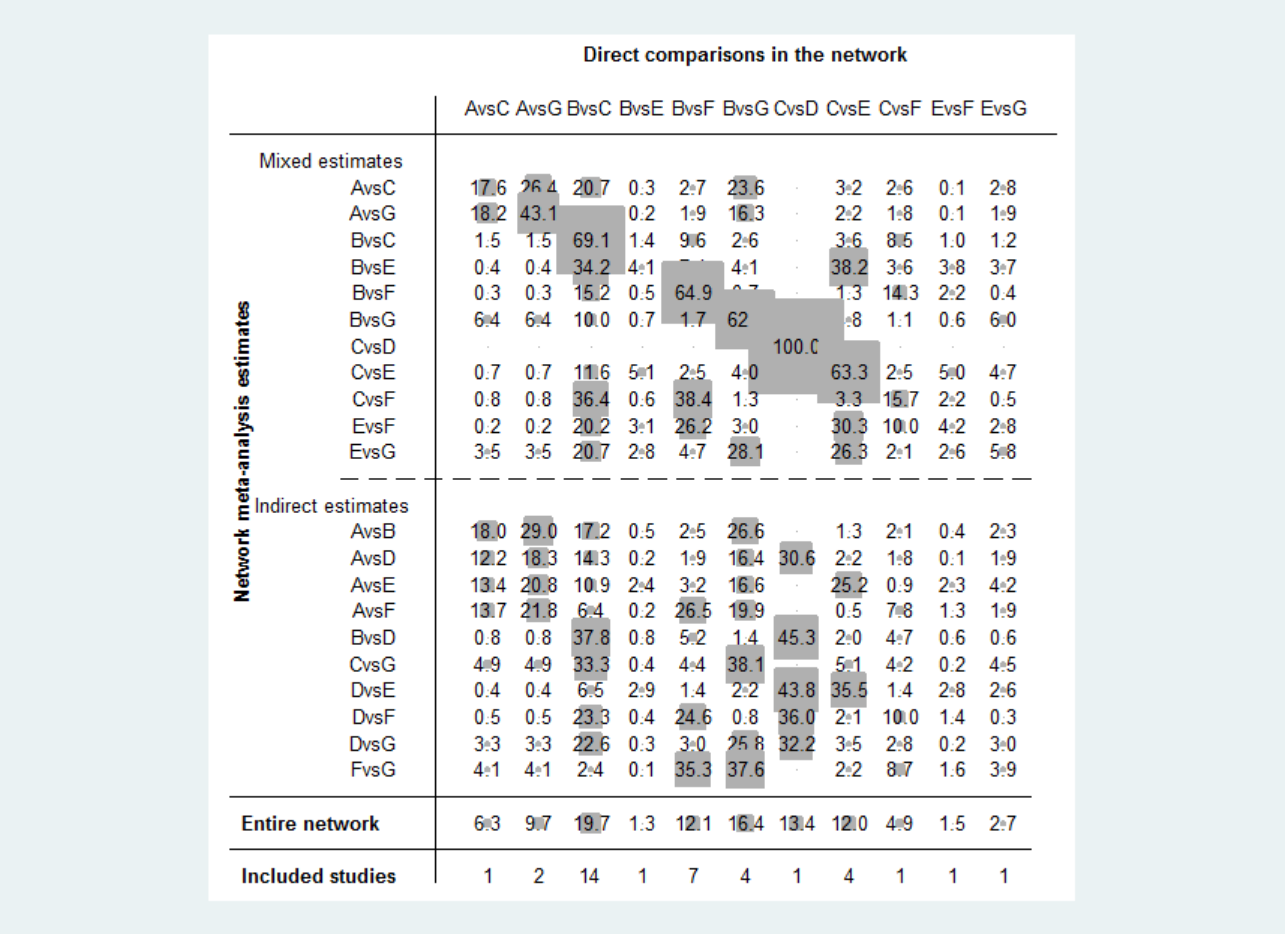
see next page

	Interventions	OSI in intervention group	OSI in control group	Method of diagnosis of OSI	SSI in intervention group	SSI in control group	Definition of SSI
Endoloop							
Attwood et al	Endoloop vs conventional	NR	NR	NR	0/30	1/32	NR
Tate et al	Endoloop vs conventional	1/70	0/70	U/S	7/46	10/42	Erythema or wound discharge
Kum et al	Endoloop vs conventional	0/52	0/57	NR	0/52	5/57	Purulent secretion from the wound
Hebebrand et al	Endoloop vs conventional	NR	NR	NR	0/25	1/23	Purulent secretion and positive culture
Ortega et al* **	Endoloop vs stapler vs conventional	4/89	2/78	NR	4/89	0/78	NR
Hansen et al	Endoloop vs conventional	NR	NR	NR	2/79	8/72	NR
Mutter et al	Endoloop vs conventional	NR	NR	NR	1/50	0/50	NR
Cox et al	Endoloop vs conventional	NR	NR	NR	0/33	2/31	NR
Hart et al	Endoloop vs conventional	3/44	0/37	U/S or C/T	3/44	3/37	Cellulitis and excessive incisional pain
Reiertsen et al	Endoloop vs conventional	2/42	2/42	NR	1/42	NR	NR
Pedersen et al	Endoloop vs conventional	13/282	3/301	U/S or C/T	8/282	21/301	Discharge of pus requiring surgical drainage
Little et al	Endoloop vs conventional	1/44	1/44	NR	2/44	1/44	NR
Al-Mulhim et al	Endoloop vs conventional	NR	NR	NR	0/30	3/30	NR
Lintula et al	Endoloop vs conventional	1/48	0/54	NR	0/48	5/54	NR
Milewczyk et al	Endoloop vs conventional	3/96	0/104	NR	3/96	4/104	Edema, erythema and purulent discharge
Lau et al	Endoloop vs needlescopic	3/189	7/174	NR	2/189	0/174	NR
Ricca et al	Endoloop vs conventional	NR	NR	NR	0/27	0/24	NR
Shaikh et al	Endoloop vs conventional	2/48	NR	NR	3/48	7/52	NR
Wei et al	Endoloop vs conventional	2/112	1/52	NR	0/112	14/108	NR
Tzovaras et al	Endoloop vs conventional	2/72	9/108	NR	4/75	2/72	NR
Khalil et al	Endoloop vs conventional	0/72	0/75	NR	3/72	8/75	Erythema or purulent/seropurulent discharge
Goudar et al	Endoloop vs conventional	0/114	0/120	NR	9/114	14/120	Erythema or purulent/seropurulent discharge
Park et al	Endoloop vs SILS	0/62	0/42	NR	2/62	3/42	NR
Teoh et al	Endoloop vs SILS	3/97	4/98	"Radiographic imaging"	5/97	8/98	Erythema, wound discharge and positive culture
Colac et al	Endoloop vs clip	1/27	0/26	NR	1/27	2/26	NR
Kye et al	Endoloop vs SILS	1/51	1/51	NR	1/52	0/52	NR
Cipe et al	Endoloop vs conventional	6/121	4/120	NR	2/121	6/120	NR
Wu et al	Endoloop vs SILS	1/30	1/30	NR	0/30	0/30	NR
Stapler							
Ortega et al[† ‡]	Stapler vs endoloop vs conventional	2/78	4/89	NR	0/78	4/89	NR
Martin et al	Stapler vs conventional	3/81	3/88	NR	3/81	6/88	NR
Laine et al	Stapler vs conventional	NR	NR	NR	1/25	1/25	NR
Klingler et al	Stapler vs conventional	2/87	2/82	NR	5/87	6/82	NR
Bauwens et al	Stapler vs conventional	NR	NR	NR	1/26	3/28	NR
Katkhouda et al	Stapler vs conventional	6/113	4/134	Fever, elevated WBC and evidence from CT	7/113	9/134	Erythema and wound discharge requiring opening of the incision
Moberg et al	Stapler vs conventional	0/81	1/82	NR	1/81	1/82	NR
Simon et al	Stapler vs conventional	0/20	0/20	NR	0/20	0/20	NR
Frutos et al	Stapler vs SILS	NR	NR	NR	0/91	0/93	NR
Perez et al	Stapler vs SILS	0/25	0/25	NR	NR	NR	NR
Suture							
Olmi et al	Suture vs conventional	2/150	1/138	NR	0/150	11/138	Purulent secretion from the wound
Kaplan et al	Suture vs conventional	0/50	1/50	NR	2/50	12/50	NR
Ates et al	Suture vs clip	0/31	1/30	NR	1/31	0/30	NR
Gonenc et al	Suture vs clip	0/46	1/61	NR	1/46	1/61	NR
Sozutek et al[§ ¶]	Suture vs SILS vs conventional	0/25	0/25	NR	1/25	1/25	NR
Kocatas et al	Suture vs conventional	1/50	1/46	NR	1/50	3/46	NR

	Interventions	OSI in intervention group	OSI in control group	Method of diagnosis of OSI	SSI in intervention group	SSI in control group	Definition of SSI
Clip							
Ates et al	Clip vs suture	1/30	0/31	NR	0/30	1/31	NR
Gonenc et al	Clip vs suture	1/61	0/46	NR	1/61	1/46	NR
Colac et al	Clip vs endoloop	0/26	1/27	NR	2/26	1/27	NR

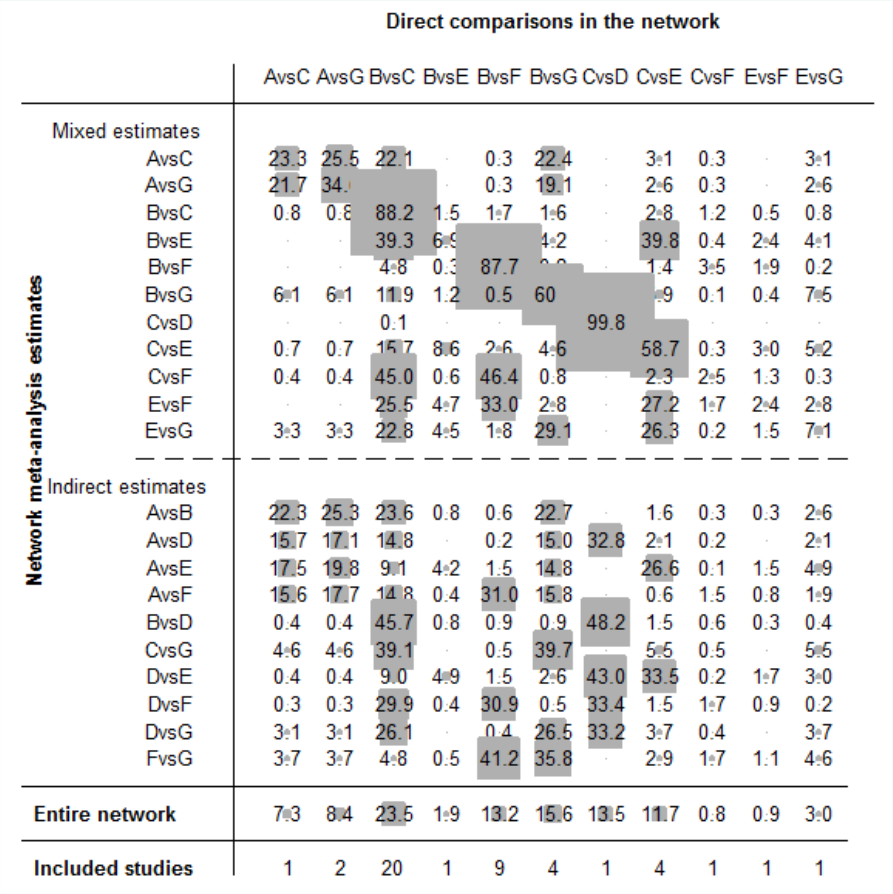
OSI: organ/space infection
SSI: surgical site infection
U/S: ultrasonography examination
CT: computed tomography examination
WBC: white blood cell count
SILS: single-incision laparoscopic surgery
NR: not reported
* Incidence of OSI was 0/86 in the conventional group
** Incidence of SSI was 0/78 in the conventional group
† Incidence of OSI was 0/86 in the conventional group
‡ Incidence of SSI was 11/86 in the conventional group
§ Incidence of OSI was 0/25 in the conventional group
¶ Incidence of SSI was 3/25 in the conventional group

9. Contribution plot for the outcome organ/space infection



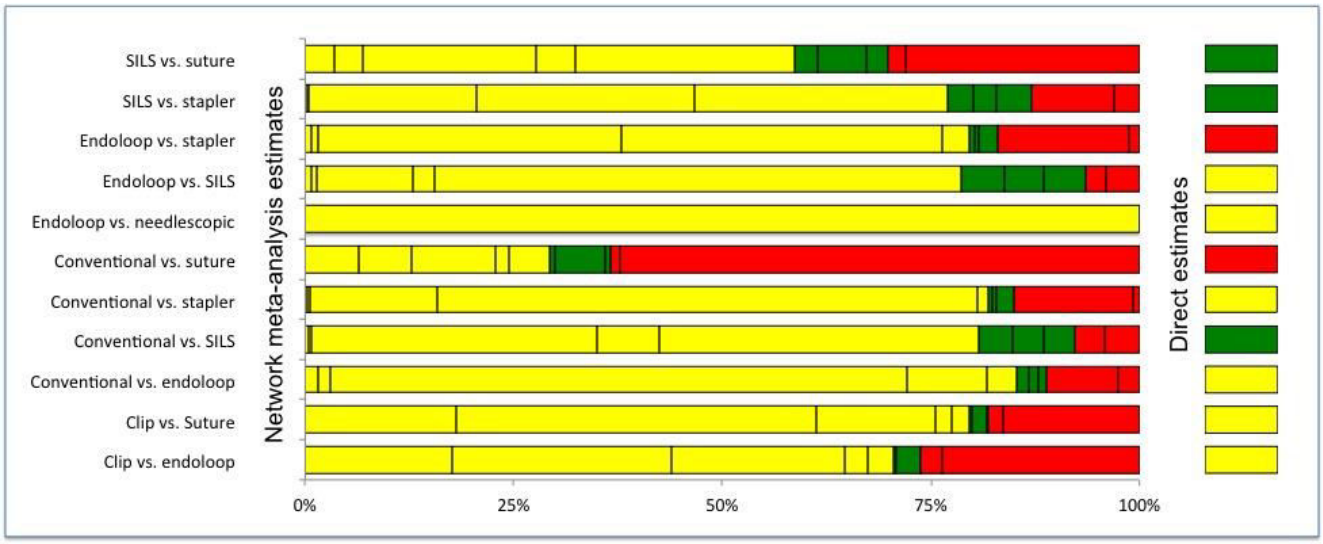
A: Clip
B: Conventional
C: Endoloop
D: Needlescopic
E: Single-incision laparoscopic surgery
F: Stapler
G: Suture

10. Contribution plot for the outcome surgical site infection



A: Clip
B: Conventional
C: Endoloop
D: Needlescopic
E: Single-incision laparoscopic surgery
F: Stapler
G: Suture

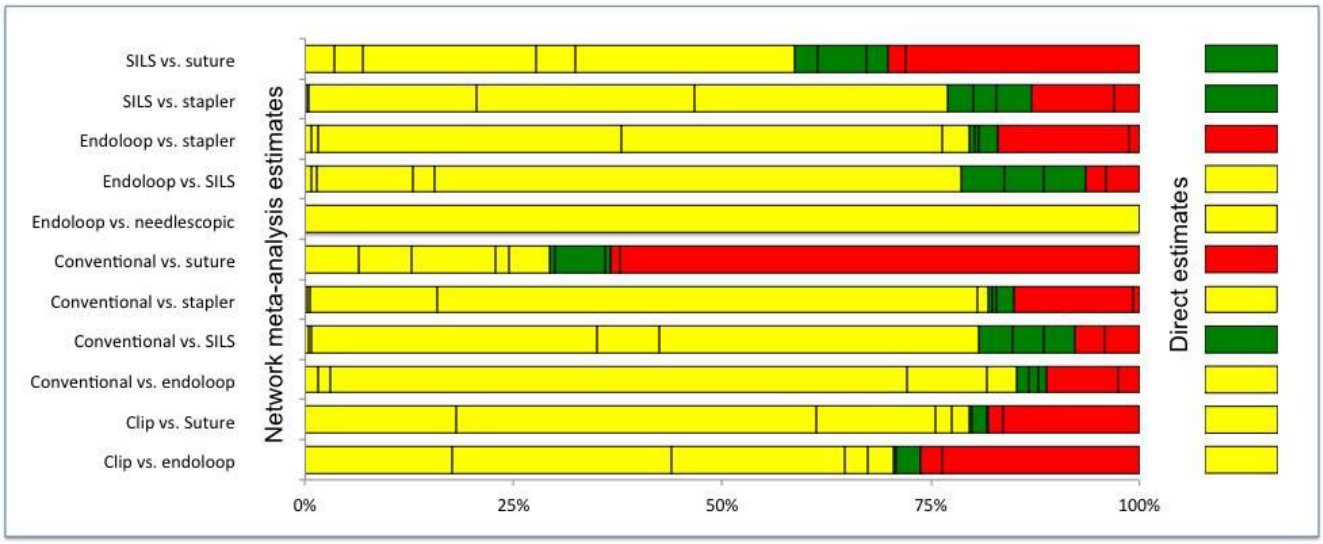
11. Bar chart of study limitations for the outcome organ/space infection



For each direct estimate, the average bias level of the included studies has been assumed as the comparison-specific level of bias.

Green: Low risk of bias
Red: High risk of bias
Yellow: Unknown risk of bias

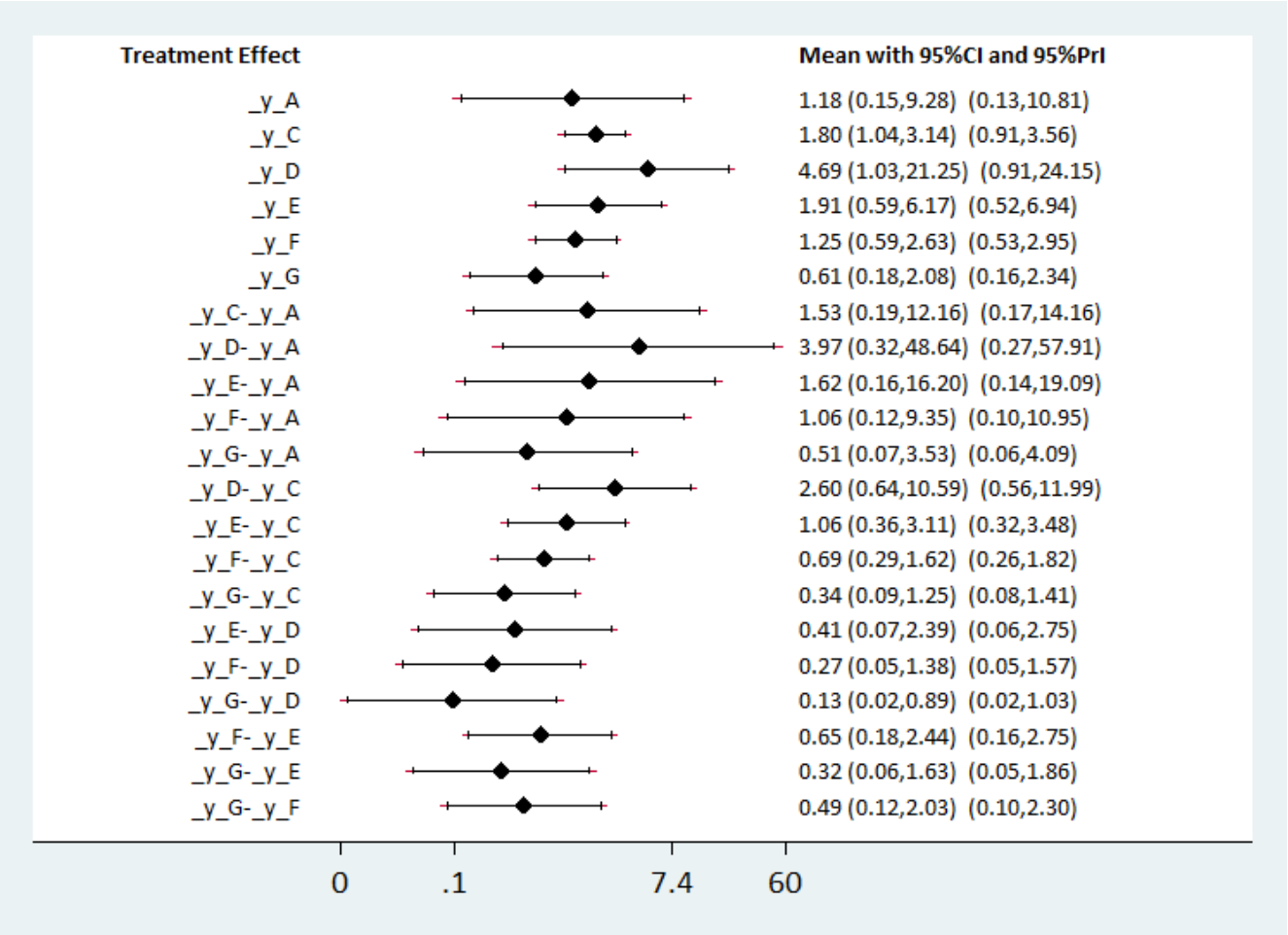
12. Bar chart of study limitations for the outcome surgical site infection



For each direct estimate, the average bias level of the included studies has been assumed as the comparison-specific level of bias.

Green: Low risk of bias
Red: High risk of bias
Yellow: Unknown risk of bias

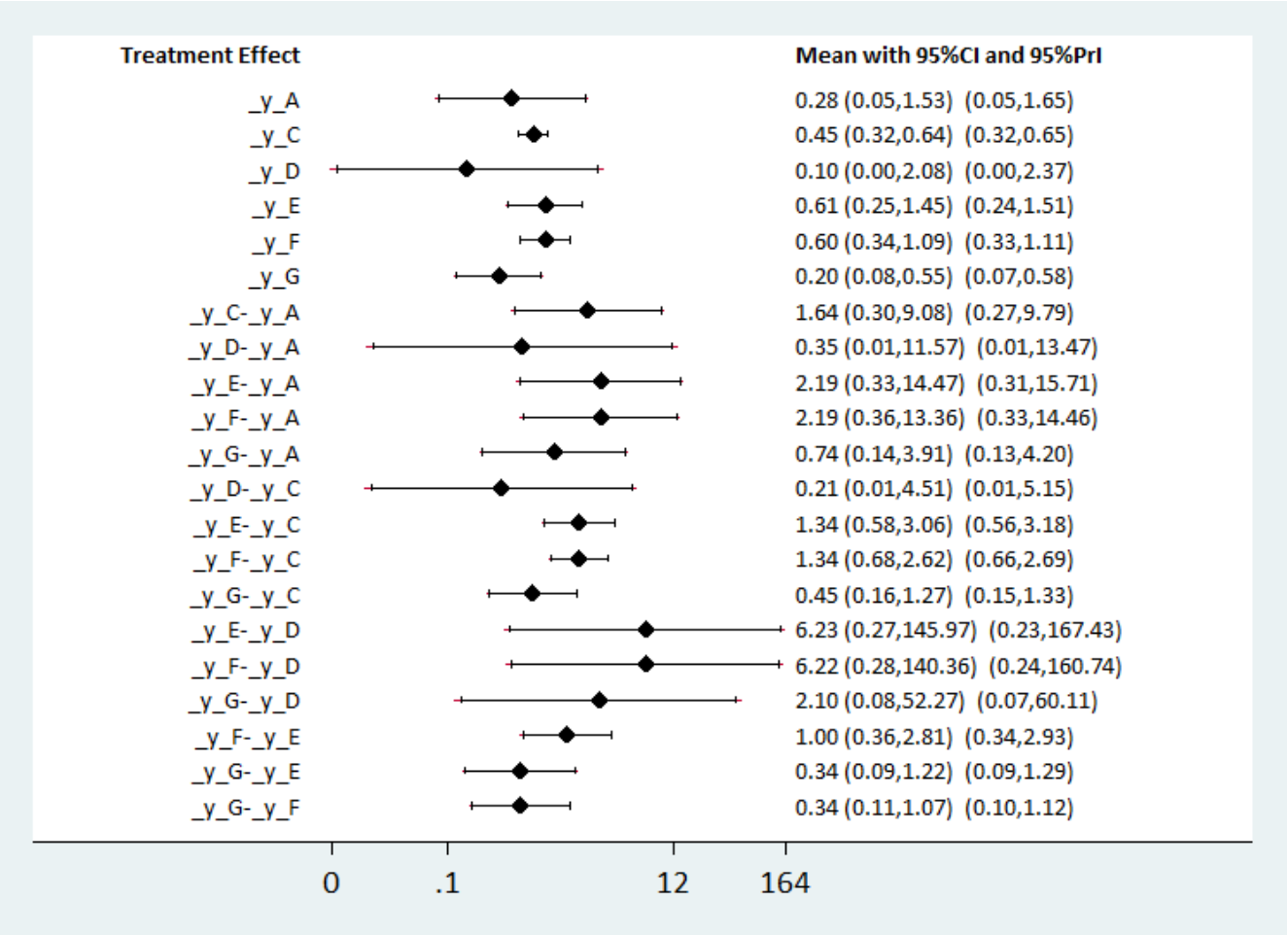
13. Interval plot for the outcome organ/space infection



Labeling of treatments
A: Clip
B: Conventional
C: Endoloop
D: Needlescopic
E: Single-incision laparoscopic surgery
F: Stapler
G: Suture

Conventional surgery is considered as the reference treatment for the purposes of this analysis.

14. Interval plot for the outcome surgical site infection



Labeling of treatments
A: Clip
B: Conventional
C: Endoloop
D: Needlescopic
E: Single-incision laparoscopic surgery
F: Stapler
G: Suture

Conventional surgery is considered as the reference treatment for the purposes of this analysis.

15. Assessment of inconsistency for the outcome organ/space infection using loop-specific heterogeneity estimates

Loop	IF	95% CI	p-value	Loop heterogeneity τ^2
Clip-Endoloop-SILS-Suture	2.296	0.00-8.02	0.432	0.000
Clip-Conventional-Endoloop-Suture	1.030	0.00-5.25	0.632	0.000
Conventional-Endoloop-SILS	0.810	0.00-4.97	0.703	0.000
Endoloop-SILS-Stapler	0.675	0.00-5.09	0.764	0.000
Conventional-SILS-Suture	0.511	0.00-6.27	0.862	0.000
Conventional-SILS-Stapler	0.296	0.00-5.95	0.918	0.000
Conventional-Endoloop-Stapler	0.227	0.00-2.09	0.811	0.000

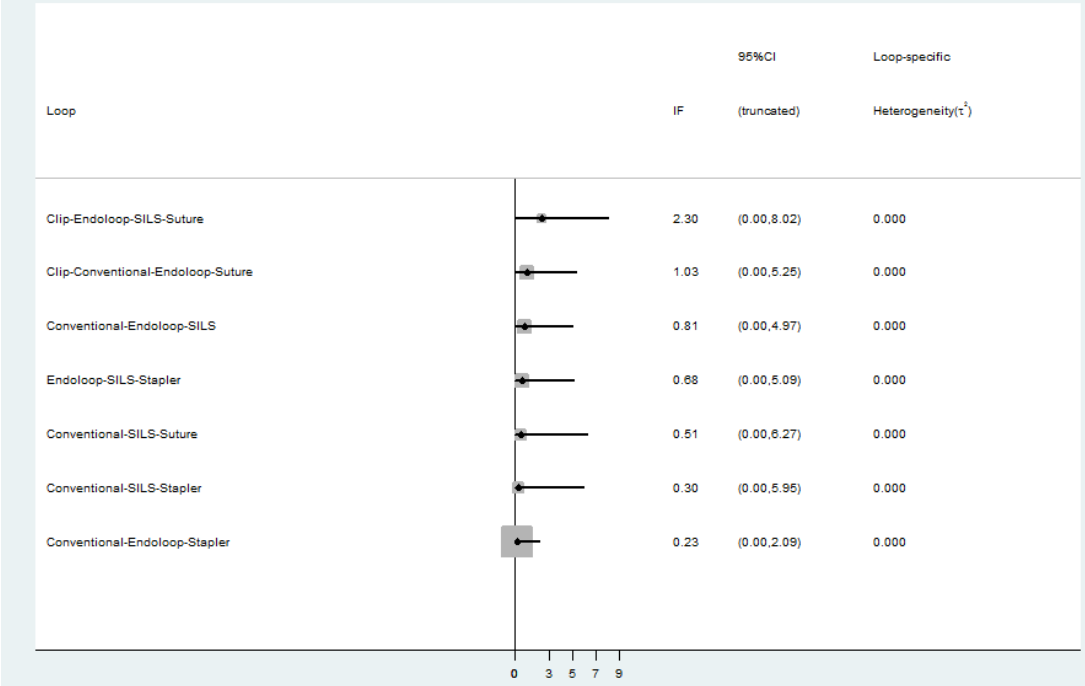
IF: Inconsistency factor
CI: Confidence interval
SILS: Single-incision laparoscopic surgery

16. Assessment of inconsistency for the outcome surgical site infection using loop-specific heterogeneity estimates

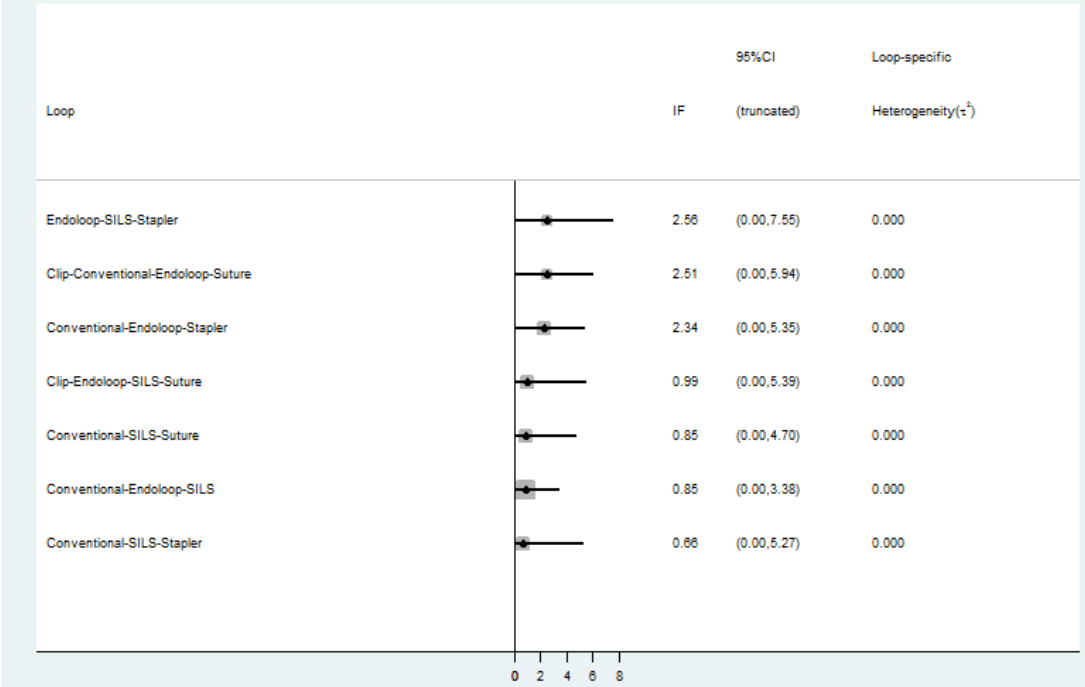
Loop	IF	95% CI	p-value	Loop heterogeneity τ^2
Endoloop-SILS-Stapler	2.556	0.00-7.55	0.316	0.000
Clip-Conventional-Endoloop-Suture	2.511	0.00-5.94	0.152	0.000
Conventional-Endoloop-Stapler	2.336	0.00-5.35	0.129	0.000
Clip-Endoloop-SILS-Suture	0.985	0.00-5.39	0.661	0.000
Conventional-SILS-Suture	0.850	0.00-4.70	0.665	0.000
Conventional-Endoloop-SILS	0.847	0.00-3.38	0.512	0.000
Conventional-SILS-Stapler	0.658	0.00-5.27	0.780	0.000

IF: Inconsistency factor
CI: Confidence interval
SILS: Single-incision laparoscopic surgery

17. Inconsistency plot for the outcome measure organ/space infection



18. Inconsistency plot for the outcome measure surgical site infection



19. Sidesplit approach for assessment of inconsistency for the outcome organ/space infection

Side	Direct		Indirect		Difference		
	Coefficient	Standard error	Coefficient	Standard error	Coefficient	Standard error	P>|z|
BC	.614608	.3056833	.3532942	1.061743	.2613138	1.125561	0.816
BE	-2.67e-10	2.02759	.7073944	.6285456	-.7073944	2.122779	0.739
BF	.2688288	.4205052	-.1642508	1.362201	.4330795	1.4749	0.769
BG	-.4556322	.6713966	-.8221191	1.819371	.3664869	1.939304	0.850
AC	1.098595	1.666338	-.0322731	1.372882	1.130868	2.159039	0.600
AG	-.9989964	1.173239	.1319179	1.812466	-1.130914	2.159065	0.600
CD	.9550508	.7170185	-1.352784	386.0877	2.307834	386.0889	0.995
CE	.1968412	.6012599	-.6879393	1.374379	.8847806	1.49996	0.555
CF	-.5393996	.8384138	-.3080646	.5240254	-.231335	.9870733	0.815
EF	-5.19e-10	2.028114	-.4769048	.7151562	.4769048	2.15051	0.824
EG	-1.54e-10	2.027387	-1.378558	.915418	1.378558	2.224475	0.535

Labeling of treatments:
A: Clip
B: Conventional
C: Endoloop
D: Needlescopic
E: Single-incision laparoscopic surgery
F: Stapler
G: Suture

20. Sidesplit approach for assessment of inconsistency for the outcome surgical site infection

Side	Direct		Indirect		Difference		
	Coefficient	Standard error	Coefficient	Standard error	Coefficient	Standard error	P>|z|
BC	-.7695205	.1770239	-1.435535	.904795	.6660147	.9207185	0.469
BE	-1.007006	1.165489	-.4242189	.4747863	-.5827872	1.24156	0.639
BF	-.5096143	.2996576	-.2622199	1.069614	-.2473944	1.054513	0.815
BG	-1.857453	.5332502	.5155716	1.396627	-2.373025	1.467499	0.106
AC	-.7732105	1.25703	1.678626	1.215671	-2.451837	1.748714	0.161
AG	.6342317	1.080551	-1.81777	1.374904	2.452002	1.748696	0.161
CD	-1.537584	1.55276	1.000004	701.5454	-2.537588	701.5449	0.997
CE	.4223762	.4642552	-.3376819	1.019353	.7600582	1.120096	0.497
CF	-.1427448	1.051868	.3246991	.3517965	-.4674439	1.074089	0.663
EF	.0216225	2.005399	-.0034835	.5464688	.0251059	2.078522	0.990
EG	-2.38e-12	1.443376	-1.370317	.7360616	1.370317	1.620222	0.398

Labeling of treatments:
A: Clip
B: Conventional
C: Endoloop
D: Needlescopic
E: Single-incision laparoscopic surgery
F: Stapler
G: Suture