

Are endoscopic loop ties safe even in complicated acute appendicitis? A systematic review and meta-analysis



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ABSTRACT

Background: Appendectomy is amongst the most common general surgical procedures and the laparoscopic approach is recognized and recommended by international guidelines as a valid option. The different closure techniques of the appendicular stump constitute a matter of debate since their possible implication in determining postoperative infectious complications. The aim of the present meta-analysis is to compare endostapler versus endoscopic loop ties for stump closure during laparoscopic appendectomy.

Methods: This is a systematic review with meta-analysis of randomized trials and cohort studies comparing endostapler with endoscopic loop ties for the closure of appendicular sump in laparoscopy appendectomy. Subgroup analysis of pediatric patients and patients with complicated appendicitis were performed when data were available. Complicated acute appendicitis was defined as in case of gangrenous/necrotic appendix or perforated appendix. Main outcomes were wound infection rate, intra-abdominal infection rate, length of stay, readmission and reoperation rates.

Results: a total of 5934 patients from 14 studies were included in the analysis. Endostapler was associated with a similar intra-abdominal abscess rate (RR 0.88, 95%C.I. 0.54–1.43) but a lower incidence of wound infection (RR 0.54, 95%C.I. 0.22–0.97) Length of stay, readmission and reoperation rates were similar. In subgroups analysis endostapler reduces significantly the wound infection rate in pediatric patients; no differences in main outcomes were observed in patients with complicated acute appendicitis.

Conclusion: In complicated acute appendicitis the stump closure technique did not affect outcomes; the use of endostapler seems to be associated to a reduction of wound infection rate in pediatric patients with non-complicated acute appendicitis.

1. Introduction

Appendectomy is amongst the most common general surgical procedures performed in the developed world. Laparoscopic approach is recognized and recommended by international guidelines as a valid option for appendectomy in acute appendicitis because of faster recovery, less postoperative pain and fewer wound infections when compared to open surgery [1–3]. The different closure techniques of the appendicular stump during laparoscopic appendectomy constitute a matter of debate since their possible implication in determining postoperative infectious complications. Several techniques to close the appendicular stump during laparoscopic appendectomy, such as endostapler, endoscopic loop ties, metal or polymer clips and laparoscopic ligature have been proposed over years [4–7]. The superiority of one technique over the others has not been already clearly demonstrated,

despite several studies have been published. All of these studies analyzed the issue in very heterogeneous and not comparable groups of patients. In fact, in patients with uncomplicated appendicitis (no peritonitis nor abscess or perforation), endoscopic loop closure seemed to be preferred because of the contained costs and comparable outcomes when compared to other devices [8]. However, in patients with complicated appendicitis (perforated, abscess or peritonitis) stump closure techniques remain debated since no study focused particularly on these patients. At the moment no clear evidence exists on the best technique in selected and homogeneous groups of patients such as those with complicated appendicitis.

The aim of the present meta-analysis is to compare endostapler versus endoscopic loop ties for stump closure during laparoscopic appendectomy for acute appendicitis in homogeneous groups of adult and pediatric patients.

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2. Material and methods

2.1. Literature search strategy and studies selection

A systematic research was independently performed by two different investigators (MC and LN) in Medline, Embase, PubMed, Cochrane Central Register of Controlled Trials (CCTR) and Cochrane Database of Systematic Reviews (CDSR) until July 2018. The selected search terms were: “stump closure”, “appendicitis”, “endoloop” combined with AND/OR. The references of retrieved articles were also reviewed. The review was conducted according to the PRISMA and the AMSTAR guidelines.

2.2. Selection criteria

All the studies comparing endostapler with endoscopic loop ties for the appendicular stump closure during laparoscopic appendectomy for acute appendicitis were selected. Both randomized studies and cohort studies, prospective and retrospective, were included in the analysis. Case reports, case series, letters, reviews and meta-analysis, and non-English language publications were excluded. Literature search and study selection were performed separately by two investigators (MC and LN). In case of disagreement between the two investigators a third investigator (LG) was consulted.

2.3. Data extraction, outcome measures

The selected outcomes of the study were: the wound infection rate, the intra-abdominal infection rate, the readmission and re-operation rates. For each paper were reported the study design and methodology, the year of publication, the inclusion criteria, the study population (adults, pediatric or all), the rate of normal appendix removed, the method of appendicular stump closure, the morbidity rate (wound infection and abscess) as well as the readmission and the reoperation rates. Subgroup analysis of pediatric patients and patients with complicated appendicitis were performed when data were available. Complicated acute appendicitis was defined as in case of abscess, gangrenous/necrotic appendix or perforated appendix.

2.4. Assessment of risk of bias and study quality

The risk of bias was estimated, for each randomized study, according to the guidelines of The Cochrane Collaboration [9]. Six items have been considered relevant (Table 1): 1) whether the method of allocation was truly random; 2) whether there was a proper allocation concealment; 3) whether the groups were similar at baseline; 4) whether the eligibility criteria were documented; 5) whether the loss to follow-up in each treatment arm was specified; 6) whether an intention-to-treat analysis was conducted. Since blinding was impossible due to the interventions’ nature, the absence of blindness was not evaluated as a possible source of bias. The evaluation of the quality level of the study was conducted as follows: a positive answer to all six questions was required for a trial to be considered at a low risk of bias. With a positive answer to three or fewer questions, the study was registered as low quality with high risk of bias. The study was considered as intermediate quality with middle risk of bias when three to five items were present.

The quality of the cohort studies was evaluated according to the MINORS scale [10], attributing to each study a score ranging from 0 to 24.

2.5. Statistical analysis

Data were analyzed with Review Manager (RevMan) (Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Outcomes were expressed as weighted Odds Ratio (OR) and 95% confidence interval (95% C.I.) and were calculated with

Table 1
Quality assessment of included randomized controlled trials.

study id	Randomization's method	allocation concealment	Homogeneous baseline characteristics	eligibility criteria	Blinding to participants	Lost at follow-up and drop-outs described	Intention to treat analysis	Risk of Bias
Ortega 1995	Yes	Yes	Yes	Yes	No	No	No	High
Shalaby 2001	Yes	Unclear	Yes	Yes	No	No	Unclear	High
Delibegovic 2012	No	Unclear	Unclear	Unclear	No	No	Unclear	High
Delibegovic 2018	Yes	Yes	Yes	Yes	No	No	Yes	Intermediate

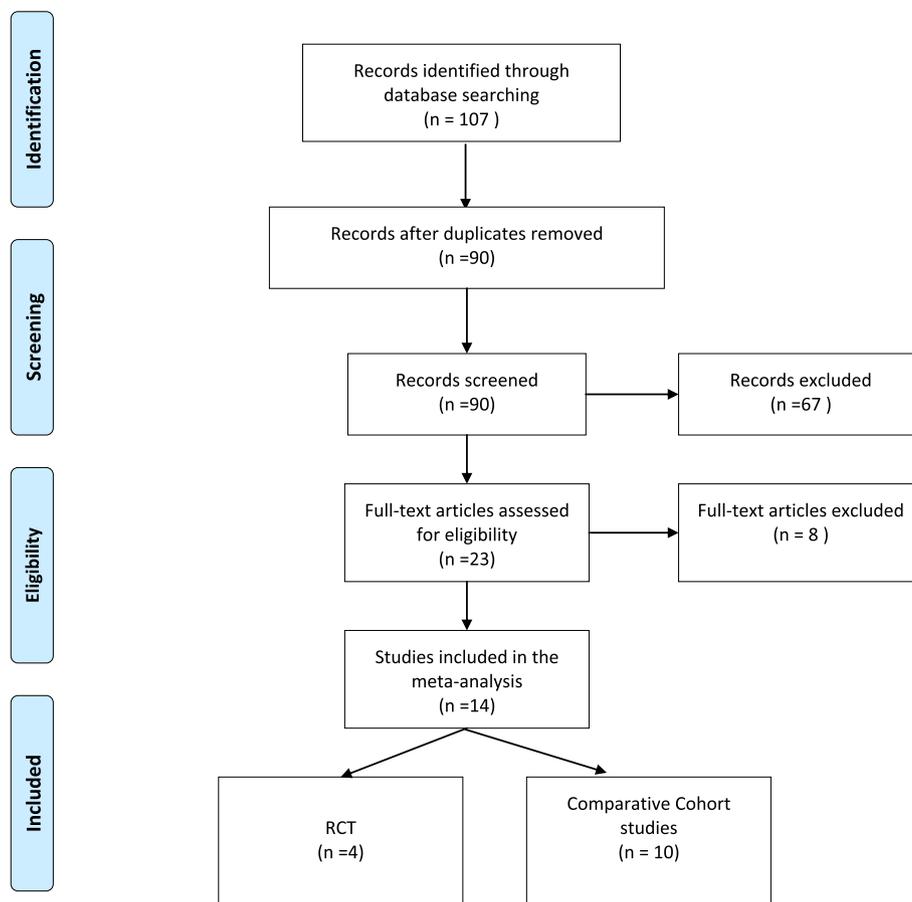


Fig. 1. Prisma flow diagram.

the fixed-effects and random-effects models [11,12]; statistical heterogeneity was quantified using the I^2 inconsistency test and, when significant ($p < 0,1$), only the results of the random-effects model were reported. Sensitivity analyses were performed repeatedly excluding one study at a time and results were reported only when significant.

3. Results

3.1. Studies selection

A total of 107 abstracts were identified from the literature search; after the title and abstract review, 23 paper were identified as potentially eligible for this meta-analysis. After a full text review, 14 studies that fulfilled the adopted inclusion criteria were selected: 4 randomized controlled trial [13–16] and 10 cohort studies [17–26]. The PRISMA flow diagram is shown in Fig. 1.

3.2. Quality of trials and studies characteristics

There was a good agreement between the reviewers (MC and LN) about the eligibility and the quality assessment of the studies. As depicted in Table 1 among the randomized trials the study by Delibegovic and coll. [13] was considered at intermediate risk of bias; the other three trials [14–16] were classified as at high risk of bias. The cohort studies were generally of poor quality, reaching a score ranging from 5 to 18 (maximum 24). Table 2 shows in detail the MINORS score for each study.

All the included studies compared different stump closure methods during laparoscopic appendectomy for acute appendicitis. Four studies were randomized trials [13–16]; four studies were prospective cohort studies [17,19,20,24] and six studies were retrospective cohort studies

[18,21–23,25,26]. None of the evaluated studies clearly defined the diagnostic criteria adopted for the diagnosis of acute appendicitis.

Some studies included all the patients with a clinical suspect of acute appendicitis [13–17,20,21,23–26]; other studies included only patients with complicated acute appendicitis [18,19]; some studies included all the patients with suspected acute appendicitis but provided data for subgroup analysis of patient with complicated acute appendicitis [18,21,22,24,25]. Results are shown for the overall population, for complicated acute appendicitis and for pediatric patients.

Included patient's characteristics varied among the different studies: some studies included only pediatric patients [16,18–22] and some included only adults [13–15,23].

Table 3 shows in detail the included studies' characteristics.

3.3. Overall population

The analysis about overall population included 14 studies involving 5934 patients treated with endostapler and 6604 patients treated with endoscopic loop ties. The closure of the appendicular stump with endostapler rather than endoscopic loop ties was associated with a similar overall morbidity rate (RR 1.07, 95%CI 0.87–1.32), similar intra-abdominal abscess rate (RR 0.88, 95%CI 0.54–1.43) but a lower incidence of wound infection (RR 0.54, 95%CI 0.22–0.97) (Fig. 2). The closure of the appendicular stump with the endostapler was associated to a significantly (but not clinically) shorter operative time (MD -6.42 min, 95%CI -8.48; -4.06). Postoperative length of stay was similar between the two groups (MD 0.04 days, 95%CI -0.19; 0.46). Readmission rate and reoperation rate were similar in the two groups (RR 0.72 95%CI 0.51–1.02 and RR 0.90, 95%CI 0.43–1.91, respectively). Sensitivity analysis showed no differences in the analysis.

Table 2
Quality assessment of comparative cohort studies included.

	Beldi 2006	Escolino 2018	Miyano (Asian J EndoscSurg)	Myiano (J LaparoendoscAdvSurg Tech)	Naidich 2015	Van Rossem 2017	Safavi 2012	Swank 2014	Yildiz 2016	Sahm 2011
The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 24 for comparative studies										
A clearly stated aim	2	2	2	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	0	0	2	2	2	0	2	0	2
Prospective collection of data	2	0	2	0	2	2	0	0	0	0
Endpoints appropriate to the aim of the study/ ITT	2	2	2	2	2	2	2	2	0	2
Unbiased assessment of the study endpoint: blind/dblind	0	0	0	0	0	0	0	0	0	0
Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	0	2	0	2
Loss to follow up less than 5%	0	0	0	0	0	0	0	0	0	0
Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0
<i>Additional criteria in the case of comparative study</i>										
An adequate control group	2	2	2	2	2	2	2	2	1	0
Contemporary groups	2	0	2	2	2	2	2	2	0	2
Baseline equivalence of groups	2	2	2	2	2	2	0	2	0	0
Adequate statistical analyses	2	2	2	2	2	2	2	2	2	2
MINORS Score	18	12	16	16	16	18	10	16	5	12

Table 3
Characteristics of included studies.

Trial ID	year	Country	Included patients	study design	Study population	diagnosis	Subgroup of complicated patients	Normal appendix	Patients per arm
Delibegovic	2012	Serbia	60	RCT	Adult (> 15 y.o.)	Clinical diagnosis		0%	30
Dellibegovic	2018	Serbia	60	RCT	Adult	Clinical diagnosis		0%	30
Ortega	1995	USA	253	RCT	Adult only	Clinical diagnosis		16.90%	78
Shalaby	2001	Saudi Arabia	100	RCT	Pediatric only	Clinical diagnosis		8%	60
Beldi	2006	Switzerland	6486	Prospective cohort	Adults and pediatric	Clinical diagnosis	X	17.43%	3921
Escolino	2018	Italy	708	Retrospective cohort	Pediatric only	operative diagnosis of complicated appendicitis	X	0%	334
Miyano (Asian J EndoscSurg)	2011	Japan	68	Prospective cohort	Pediatric only	operative diagnosis of complicated appendicitis	X	0%	31
Myiano (JLAST)	2011	Japan	156	Prospective cohort	Pediatric only	Operative diagnosis of non complicated acute appendicitis		Not indicated	81
Naidich	2015	USA	779	Retrospective cohort	Pediatric only	Clinical diagnosis	X	3.20%	391
Safavi	2012	Canada	242	Retrospective cohort	Pediatric only	Pathological diagnosis	X	0%	24
Swank	2014	Netherlands	1036	Retrospective cohort	Adult	Clinical diagnosis		3.86%	571
Van Rossem	2017	Netherlands	1369	Prospective cohort	All patients	Clinical diagnosis	X	Not indicated	318
Yildiz	2016	Turkey	60	Retrospective cohort	Not indicated	Clinical diagnosis		Not indicated	28
Sahm	2011	Germany	1790	Retrospective cohort	All patients	Clinical diagnosis	X	0.27%	43

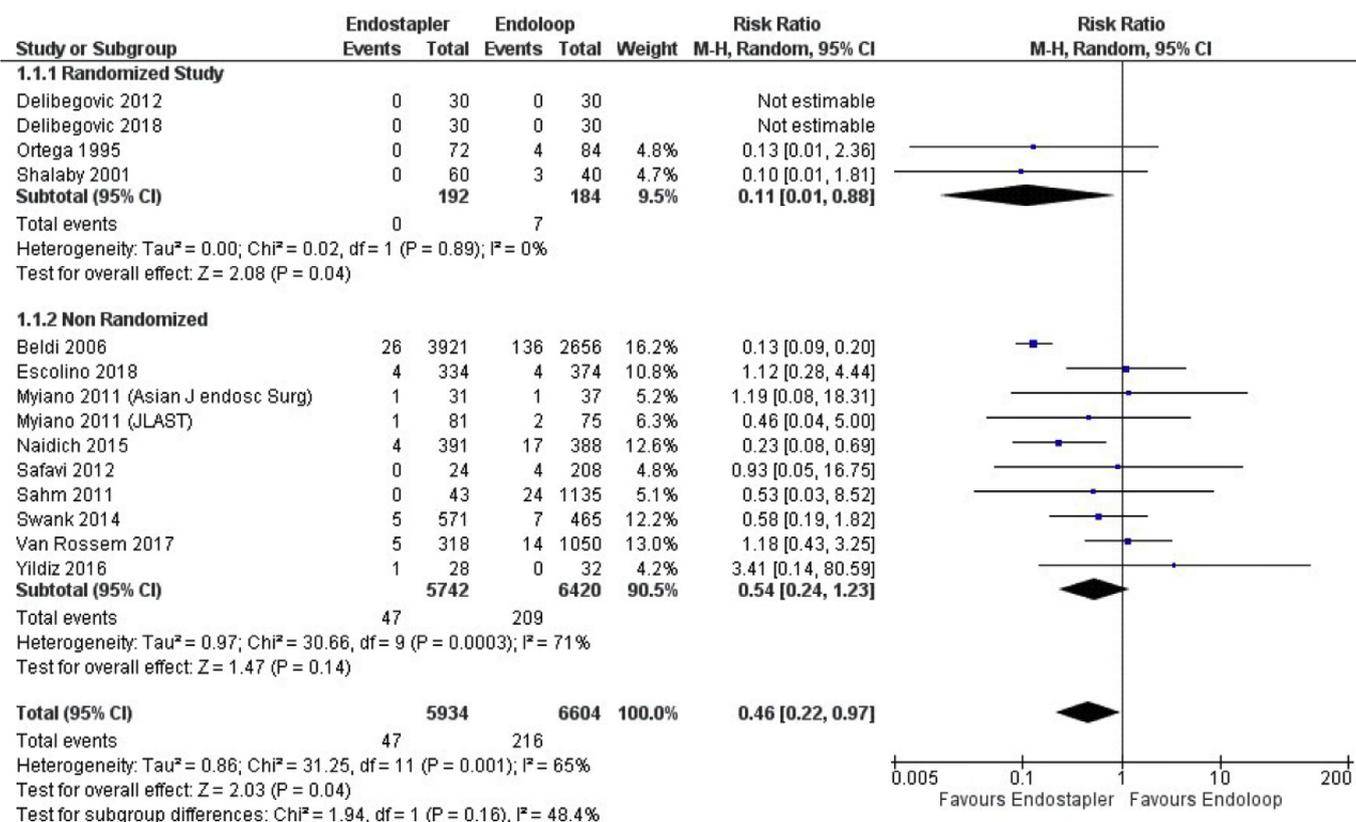


Fig. 2. Forest plot of wound infection rate in overall population.

3.4. Randomized patients

The four randomized controlled trial included 376 patients: in 192 patients the appendicular stump was closed with endostapler and in 184 patients with endoscopic loop ties. The use of endostapler was associated with a significant lower incidence of wound infection (RR 0.11, 95%C.I. 0.01–0.88) but a similar incidence of intra-abdominal abscess (RR 0.47, 95%C.I. 0.11–2.08) (Fig. 2). Only one trial provided data about readmission rate (RR 1.36, 95%C.I. 0.48–3.87) and no trial provided data about reoperations. Operative time was significantly shorter with the use of endostapler (MD -6.43 min, 95%C.I. -8.82; -4.04) and postoperative length of stay was similar between the two techniques (MD 0.04 days, 95%C.I. -0.19; 0.26). Sensitivity analysis showed no differences.

3.5. Adult population

Four studies provided data about only adult patients, including 1312 patients. The analysis showed no differences in terms of wound infection (RR 0.48, 95%C.I. 0.16–1.38) (Fig. 3) and abdominal abscess (0.68, 95%C.I. 0.37–1.23). The closure of appendicular stump was associated with a shorter operative time (MD -6.17 min, 95%C.I. -8.60; -3.75) but a similar length of stay (MD -0.05 days, 95%C.I. -0.25; 0.15); there were no differences in readmission rate (RR 0.88, 95%C.I. 0.55–1.44). Sensitivity analysis showed no differences.

3.6. Pediatric population

Six studies provided data about pediatric population with 921 patients treated with endostapler and 1122 patients treated with endoscopic loop ties. A reduction of wound infection rate has been observed in patients treated with endostapler (RR 0.44 95%C.I. 0.21–0.91). The incidence of intra-abdominal abscess (RR 1.31, 95%C.I. 0.63–2.70), the reoperation (RR 0.52, 95%C.I. 0.05–4.60) and the readmission rate (RR

0.61, 95%C.I. 0.23–1.66) were similar between the two techniques. Sensitivity analysis showed no differences. (Fig. 4).

3.7. Complicated appendicitis

Data about complicated appendicitis were available in seven studies including 2730 patients: 1339 patients have been treated with endostapler and 1391 patients with endoscopic loop ties. Wound infections and intra-abdominal abscesses were not different between the two groups (RR 1.47, 95%C.I. 0.70–3.08 and 1.08; 95%C.I. 0.72–1.62, respectively); similarly, no differences in terms of reoperation and readmission rate have been observed (RR 0.80; 95%C.I. 0.35–1.82 and RR 0.87; 95%C.I. 0.49–1.53, respectively). Sensitivity analysis showed no differences (Fig. 5A–B).

3.8. Complicated appendicitis in pediatric population

Data about complicated appendicitis in pediatric patients were available from four studies including 1156 patients. The analysis showed no differences between the two techniques in wound infection rate (RR 1.7, 95%C.I. 0.43–6.80), abdominal abscess (RR 1.19, 95%C.I. 0.17–2.49), reoperation (RR 0.52, 95%C.I. 0.06–4.60) and readmission rate (RR 0.55, 95%C.I. 0.15–2.01). Sensitivity analysis showed no differences.

4. Discussion

The present meta-analysis shows a significant reduction of superficial wound infection rate in patients treated with endostapler. This did not translate in a significant reduction of reoperations, length of hospital stay, and readmissions. Subgroup analyses showed that endostapler was associated to a reduction of superficial wound infections in pediatric patients only whereas no difference was found in adult patients and in patients with complicated acute appendicitis.

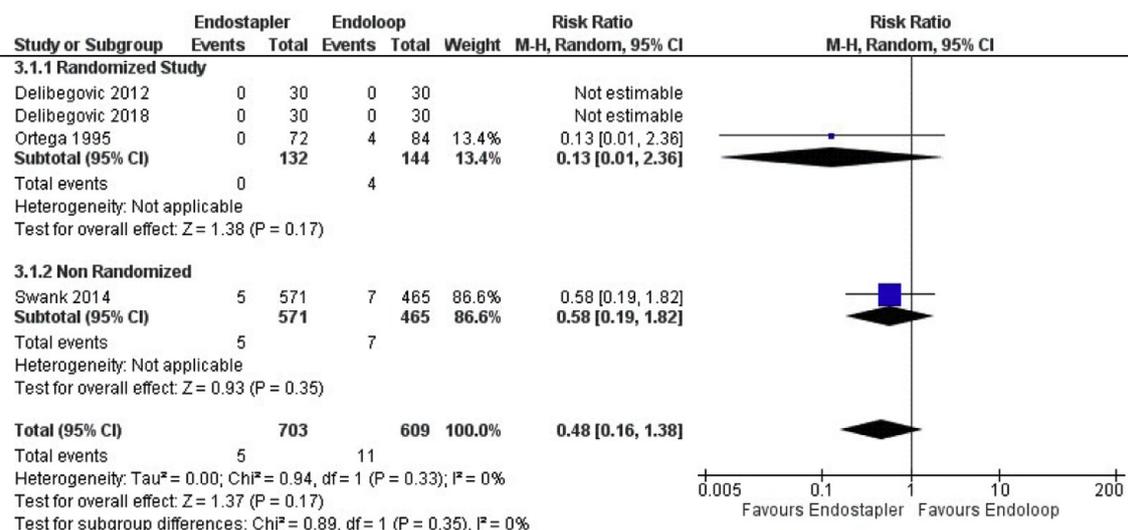


Fig. 3. Forest plot of wound infection rate in adult patients.

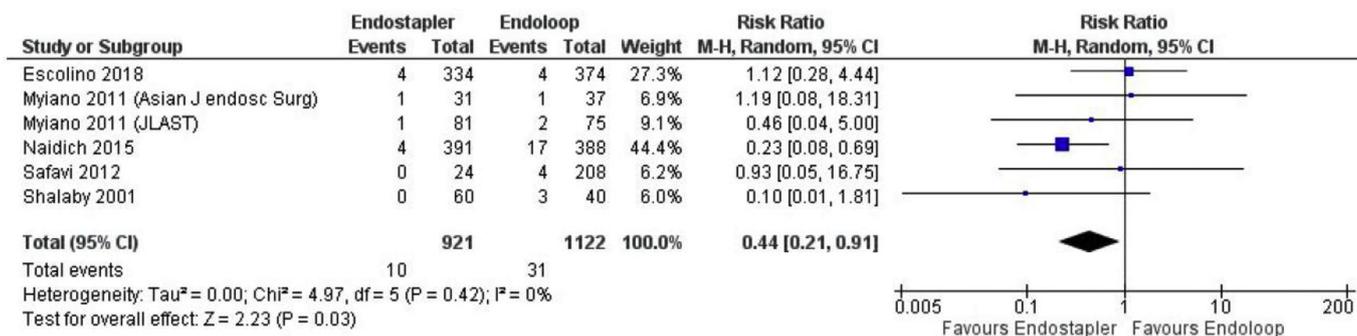


Fig. 4. Forest plot of wound infection rate in pediatric patients.

The stump closure technique during laparoscopic appendectomy still represents an open issue. In fact, the occurrence of either intra-operative or postoperative spillage can negatively affect the outcome following laparoscopic appendectomy. A safe stump closure technique is a key-point when dealing with complicated acute appendicitis because the local inflammation and the infection of the surgical field can involve the caecum and the appendicular base. Among different techniques currently used for appendicular stump closure endoscopic loop ties and endostapler are the most popular. Endoscopic loop ties are cheaper than endostapler, however their placement requires more manipulation of the stump and they can potentially slip, especially in patients with complicated appendicitis. A recent paper by Hilsden and colleagues analyzed the economical implication of the use of the two different techniques: in two similar and homogenous groups of patients the use of endostapler was associated with a mean cost of \$2253.48 (± \$99) vs. a mean cost of \$1988.50 (± \$143) when endoscopic loop ties were adopted. Complications rates between the two groups were similar and costs of complications and prolonged hospitalization were also calculated in the analysis with results favoring the use of endoscopic loop ties, from an economical point of view [8]. From the other hand Endostapler is considered to provide a safer stump closure, reducing a potential leak particularly in case of severe inflammation; however, this is not supported by solid scientific evidences, mainly because of study designs and heterogeneity of patients included, as shown in Table 3.

The choice of the technique to close the appendicular stump is usually oriented by several factors: the confidence of the operating surgeon with the different techniques available, the macroscopic aspect of the appendix and its grade of inflammation, the local availability of

the technique and, last but not least, the costs.

The overall quality of available randomized trials is suboptimal and the risk of bias is high in three of them and intermediate in the other one. The sample size calculation was never reported, exposing to the risk of underpowered trials and the included patients had different severity of acute appendicitis. These limitations strongly weak the generalizability of the results and make difficult to draw reliable conclusions about the superiority of endostapler compared to endoscopic loop ties. Two previous meta-analyses [27,28] found that available data are insufficient to abandon the use of conventional endoscopic loop ties in favor of mechanical devices. This is mainly due to heterogeneity of the two groups of patients. In fact, the rate of acute appendicitis with gangrene and/or perforation was not reported, while a normal appendix was found in a variable range of patients (from 0 to 16%).

The aim of the present meta-analysis is to compare homogeneous patients focusing the attention on subgroups of pediatric and adult patients and on patients with complicated acute appendicitis.

Our results showed that endostapler reduced superficial wound infections in the subgroup of 2043 pediatric patients but not in adults. In both subgroups it was not possible to match patients for severity of acute appendicitis. Criteria to define a wound infection were not *a priori* identified and this could explain the low superficial wound infection rate reported across the included studies (ranging from 0.71% to 3.27%) compared with infection rates reported in literature: in the meta-analysis by Athanasiu and colleagues the pooled infection rate after laparoscopic appendectomy was 6.7% [29].

In the subgroup of 2730 patients with complicated acute appendicitis endostapler and endoscopic loop ties did not differ in terms of incidence of superficial wound infections, abdominal abscess, re-

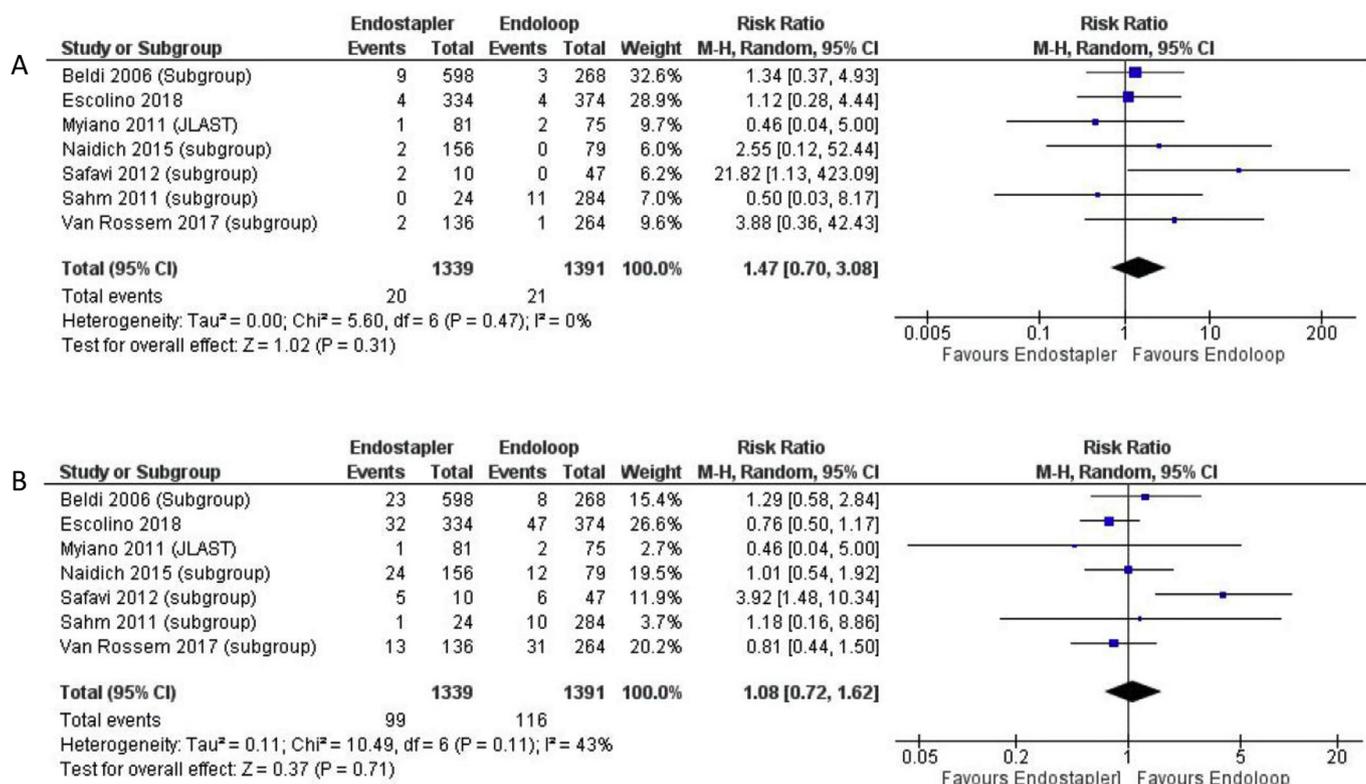


Fig. 5. Forest plot of wound infection rate (A) and intra-abdominal abscess rate (B) in complicated acute appendicitis.

operations, and readmissions. These results might be consistent with the hypothesis that the severity of appendicitis is the major determinant of the postoperative outcome, regardless of the stump closure technique.

Despite the mentioned limitations, due to suboptimal quality of the published trials, the results of the present meta-analysis analyze the issue in an innovative manner, splitting pediatric patients and adults and also focusing on patients homogeneous for severity of acute appendicitis.

5. Conclusion

The results of the present meta-analysis show that the closure of the appendicular stump during laparoscopic appendectomy for acute appendicitis seems to be feasible and safe both with endostapler and endoscopic loop ties, even in the setting of complicated acute appendicitis; the use of endostapler is associated with a reduction of superficial wound infection rate in pediatric patients. However, the quality of existing evidence is very poor, with small and underpowered and designed trials. Larger and well-designed studies are needed to better investigate the issue, considering also the costs.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

This is a systematic review of the literature; all the data presented are available and cited in the references section.

Ethical approval

n/a for this kind of research.

Sources of funding

None.

Author contribution

MC and LN design the study.
 MC, LN LG and NT reviewed literature and select studies.
 MC did statistical analysis.
 MC NT LN prepared and wrote the manuscript.
 LG and MB critically reviewed and improved.
 All the authors read and approved the final version.

Conflicts of interest

None.

Research registration number

Reviewregistry681.
<https://www.researchregistry.com/register-now#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/5cb1af8615dd010976082cd1/>

Guarantor

Marco Ceresoli.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijssu.2019.06.011>.

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