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Comparison of the efficacy and safety of antibiotic treatment and appendectomy for acute uncomplicated appendicitis: a systematic review and meta-analysis

Hongxia Xu^{1*}, Shaohui Yang¹, Jiankun Xing¹, Yan Wang¹, Weiqiang Sun¹, Lingyan Rong¹ and Huihui liu¹

Abstract

Objective This meta-analysis aimed to compare the efficacy and safety of antibiotic treatment and appendectomy for acute uncomplicated appendicitis.

Methods We searched the randomized controlled studies (RCTs) comparing appendectomy with antibiotic treatment for uncomplicated acute appendicitis in the electronic database including Pubmed, Embase, Cochrane, Web of Science, CNKI, VIP, and WanFang. The primary outcomes included complication-free treatment success at 1 year, complications, surgical complications, and the complicated appendicitis rates. Secondary outcomes included negative appendicitis, length of hospital stay, the quality of life at 1 month, and the impact of an appendicolith on antibiotic therapy.

Results Twelve randomized controlled studies were included. Compared with surgery group, the antibiotic group decreased the complication-free treatment success at 1 year (RR 0.81; 95% CI 0.73–0.91; $z=3.65$; $p=0.000$). Statistically significance was existed between antibiotic group and surgical group with both surgical types(open and laparoscopic) (RR 0.43; 95% CI 0.31–0.58; $z=5.36$; $p=0.000$), while no between the antibiotic treatment and laparoscopic surgery (RR 0.72; 95% CI 0.41–1.24; $z=1.19$; $p=0.236$). There was no statistically significant differences between two groups of surgical complications (RR 1.38; 95% CI 0.70–2.73; $z=0.93$; $p=0.353$), the complicated appendicitis rate (RR 0.71; 95% CI 0.36–1.42; $z=0.96$; $p=0.338$), negative appendectomy rate (RR 1.11; 95% CI 0.69–1.79; $z=0.43$; $p=0.670$), duration of hospital stay (SMD 0.08; 95%CI -0.11-0.27; $z=0.80$; $p=0.422$), and quality of life at 1 month (SMD 0.09; 95%CI -0.03-0.20; $z=1.53$; $p=0.127$). However, in the antibiotic treatment group, appendicolith rates were statistically higher in those whose symptoms did not improve (RR 2.94; 95% CI 1.28–6.74; $z=2.55$; $p=0.011$).

Conclusions Although the cure rate of antibiotics is lower than surgery, antibiotic treatment is still a reasonable option for patients with uncomplicated acute appendicitis who do not want surgery without having to worry about complications or complicating the original illness.

Keywords Antibiotic, Appendectomy, Acute uncomplicated appendicitis, Meta-analysis

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Introduction

Acute appendicitis with the incidence of approximate 1/1000 person-years, which affect 8 million annually, is the most common reason for emergency abdominal surgery [1]. The etiology of acute appendicitis is generally fecal residue or lymphoid tissue proliferation blocking the appendiceal lumen, resulting in high pressure in the lumen and damage to the integrity of the mucosa [2, 3]. Acute appendicitis is classified as either uncomplicated or complicated acute appendicitis [4]. Though the definition of them varies among studies [5], generally the uncomplicated acute appendicitis may absence of perforation, abscess or peritonitis and may or may not include non-perforated gangrenous or a fecalith [6–9].

For many years, appendectomy has been recommended for acute uncomplicated appendicitis [10]. Complication after appendectomy, such as wound infection, intestinal adhesions, incisional hernias and so on, are between 2% and 23% [11–13]. Laparoscopic appendectomy is preferred to an open approach with a lower incidence of complications [5]. However, open appendectomy is still used if the appendix has burst or if access is difficult [14].

As early as 1950, people began to try non-surgical treatment for acute simple appendicitis, but it was not generally accepted [15]. For a long time, it was believed that every uncomplicated appendicitis would ultimately progress into a complicated appendicitis [16]. However, growing evidence shows that uncomplicated and complicated acute appendicitis have followed different epidemiological trends which may be treated differently [17, 18]. This has increased new interest for the use of antibiotics in the uncomplicated acute appendicitis. Recently, an increasing amount of evidence supports the use of antibiotics instead of surgery for treating patients with uncomplicated acute appendicitis [19–22]. The cure rate of the uncomplicated acute appendicitis treated with antibiotics is generally 73–88% [7, 8, 23], but over time, within five years it is generally 54–61% [24, 25], which is lower than that after surgery. The complications induced by antibiotic therapy were less than 6.5% and 4.5–24.4% in the appendectomy group [24, 26]. Although cure rate in the antibiotic group was lower, but about half of the participants preferred antibiotics for avoiding surgery [27], and people under the high risk of appendectomy because of comorbidities had to choose conservative treatment [28]. The appendix has a certain immune function and can store intestinal flora, both of which affect the progression of disease, such as cancer [29], so the significance of appendix retention is increased. And during the COVID-19 pandemic, antibiotic treatment of uncomplicated appendicitis showed attraction [30].

However, antibiotic treatment of uncomplicated appendicitis is still limited by conflicting results coming from

studies [31, 32] and some guidelines [5, 28, 33, 34]. This inconsistency may be largely due to a lack of evidence. Recently, the new literature on antibiotic therapy has made progress [7, 9, 35, 36]. Meanwhile, we found that different outcomes of the treatment of uncomplicated appendicitis between randomized and non-randomized controlled trials [20]. And we also found that the meta-analyses that included all randomized trials were rare, and the number of relevant literature is small [22, 37]. Additionally, although more randomized controls were included, semi-randomized controlled trials or complicated appendicitis were included [21, 38].

To help patients better choose their treatment solutions, we made a systematic review and meta-analysis that only RCTs studied on uncomplicated appendicitis included to compare the efficiency of antibiotic treatment with appendectomy, which included indicators of cure rates, complications, and examining whether delayed surgery with antibiotics treatment resulted in a higher rate of complicated appendicitis, et al., to fully discuss the advantages and disadvantages of both treatment options for clinic patients.

Methods

Registration

The systematic review and meta-analysis were carried out in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [39], and was specified in a registered protocol CRD42022374759.

Search strategy

Seven databases, including Pubmed, Embase, Cochrane, Web of Science, CNKI, VIP, and WanFang were searched from their inception to May 2022.

All stages of study identification, selection, quality assessment and data abstraction were carried out independently by 2 reviewers (Hongxia Xu and Shaohui Yang). Any discrepancies were resolved by consulting a third reviewer (Jiankun Xing). The search strategy consisted of medical subject headings (MeSH), including appendicitis, appendectomy, anti-bacterial agents and randomized controlled trial ,and text words. For example, the search strategy in Pubmed was as followed:(Appendicitis [Mesh] OR Ruptured Appendicitis [Title/Abstract] OR Appendicitis, Ruptured [Title/Abstract] OR Perforated Appendicitis [Title/Abstract]) OR Appendicitis, Perforated [Title/Abstract]) AND (Appendectomy [Mesh] OR Appendectomies [Title/Abstract]) AND (Anti-Bacterial Agents [Mesh] OR Agents, Anti-Bacterial [Title/Abstract] OR Anti Bacterial Agents [Title/Abstract] OR Antibacterial Agents [Title/Abstract] OR Agents, Antibacterial [Title/Abstract] OR Antibacterial Agent [Title/Abstract] OR

Agent, Antibacterial [Title/Abstract] OR Anti-Bacterial Compounds [Title/Abstract] OR Anti Bacterial Compounds [Title/Abstract] OR Compounds, Anti-Bacterial [Title/Abstract] OR Anti-Bacterial Agent [Title/Abstract] OR Agent, Anti-Bacterial [Title/Abstract] OR Anti Bacterial Compound [Title/Abstract] OR Anti Bacterial Compound [Title/Abstract] OR Compound, Anti-Bacterial [Title/Abstract] OR Bacteriocidal Agents [Title/Abstract] OR Agents, Bacteriocidal [Title/Abstract] OR Bacteriocidal Agent [Title/Abstract] OR Agent, Bacteriocidal [Title/Abstract] OR Bactericide[Title/Abstract] OR Bactericides[Title/Abstract] OR Anti-Mycobacterial Agents [Title/Abstract] OR Agents, Anti-Mycobacterial [Title/Abstract] OR Anti Mycobacterial Agents [Title/Abstract] OR Anti Mycobacterial Agent [Title/Abstract])) OR Agent, Anti-Mycobacterial [Title/Abstract] OR Anti Mycobacterial Agent [Title/Abstract] OR Antimycobacterial Agent [Title/Abstract] OR Agent, Antimycobacterial [Title/Abstract] OR Antimycobacterial Agents [Title/Abstract] OR Agents, Antimycobacterial [Title/Abstract] OR Antibiotics [Title/Abstract] OR Antibiotic [Title/Abstract]) AND (Randomized Controlled Trial [Publication Type] OR rct) AND (1000/1/1:2022/5/31 [pdat]) AND (1000/1/1:2022/5/31 [pdat]) Filters: from 1000/1/1–2022/5/31.

The search strategies of databases were shown in Supplementary Table 1.

Study selection criteria

- (1) Studies including people who diagnosed as uncomplicated appendicitis. In this article, uncomplicated appendicitis defines as absence of perforation, abscess, peritonitis, fecalith, perforated gangrenous or phlegmonous.
- (2) Only RCTs were included.
- (3) Only English and Chinese literatures (only included in the core above journals) were included.

Risk of bias assessment

The risk of bias for the studies enrolled in the systematic review and meta-analysis was assessed according to the Cochrane handbook for systematic reviews of interventions [40], using the Cochrane risk of bias tool for RCTs.

Outcome measures

The primary outcome measure

1. **Cure rate of complication-free treatment at 1 year:**
1-year cure rate without complications

In antibiotic treatment group, no recurrence, no moderate or serious adverse events required hospitalization, and in appendectomy treatment group, there were no post-operative complications.

2. **Total complications**

The complications in the appendectomy group were defined as postoperative complications, while in antibiotic group were adverse events requiring hospitalization.

3. **Complications after appendectomy**

The patients in the appendectomy group and in the antibiotic group who needed surgical had postoperative complications.

4. **The rate of complicated appendicitis formed after treatments**

If antibiotics delayed the initial treatment of uncomplicated appendicitis, the disease was defined as complicated appendicitis was found after antibiotic therapy.

The secondary outcome measure

1. Negative appendicitis

Negative appendicitis was defined as non-appendicitis was found after appendectomy.

2. Length of hospital stay
3. Quality of life after treatments
4. The effect of appendicoliths on the effectiveness of antibiotic treatment

In the antibiotic group, appendicolith rate was compared between patients whose symptoms improved and not.

Data extraction

The data extraction was performed by two independent authors (Hongxia Xu and Shaohui Yang), and a third author (Jiankun Xing) adjudicated discordant assessments.

Statistical analysis

Stata 16 was applied for data analysis. Heterogeneity of the results across studies was assessed using Higgins' I^2 and chi-square tests. A p -value of chi-square test less than 0.05 with an I^2 value of greater than 50% was considered indicative of substantial heterogeneity.

Fixed-effects model was implemented if statistically significant heterogeneity was absent. Otherwise, a random-effects model was used for meta-analysis if statistically significant heterogeneity was found.

Results

Literature search, study selection, and characteristic

A total of 768 references were identified through data base searching (Fig. 1). The inclusion criteria were met by 20 articles. However, three studies which met the inclusion criteria were excluded after closer review: one is a quasi-randomization trial [41], one lacks evidence of randomization [42], and the third was retracted after publication [43]. So finally 17 articles were included [6–9, 23–26, 35, 36, 44–50]. Salminen 2018 [24], Hainanen 2019 [50], Sippola 2017 [48], and Sippola 2020 [49] were follow-up trial studies of Salminen 2015 [8]. Patkova 2020 [25] is a follow-up study to the Svensson 2015 [46] trial. Although the number of articles included was 17,

there were 12 RCTs in this study. The characteristics of included RCTs were list in Table 1.

In addition to data directly extracted from the articles, some data was deduced from graphs, or proportions (Peter O'Leary 2021) [35], some was calculated from other data given in the article (CODA Collaborative 2020, Vons 2011, Styrud 2006.) [7, 23, 26], and some were derived from composite data, such as data without an appendicolith representing uncomplicated appendicitis (CODA Collaborative 2020) [7].

If the format of the measure is not mean and standard deviation, manual calculation into mean (standard deviation) was used if it is the mean (95% CI), and calculation software is applied if it is the median [51, 52].

Risk of Bias

Twelve trials were included for quality evaluation, which used revman 5.3 (Fig. 2).

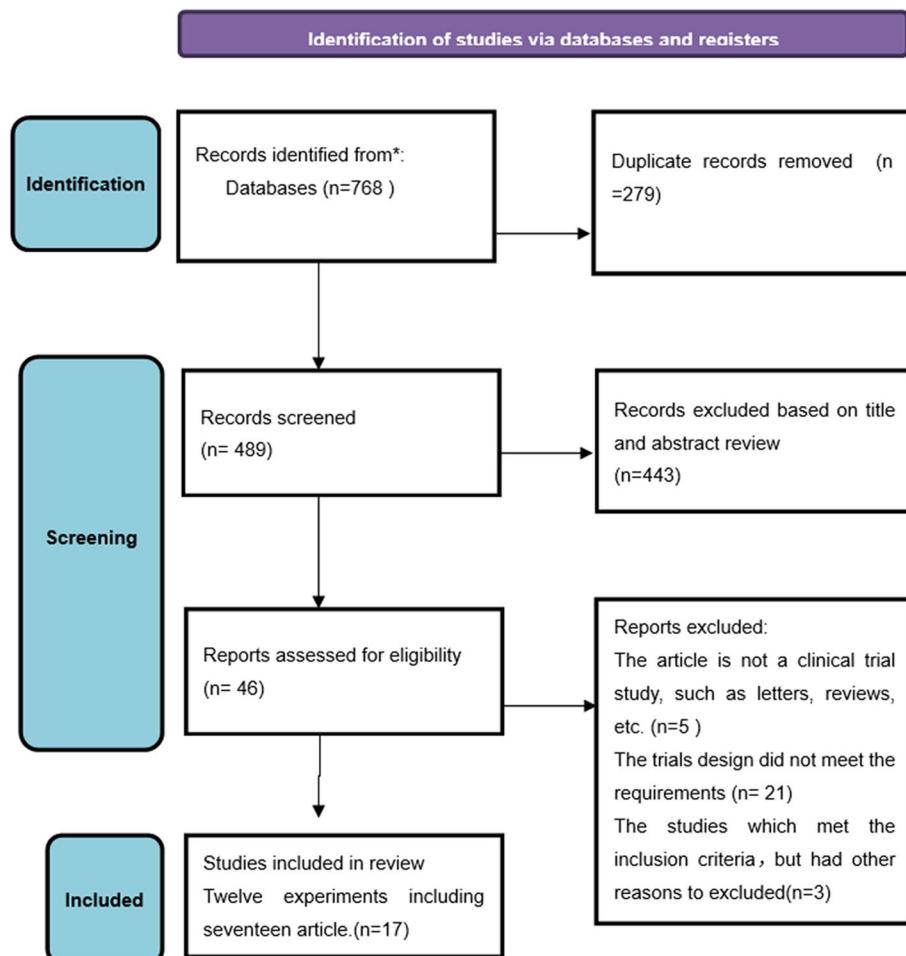


Fig. 1 Flow diagram of literature screening and selection process

Table 1 Characteristics of included RCTs

Number	Follow-up test	Test type	Included population	Diagnostic method	Antibiotic group	Operation group	Outcome indicators
Vons 2011 [23]	RCT,multicenter(6 centers)	n = 239 adult:>18 years;uncomplicated appendicitis	CT	n=120 amoxicillin plus clavulanic acid 3 g,iv 48 h,oral amoxicillin plus clavulanic for 8 days.	n=119 a McBurney incision or laparoscopy	n=119 a McBurney incision or laparoscopy	primary endpoint: occurrence of peritonitis within 30 days of initial treatment. Secondary endpoints: 1.the number of days with a postintervention visual-analogue-scale pain score ≥4. 2.length of hospital stay. 3.absence from work. 4.incidence of complications other than peri tonitis within 1 year. 5.reurrence of appendicitis after antibiotic treatment
Salminen 2015 [8]	Salminen 2018 [24], Haijnen 2019 [50], Sippola 2017, Sippola 2020	RCT,multicenter(6 centers)	n = 530 adult:aged 18–60 years;uncomplicated appendicitis.	CT	n=257 Ertpenem 1 g/d IV for 3 days, followed by 7 days of oral levofloxacin (500 mg once daily) and metronidazole(500 mg 3 times per day).	n=273 mostly Open appendectomy,laparoscopic appendectomy 5.5%.	primary endpoint: successful treatment. antibiotic group. Secondary endpoints: 1.overall post intervention complications. 2.late recurrence (after 1 year) of acute appendicitis after conservative treatment 3.length of hospital stay 4.sick leave 5.postintervention pain scores 6.treatment costs
Otero 2022 [6]	RCT,multicenter(3 centers)	n = 39 children: aged 6–17 years; uncomplicated appendicitis.	ultrasound and/or computed tomography (CT)	n=20 piperacillin/tazobactam iv for 24–48 h, followed by 10 days of oral ciprofloxacin and metronidazole	n= 19 laparoscopic appendectomy	Primary endpoint: (1) one-year success rate of antibiotics-alone. (2) QOL measures assessed 1 month post discharge. Secondary endpoints: length of stay and readmission rate.	

Table 1 (continued)

Number	Follow-up test	Test type	Included population	Diagnostic method	Antibiotic group	Operation group	Outcome indicators
Svensson 2015 [46]	Pattkova 2020	Pilot RCT(2 centers).	n = 50 children: aged 5–15 years. acute appendicitis(excluding perforated appendicitis on the basis of generalized peritonitis , appendiceal mass.	ultrasound and/ or computed tomogra- phy(CT)	n=24 meropenem (10 mg/kg × 3 per 24 h) and met- ronidazole (20 mg/ kg × 1 per 24 h) IV for at least 48 h,followed by 8 days of oral cipro- floxacin (20 mg/ kg×2 per 24 h) and metronidazole (20 mg/kg × 1 per 24 h).	n= 26 laparoscopic appen- dectomy	primary endpoint: resolution of symp- toms without signifi- cant complications. Secondary end- points: 1.the time from randomization to discharge. 2.com- plications 3.recurrent appendicitis within 1 year 4.cost of treat- ment
Styrud 2006 [26]	RCT,multicenter(6 centers)	n = 252 adult,men:18–50 years.Excluded were patients with suspicion of perforation of the appen- dix.	laboratory results;the other diagnosis not clearbut The fre- quency of appendicitis was 97% in the surgery group.	n=128 2 days of i.v. cefotaxime 2 g 12 hourly, and tinida- zole 0.8 g daily, and received oral treat- ment with ofloxacin 200 mg twice daily, and tinidazole 500 mg twice daily for 10 days.	n= 124 open or laparoscopi- cally	1.The cure rate of antibiotic group and operation group. 2.Recurrence rate of antibiotic group within one year 3.the time off work 4.Sick leave 5.Hospital stay	primary endpoint: 1.The cure rate of antibiotic group and operation group. 2.Recurrence rate of antibiotic group within one year 3.the time off work 4.Sick leave 5.Hospital stay
Peter O'Leary 2021 [35]	RCT	n = 186 adult:>16 years; uncomplicated appendicitis	<45 years,US +/- MRI,>45 years,CT	n=91 co- amoxiclav(1.2 g)IV 3 times daily	n= 89 laparoscopic appen- dectomy	primary endpoint: evaluated the success rate for acute uncom- plicated appendicitis at 1-year follow-up. Secondary endpoints: 1.quality of life 2.cost 3.length of stay 4.sick- ness days	primary endpoint: evaluated the success rate for acute uncom- plicated appendicitis at 1-year follow-up. Secondary endpoints: 1.quality of life 2.cost 3.length of stay 4.sick- ness days

Table 1 (continued)

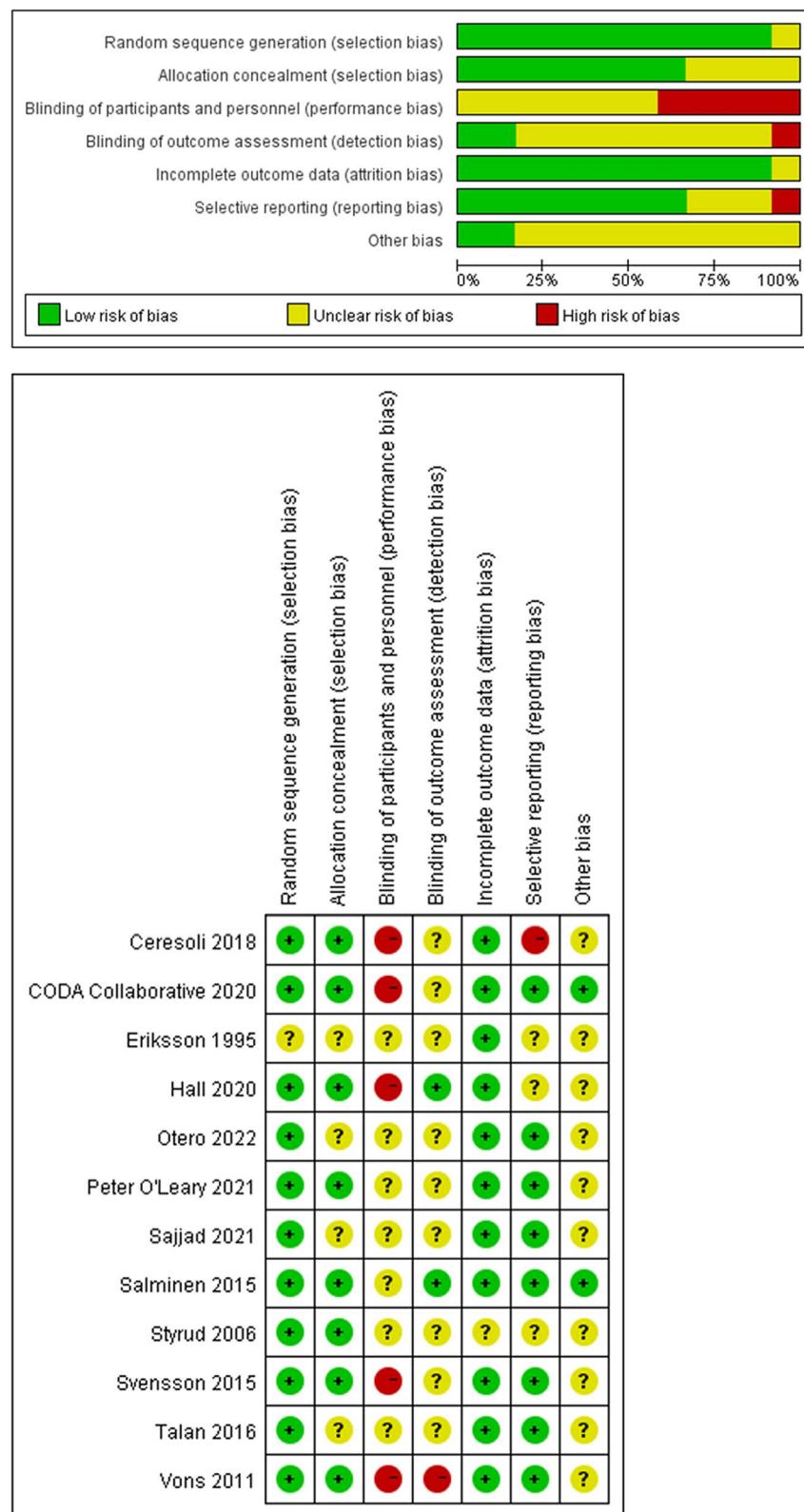
Number	Follow-up test	Test type	Included population	Diagnostic method	Antibiotic group	Operation group	Outcome indicators
Hall 2020	RCT		<i>n</i> =54 children aged 3–16 years, uncomplicated appendicitis.	clinical and laboratory parameters + abdominal assessment. In this trial, just 28% of participants received an ultrasound.	<i>n</i> =27 a minimum of 24 h broad spectrum intravenous antibiotics. After the initial 12-hour period of NBM(nil by mouth), oral intake was advanced as tolerated, received a total of 10 days antibiotics following randomisation.	<i>n</i> =27 open or laparoscopic appendectomy	primary endpoint: the recruitment rate into the trial. Secondary endpoints: 1. Performance of study procedures. 2. Willingness of parents, children and surgeons to take part in a randomised study comparing operative versus non-operative treatment and identify anticipated recruitment rate. 3. Clinical outcomes of trial treatment pathways.
Ceresoli 2018	prospective RCT		adults aged 18–65 years, uncomplicated appendicitis.	appendicitis inflammatory response (AIR) score with the adjunct of ultrasound.	<i>n</i> =19 intravenous administration of 1 g of Ertapenem once a day for 3 days during hospitalization and further administration of amoxicillin/clavulanate 1 g every 8 h for 5 days.	<i>n</i> =22 laparoscopic appendectomy	primary endpoint: the success rate of the treatment. Secondary endpoints: 1. complication rate 2. negative appendectomy rate 3. long-term negative outcomes within a year 4. length of hospital stay 5. work absence

Table 1 (continued)

Number	Follow-up test	Test type	Included population	Diagnostic method	Antibiotic group	Operation group	Outcome indicators
Talan 2016	Pilot RCT		<i>n</i> = 30 children (<i>n</i> = 1) + adult: aged > 5 years, uncomplicated appendicitis	CT and/or ultrasonography; CT with intravenous contrast in adults and ultrasonography in persons younger than 18 years, followed by CT if indicated.	<i>n</i> = 16 intravenousertapenem for 2 day/followed 8-day supply of an oral antibiotic regimen of cefdinir and metronidazole.	<i>n</i> = 14 open or laparoscopic appendectomy	primary endpoint: the one-month major complication rate. Secondary endpoints: 1. appendectomy rate in the antibiotics-first group 2. quality of life 3. days unable to perform normal activities and work or school 4. days of analgesic use 5. pain scores 6. total 1 hours in the ED and hospital at the initial visit from triage until ED or hospital discharge 7. total hours in the hospital (including the ED) through 1 month 8. Alvarado scores on day 1 for both groups and day 2 for antibiotics-first participants 9. hospital charges.
Sajjad 2021 [36]	RCT		<i>n</i> = 180 children: aged 5–15 years, uncomplicated appendicitis.	Ultrasound (USG) findings , PAS score , laboratory results	<i>n</i> = 90 intravenous metronidazole (10 mg/kg/dose intravenous infusion 8 hourly) and metronidazole (20 mg/kg/day intravenous divided doses 8 hourly) for at least 48 h. Followed oral ciprofloxacin (10 mg/kg/dose twice daily) and metronidazole (20 mg/kg/day two divided doses) for another 8 days	<i>n</i> = 90 open appendectomy	1.successful cure rate 2.Total leukocyte count 3. C reactive protein

Table 1 (continued)

Number	Follow-up test	Test type	Included population	Diagnostic method	Antibiotic group	Operation group	Outcome indicators
Eriksson 1995 [47]	RCT	n=40 adult: aged 18–75 years, acute appendicitis.	n = 20 Cefotaxime 2 g 12 hourly and tinidazole 800 mg daily were given for 2 days followed oral treatment with ofloxacin 200 mg twice daily and tinidazole 500 mg twice daily for 8 days.	n = 20 open appendectomy	1.Mean concentration of C-reactive protein during hospitalization and at 30 days of follow-up 2.Mean total white blood cell count during hospitalization and at 30 days of follow-up 3.Pain record during hospitalization and at 30 days of follow-up 4.cure rate		
CODA collaborative 2020 [7]	RCT, multicenter(25 centers)	n = 1552 adult	computed tomography (CT) alone or in combination with ultrasound or magnetic resonance imaging	n=776 received an intravenous formulation for at least 24 h, followed by pills, for a 10-day total course. Clinical teams selected antibiotics from Surgical Infection Society and Infectious Diseases Society of America guidelines for intraabdominal infections.	n=776 laparoscopic(96%) and open appendectomy	primary endpoint: 30-day health status Secondary endpoints: 1.patient-reported resolution of symptoms 2.Visits to the emergency department or urgent care clinic for related symptoms 3. days in the emergency department or hospital related to appendicitis symptoms or treatment-related complications 4.days of missed work for the participant and the caregiver	

**Fig. 2** Risk of bias graph

Publication bias

Total complications

A total of 11 RCTS were included in the “complications” analysis, and the Egger’s test result was that $p=0.952$ was greater than 0.05, and there was no evidence for publication bias in the articles. See Annex 1 for details.

Complications after appendectomy

A total of 11 RCTS were included in the “surgical complications” analysis, and the Egger’s test result was that $p=0.838$ was greater than 0.05, and there was no evidence for publication bias between the articles. See Annex 2 for details.

The rate of complicated appendicitis formed after treatments

A total of 10 RCTS were included in the “The Complementary Rate” analysis, and the result of Egger’s test was that $p=0.177$ was greater than 0.05, so there was no evidence of publication bias between the articles. See Annex 3 for details.

Negative appendicectomies

A total of 10 RCTS were included in the “The Complementary Rate” analysis, and the Egger’s test result was that $p=0.475$ was greater than 0.05, and there was no evidence for publication bias between the articles. See Annex 4 for details.

Conclusion

Leading indicators

Cure rate of complication-free treatment at 1 year

Eight studies reported the results of treatment success at 1year. The complication-free treatment success rate of antibiotic group (69.4%,468/674) was inferior to that of surgery group (88.8%,609/686) (RR 0.81; 95% CI 0.73–0.91; $z=3.65$; $p=0.000$), has a significant difference (Table 2) (Fig. 3).

Total complications

Eleven studies reported data on complications, of which five studies were mostly laparoscopic surgery, six mostly open surgery.

The complications between antibiotic group(3.9%, 50/1270) and surgical group with both surgical types (open and laparoscopic) (9.5%, 119/1257) had statistically significant (RR 0.43; 95% CI 0.31–0.58; $z=5.36$; $p=0.000$).Subgroup analyses revealed significant differences between antibiotic treatment (4.8%, 30/631) and open surgery (14.5%, 91/626) (RR 0.34; 95% CI 0.23–0.49; $z=5.55$; $p=0.000$). However, there was no statistically significant between antibiotic treatment (3.1%, 20/639) and laparoscopic surgery (4.4%, 28/631) (RR 0.72; 95% CI 0.41–1.24; $z=1.19$; $p=0.236$). (Table 2) (Fig. 4).

Complications after appendectomy

No statistically significant differences were found between antibiotic group who eventually underwent appendectomy (9.5%, 119/1257) and surgical group (11.9%, 47/394) for complications (RR 1.38; 95%CI 0.70–2.73; $z=0.93$; $p=0.353$), though complications rate of antibiotic group is higher than surgical group (Table 2) (Fig. 5).

Table 2 Outcomes of the primary and secondary indicators

Indicators	Antibiotic group	Surgery group	RR (95% CI)	z	p
Cure rate of complication-free treatment at 1 year	69.4%(468/674)	88.8%(609/686)	0.81(0.73–0.91)	3.65	0.000<0.05
Total complications	3.9%(50/1270)	9.5%(119/1257)	0.43(0.31–0.58)	5.36	0.000<0.05
Complications after appendectomy	4.8%(30/631)	14.5%(91/626) ^a	0.34(0.23–0.49)	5.55	0.000<0.05
Therate of complicated appendicitis formed after treatments	3.1%(20/639)	4.4%(28/631) ^b	0.72(0.41–1.24)	1.19	0.236
The rate of appendectomy with non-appendicitis	9.5%(119/1257)	11.9%(47/394)	1.38(0.70–2.73)	0.93	0.353
Length of hospital stay	5%(63/1264)	9.9%(128/1289)	0.71(0.36–1.42)	0.96	0.338
Quality of life after treatments	4.2%(30/721)	3.7%(27/732)	1.11(0.69–1.79)	0.43	0.670
The effect of appendicoliths on the effectiveness of antibiotic treatment	NA	NA	0.08(-0.11-0.27) ^c	0.80	0.422
NA Not Available	NA	NA	0.09(-0.03-0.20) ^c	1.53	0.127
^a Open surgery	38.1%(101/265) ^d	18.9%(140/740) ^e	2.94(1.28–6.74)	2.55	0.011<0.05

NA Not Available

^a Open surgery

^b Laparoscopic surgery

^c SMD (95%CI)

^d The appendicolith rate of the patients whose symptoms were not improved in the antibiotic treatment group

^e The appendicolith rate of the patients whose symptoms were improved in the antibiotic treatment group

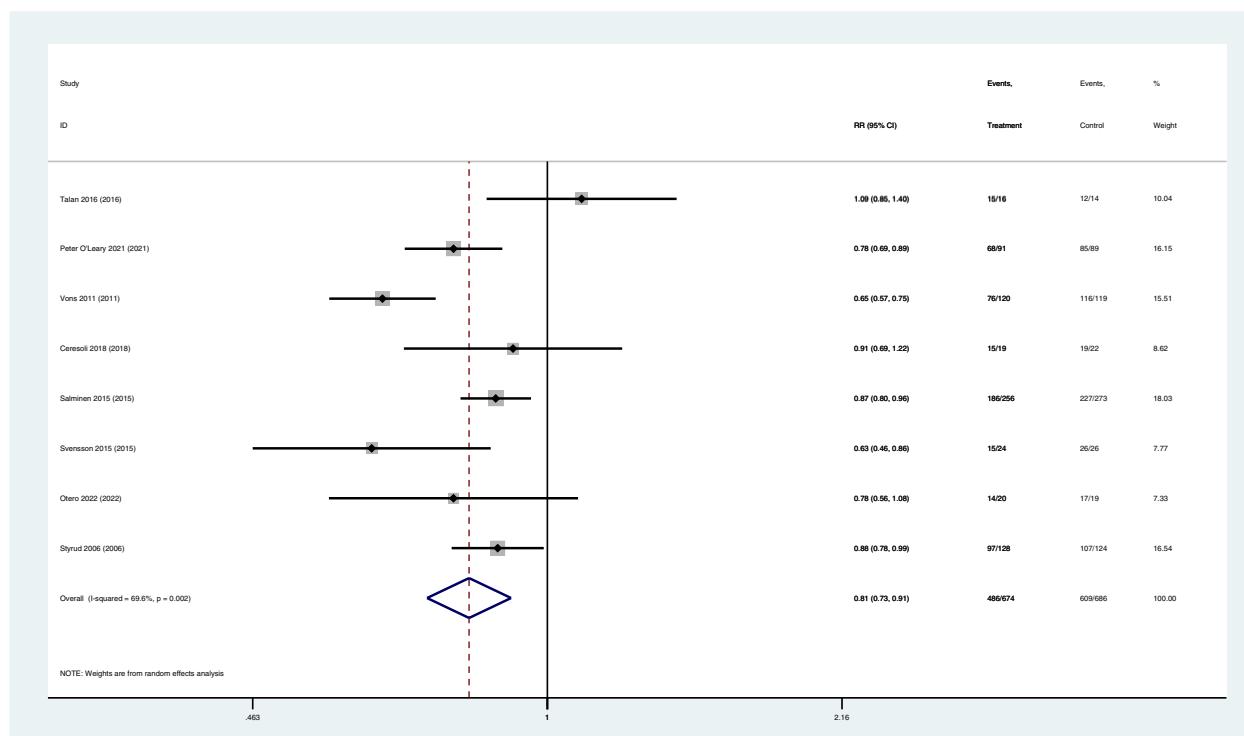


Fig. 3 Forest diagram of complication-free treatment success at 1year

The rate of complicated appendicitis formed after treatments
Ten studies reported the incidence of complicated appendicitis undergoing surgery in both antibiotic and surgical groups. Compared to surgical groups, the complicated appendicitis rate was lower in antibiotic groups (5%, 63/1264; 9.9%, 128/1289), however there is no statistically significant differences between two groups (RR 0.71; 95% CI 0.36–1.42; z=0.96; p=0.338) (Fig. 6).

Secondary indicators

Negative appendectomies

Ten studies reported negative appendectomy in both groups.

The rates of negative appendectomy in antibiotic group after antibiotic treatment failure and surgical group were equivalent (4.2%, 30/721; 3.7%, 27/732), the antibiotic group was slightly higher, but there is no statistically significant differences between two groups (RR 1.11; 95% CI 0.69–1.79; z=0.43; p=0.67) (Table 2). See Annex 5 for details.

Length of hospital stay

The length of hospital stay was reported in six studies. The duration of hospital stay did not differ significantly between the antibiotic and surgical group (SMD 0.08; 95%CI -0.11-0.27; z=0.80; p=0.422) (Table 2). See Annex 6 for details.

Quality of life after treatments

The literature that could be analyzed for the quality of life were small and only 3 papers were included for the quality of life at 1 month. The quality of life did not differ significantly between the antibiotic group and surgical group at one month after treatment (SMD 0.09; 95%CI -0.03-0.20; z=1.53; p=0.127) (Table 2). See Annex 7 for details.

The effect of appendicoliths on the effectiveness of antibiotic treatment

A total of four studies reported the effect of an appendicolith on the effectiveness of antibiotics. The appendicolith rate was about twice in patients whose symptoms did not improve(38.1%, 101/265)than those whose symptoms improved (18.9%, 140/740).There was a statistically significant difference between two groups(RR 2.94; 95% CI 1.28–6.74; z=2.55; p=0.011) (Table 2). See Annex 8 for details.

Discussion

Comparing treatment success between the antibiotic and surgical groups, the complication-free cure rate is more objective. The cure rate of antibiotic group in this study is 69.4%, which is consistent with the previous study [20, 53]. In comparison with surgical, the cure rate

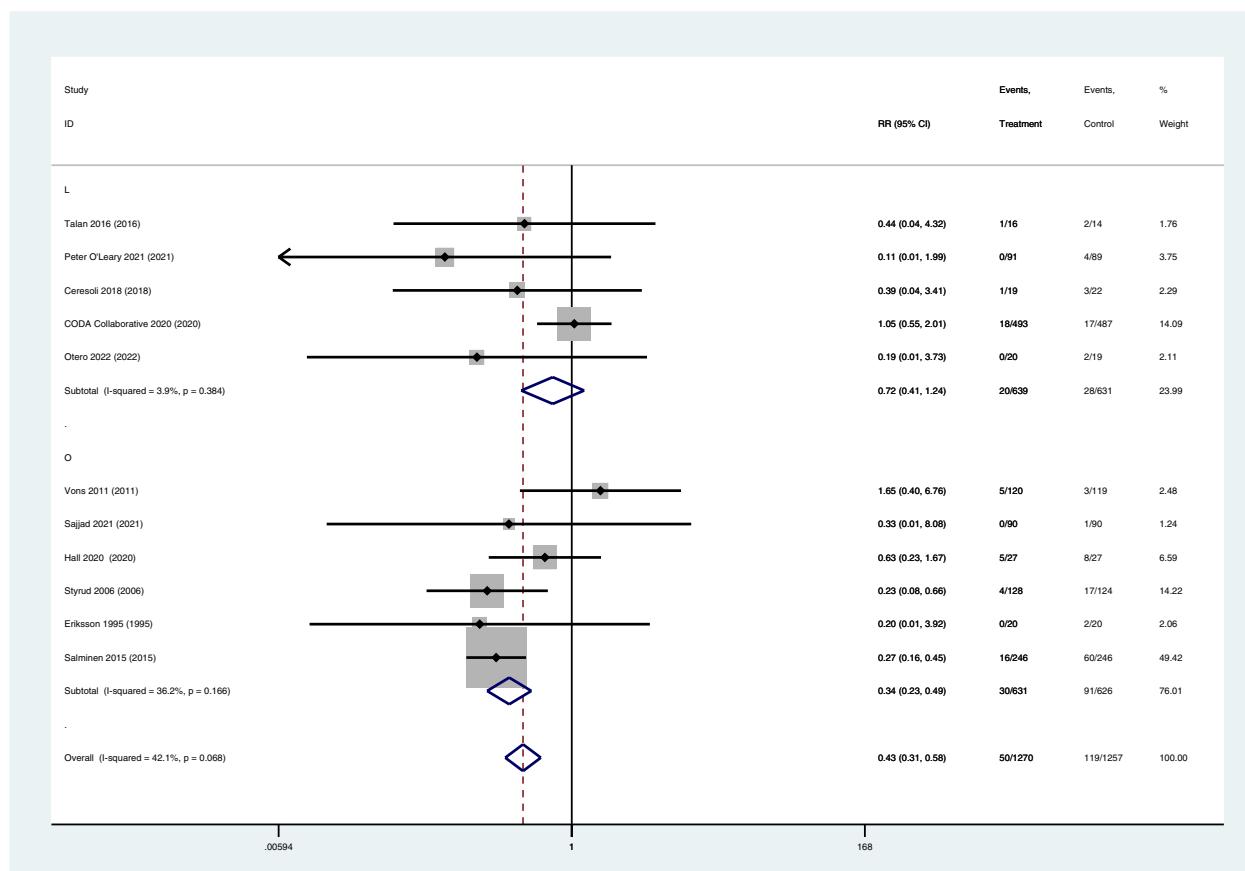


Fig. 4 Forest diagram of complications

of the antibiotic group is significantly lower, suggesting that it may not be the optimum treatment for uncomplicated acute appendicitis only considering of recurrence. However, there were certain patients who were not fit or willing for surgery. Bom WJ et al. [27] found that about half of the participants preferred antibiotic treatment for avoiding surgery and would accept a recurrence risk of more than 50% within 1 year. However, participants who prefer surgery for radical treatment of appendicitis, may tolerate a recurrence risk of no more than 10% when treated with antibiotics.

In general, the complications in the antimicrobial therapy group were lower than those in the surgical group. However, the surgical procedures included open and laparoscopic surgery, and the complications of open surgery were higher than those of laparoscopic surgery [54]. Complications of antibiotic therapy were 1.5–8.2% [24, 36, 42], and 1%~3% of laparoscopic operation [55–57]. According to this study, the complications rates between laparoscopically operated people (4.4%) and antibiotic treated people (3.1%) were similar. With the introduction of laparoscopic surgery, the complications of surgery are greatly reduced and comparable to

conservative treatment, which is a significant advantage of laparoscopic appendectomy.

This study showed that patients who underwent surgery after failing antibiotic treatment had similar surgical complications rates as the surgical group (9.5% vs. 11.9%), suggesting that delaying the appendectomy due to antibiotic failure might not possibly result in a higher risk of postoperative complications. The previous study found that the rate of complicated appendicitis was lower in the antibiotics treatment than surgical group (2.7% vs. 12.3%) at 1 year. Antibiotics treatment does not increase the rate of complicated appendicitis [58], which is familiar with the present study(antibiotics treatment vs. surgery group :5% vs. 9.9%). Uncomplicated acute appendicitis treated with antibiotics first was safe and effective with no significant increase in the number of complicated acute appendicitis [5, 32, 59, 60]. Also, evidence suggests that spontaneous resolution of untreated, non-perforated appendicitis is common and the perforation can rarely be prevented [17]. However, the previous Meta-analysis study [20] showed the opposite conclusion because it used the number of surgical patients instead of all patients (which generally applied) of antibiotic group as a

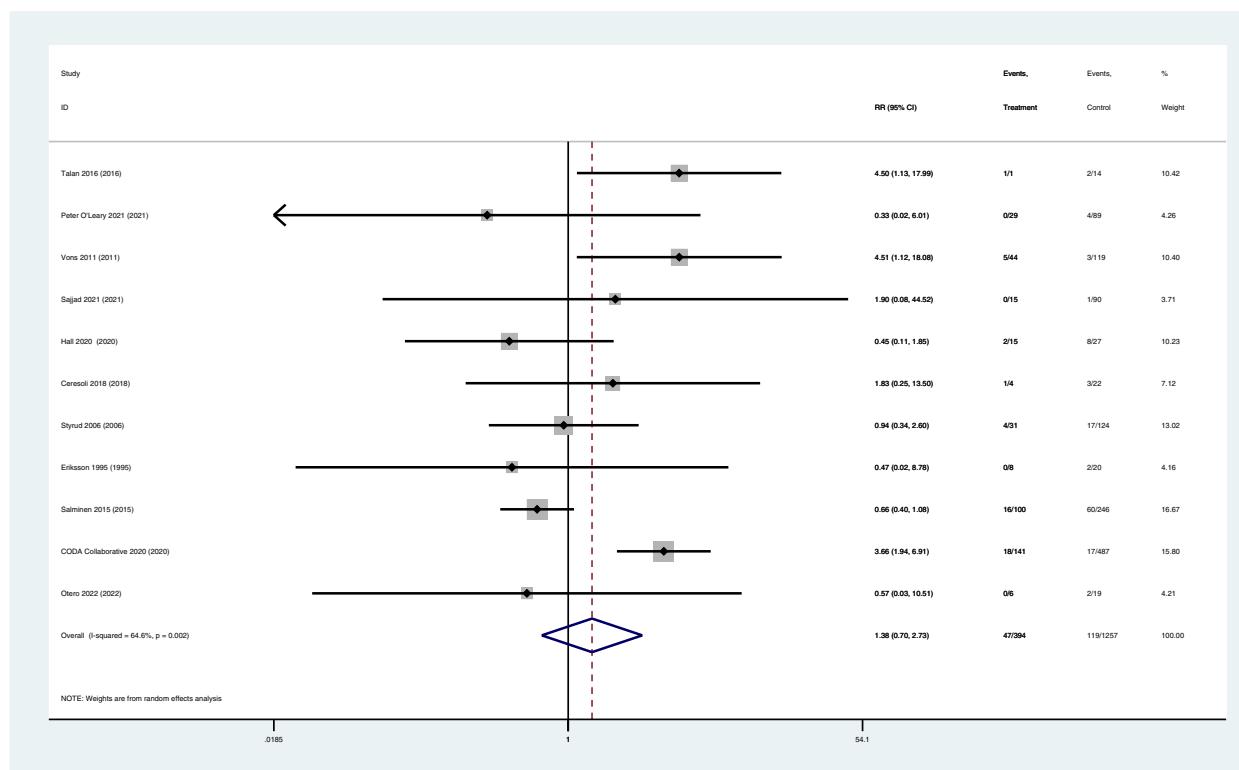


Fig. 5 Forest diagram of postoperative complications

parameter. Additionally, it is possible that some patients may have had complicated appendicitis at first that was not diagnosed, as opposed to uncomplicated appendicitis progressing to complicated appendicitis due to antibiotic treatment failure. Therefore, the conclusion that uncomplicated appendicitis will progress to complicated appendicitis can only be overestimated.

Dozens of studies found that the incidence of negative appendectomies varies greatly from approximately 3.75–21% [57, 61, 62]. Normally, there are two reasons for such wide range as follows: (1)Preoperative imaging such as Computed Tomography(CT) and Ultrasound (US), has widespread used to greatly reduce the proportion of negative appendices in recent years. CT has been shown greater sensitivity and specificity than US for the diagnosis of appendicitis [63–65]; (2)Some considered completely normal appendicitis as a negative appendectomy, while the others included hyperplasia, atrophy and fibrosis. The present study applies the latter definition. The incidence of negative appendectomy was lower in both groups(antibiotics treatment vs. surgery group:4.2% vs. 3.7%), similar to another study [57]. In this meta-analysis, ten studies reported negative appendectomies, only one trials (Styrud2006) [26] did not explicit mention

if preoperative imaging was used. Therefore, we should increase the accuracy of preoperative imaging diagnosis, and if US is difficult to clarify, CT, even Magnetic Resonance Imaging(MRI), can be added [66].

A majority of articles documented similar hospital stay with both treatment methods [22, 32, 37, 67], which is consistent with our study. However, some reported that the length of hospital stay in the antibiotics group was longer than that of the surgery group [38, 68], while others reported that the conservative group's hospital stay was shorter than the surgery group [53].

This meta-analysis only analyzed the quality of life at 1 month and there was no significant difference. Podda M et al. concluded that the score of quality of life was significantly higher in patients with the appendectomy treatment at the 30-day, while the score was lower in the appendectomy group at the 1-year [69]. Minneci PC reported that patients who selected nonoperative management had high quality-of-life scores and remained satisfied with their health care decision at both 30 days and 1 year [65].

Dozens of studies have shown that presence of an appendicolith is associated with both an increased risk of antibiotic failure and recurrence [70–72], which is consistent with this study.

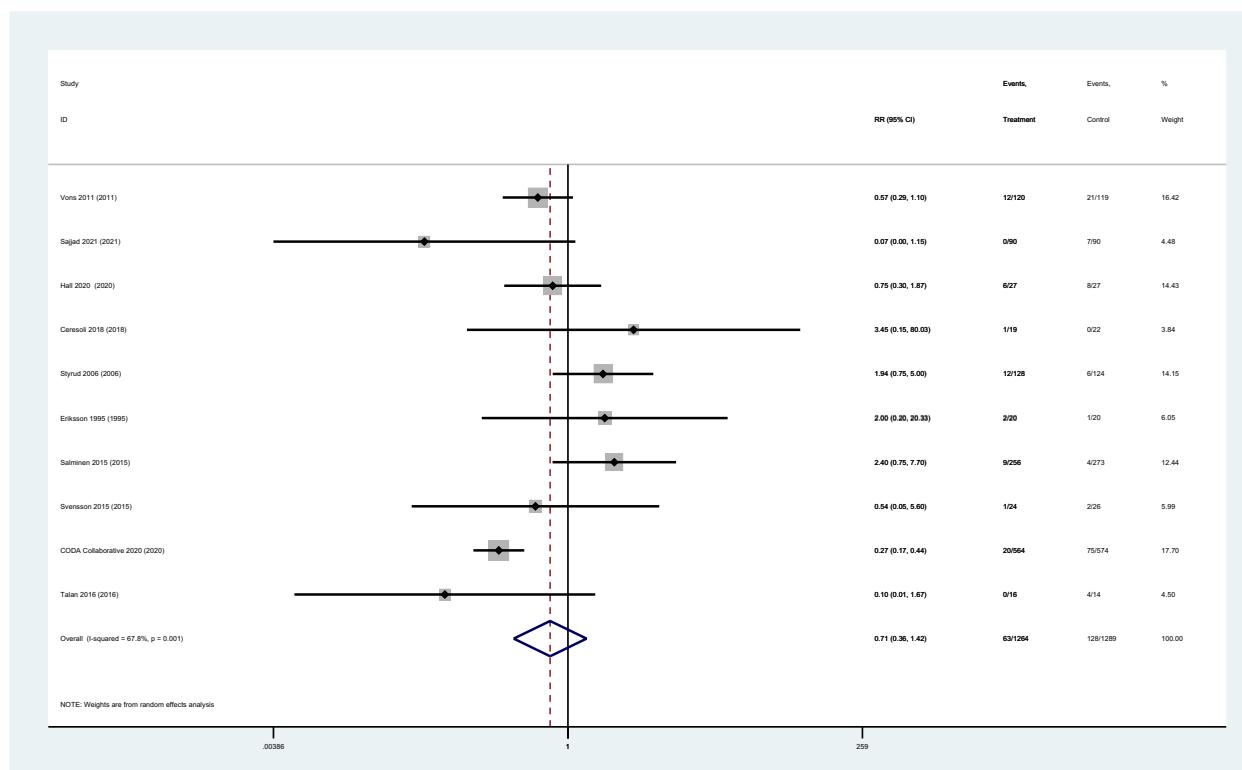


Fig. 6 Forest diagram of the complicated appendicitis rate

Appendiceal tumors were found in only 2 studies. Salminen 2015 [8] reported that four patients had appendiceal tumors in surgical group and no appendiceal tumors were found in antibiotic group, while CODA Collaborative 2020 [7] reported seven and two respectively. Fewer appendiceal tumors were reported in the antibiotic group. The rate of misdiagnosis of appendiceal tumors was high, which is reported between 0.7 and 2.5% [73–77]. Currently known risk factors for appendiceal tumors are age and complicated appendicitis [78, 79].

During relapse of failed treatment in the antibiotic group, antibiotics can be treated again. The previous study [44] reported that 2 patients successfully treated with antibiotics again when had recurrence appendicitis. Di Saverio S et al. pointed that a second attempt with antibiotic treatment could be a successful option for over 60% of patients who present with a recurrent episode of appendicitis at follow-up [80]. Poillucci G et al. found that 3.3% of patients who presented with a recurrence at follow-up were successfully treated with a further cycle of antibiotics [81]. Antibiotics treatment will not aggravate the progression of uncomplicated appendicitis. Thus, when the patient relapses

after initial antibiotic treatment, antimicrobial therapy can be used again if the diagnosis of appendicitis is confirmed.

This study suggested the treatment of uncomplicated appendicitis included: it is necessary to increase the accuracy of preoperative imaging diagnosis to decrease the rate of appendectomy in non-appendicitis patients. If the patient is extremely concerned about the cure and recurrence rate of appendicitis, we recommend surgical intervention instead of antimicrobial therapy for them and laparoscopic surgery is recommended. If patients resist surgery and wish to be treated with antibiotics, they should be informed that the recurrence rate of antibiotics is significantly higher than surgery. However, there is no need to worry about uncomplicated appendicitis developing into complicated appendicitis. If patients had uncomplicated appendicitis with appendicoliths, surgery should be recommended.

There are still some limitations in this meta-analysis. The large difference in trial scale for inclusion articles may lead to result bias. Meanwhile, some outcome indicators were included in relatively few articles, which might have an impact on the outcome analysis.

Conclusions

In this meta-analysis, we found strong evidence that antibiotics has a significantly lower complication-free cure rate than surgical treatment to the uncomplicated acute appendicitis, and the total complications of laparoscopic surgery are comparable to antibiotic treatment. Notably, patients who are particularly concerned about appendicitis recurrence should be cautious when choosing antibacterial drugs for the treatment of uncomplicated appendicitis. Patients who failed antibiotic treatment first and underwent surgery later could not possibly result in a higher risk of postoperative complications and the uncomplicated appendicitis does not develop to complicated appendicitis in this course, which made antibiotic treatment appealing for patients with uncomplicated acute appendicitis who do not want surgery without having to worry about complications or complicating the original illness. The negative appendectomy results depend on the preoperative imaging and the presence of an appendicolith is associated with an increased risk of antibiotic failure.

Supplementary Information

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Additional file 1.

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Authors' contributions

Hongxia Xu, Shaohui Yang and Jiankun Xing wrote the main manuscript text and Yan Wang, Weiqiang Sun prepared figures . All authors reviewed the manuscript.

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Availability of data and materials

All data analyzed in this study are included in the references. Further information about the data can be accessed through the corresponding authors of the references.

Declarations

Ethics approval and consent to participate

Not applicable. This study does not involve human participants.

Consent for publication

Not applicable. This study does not involve animal and human participants.

Competing interests

The authors declare that they have no conflict of interest.

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