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Review Article

Simple ligation versus stump invagination for the appendix stump: a systematic review and meta-analysis

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Abstract: *Aim:* To evaluate the clinical efficacy and safety of simple ligation (SL) and stump invagination (SI) to treat the appendix stump. *Methods:* The Cochrane Library, Embase, Pubmed, Web of science, VIP, and Wanfang databases were searched systematically to identify relevant randomized controlled trials (RCTs) and quasi-RCTs. The study quality was assessed and the relevant data was extracted. Inter-study heterogeneity was assessed using the Cochran Q test, the I^2 test, and the Galbraith figure. The source of heterogeneity was determined using subgroup and sensitivity analyses. Publication bias was tested using funnel plots. *Results:* Twenty RCTs including 3677 patients were included in this meta-analysis. In open surgery group, there were no differences in adhesive intestinal obstruction, wound infection, and post-operative fever between the SL and SI groups. The patients in the SL group had shorter hospitalization and operating time, a lower rate of paralytic ileus, and shorter temperature recovery time after surgery. In the laparoscopy group, the SL group had a higher rate of adhesive intestinal obstruction, longer hospital stay of hospital, and shorter surgery time compared with those in the SI group. *Conclusions:* Our meta-analysis revealed that SL might be a superior method when applying in open surgery. By contrast, SI seemed to be a better solution in laparoscopic surgery.

Keywords: Simple ligation, stump invagination, appendix stump, meta-analysis

Introduction

In general surgery, appendicitis is a common disease, comprising inflammatory changes in the appendix caused by a variety of factors. To treat appendicitis, surgery is usually performed, including open and laparoscopic methods. Open appendectomy (OA) has been the classical treatment for acute appendicitis in adults for decades. In 1983, the German gynecologist Semm successfully performed a laparoscopic appendectomy (LA) for the first time [1]. LA has been recognized by surgeons and physicians to have advantages in terms of accurate diagnosis, less trauma, mild postoperative pain, rapid recovery, and fewer complications [2]. The treatment of the appendix stump is the key to the success of the operation, and is mainly achieved by simple ligation (SL) or stump invagination (SI); however, there is controversy concerning the selection of these two methods. In SL, the root of the appendix is ligated using silk thread. In SI, the appendix stump is taken into the cecum wall and subjected to a pouch suture. In the present study, we carried out a meta-analysis to compare the clinical efficacy and safety of SL and SI to treat the appendix stump.

Materials and methods

Search strategy

We searched the Cochrane Library, Embase, Medline, CNKI (China Academic Journals Full-text Database), VIP (a database of Chinese scientific journal resources), and the Wanfang databases to identify relevant randomized controlled trials (RCTs) and quasi-RCTs, with a deadline for literature searches of September 2017. The search terms included "appendectomy" OR "appendectomy" OR "appendicitis" OR "appendix" OR "appendiceal" and "simple ligation" OR "invagination" OR "bury" OR "inversion". We manually searched for relevant articles. Two individuals completed the literature search process independently.

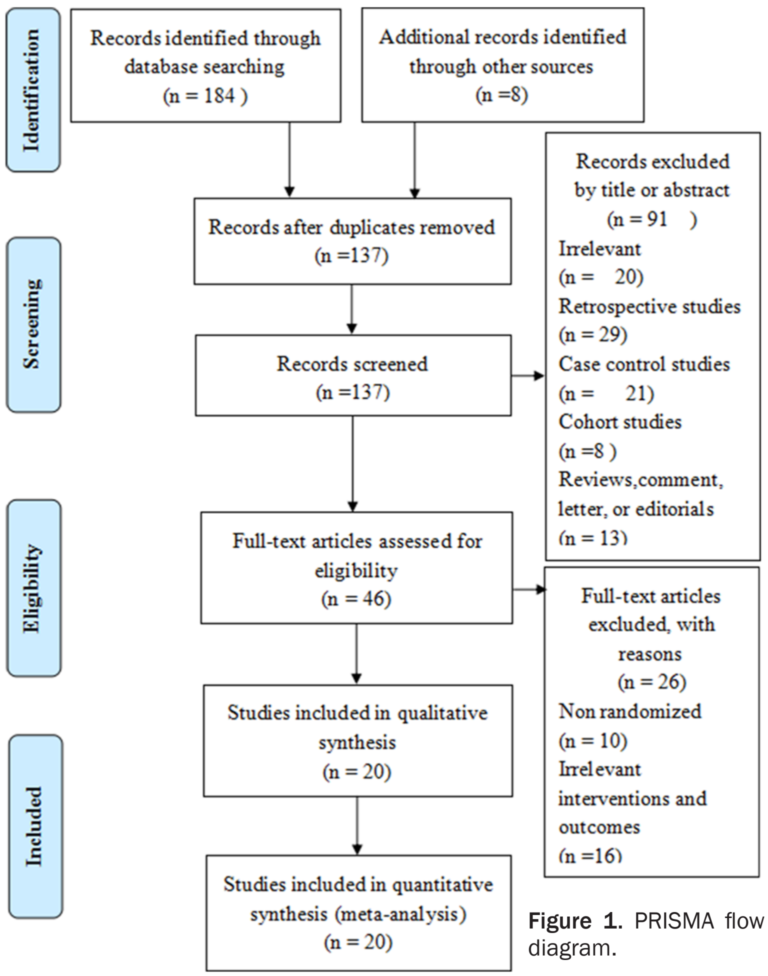


Figure 1. PRISMA flow diagram.

Inclusion criteria and exclusion criteria

The inclusion criteria were: (1) A clear diagnosis of acute or chronic appendicitis in the clinic; (2) A quantitative comparison was made between simple ligation and stump invagination; (3) The study monitored the patients using objective and relevant indicators; (4) There were no age, gender, race, language, or publication status restrictions; (5) The study was an RCT or quasi-RCT. The exclusion criteria were: (1) Ambiguous diagnosis; (2) Duplicate studies; and (3) Observational studies or other non-RCT studies.

Data extraction

Studies were retrieved, screened, and extracted independently by two researchers, and selected according to the inclusion and exclusion criteria. If there were inconsistent opinions between them, a third researcher decided whether to include the study or not. The main data extracted were as follows: (1) General information (title, author, date of publication); (2) Studies characteristics (country, operation method, sex, age, sample size); (3) Outcome measures (the rate of adhesive intestinal obstruction, hospitalization time, wound infection, operating time, postoperative fever, paralytic ileus (24 to 48 hours after surgery) and temperature recovery time after surgery).

Quality assessment

We used the Cochrane risk of bias tool (version 5.0) for quality evaluation, comprising analysis of the generation of random sequences, allocation concealment, the blinding method for patients and testers, the blinding method for the outcome evaluator, and Selective reporting.

Data synthesis and analysis

We used RevMan 5.3 and Stata 14.0 for data analysis. We used the Cochran Q test and I^2 test to assess inter-study heterogeneity. If the heterogeneity was small ($P \geq 0.1$, $I^2 < 50\%$), a fixed effects model was used; otherwise, a random effects model was selected. If I^2 was greater than 50%, we analyzed the sources of heterogeneity using subgroup and sensitivity analyses. If the heterogeneity was too large, descriptive analysis was used. When the number of studies was greater than nine, we conducted a funnel plot to test the publication bias.

Results

Study selection

A total of 192 articles were initially retrieved, and 137 articles were included after screening for duplicates. After excluding irrelevant studies, non-RCT, irrelevant interventions and outcomes, and not full-text studies, twenty studies [3-22] were eventually included. **Figure 1** shows the flow diagram of study identification and selection.

Table 1. Study characteristics

Author	Year	Country	Surgery	Gender (M/F)		Age (years)		Case number		Outcome measure
				SL	SI	SL	SI	SL	SI	
3 Engstrom, L	1985	Sweden	Open	196/165	187/187	29 (15-91)	29 (14-85)	361	374	Wound infection; incisional hernia; hospitalization time; adhesive intestinal obstruction; post-operative pyrexia
4 Dick J A	1984	England	Open	21/23	29/30	18.1 (5-43)	21.7 (6-46)	44	59	Wound infection; hospitalization time
5 Habel P Dass	1989	Oman	Open	48/16	48/18	NA	NA	64	66	Wound infection; adhesive intestinal obstruction
6 Khan S	2010	Nepal	Open	27/58	22/48	30.8 ± 9.8	30.0 ± 8.8	80	70	Wound infection; adhesive intestinal obstruction; hospitalization time; post-operative pyrexia; fistula; paralytic ileus (24-48 h); peritonitis
7 Chalya P L	2012	Tanzania	Open	20/23	21/23	24.12 ± 12.14	26.28 ± 14.58	43	44	Wound infection; adhesive intestinal obstruction; post-operative pyrexia; hospitalization time; operating time; paralytic ileus (24-48 h); vomiting; peritonitis; residual abdominal abscess
8 Chaudhary I A	2005	Pakistan	Open	169/213	138/157	NA	NA	382	295	Wound infection; adhesive intestinal obstruction; paralytic ileus (24-48 h); peritonitis; residual abdominal abscess
9 Mukesh S	2013	India	Open	24/30	23/33	27.11 ± 4.9	28.36 ± 15.5	54	56	Hospitalization time; wound infection; post-operative pyrexia; paralytic ileus (24-48 h); vomiting; peritonitis; residual abdominal abscess
10 Peizhi Z	2014	China	Open	NA	NA	NA	NA	99	99	Hospitalization time; the time of anal exsufflation; temperature recovery time after operation
11 Haihua Z	2015	China	Open	22/15	20/17	32.2 ± 7.1	31.6 ± 6.7	37	37	The time of anal exsufflation; white blood cell count; temperature recovery time after operation; hospitalization time
12 Xuhui L	2013	China	Open	NA	NA	NA	NA	62	62	Wound infection; white blood cell count; operating time; amount of bleeding; the time of anal exsufflation; temperature recovery time after operation
13 Guozhi X	2013	China	Laparoscopy	78/72	82/68	50.6 ± 1.4	50.2 ± 1.5	150	150	Operating time; amount of bleeding; the time of anal exsufflation
14 Long H	2016	China	Laparoscopy	19/11	18/22	30.50 ± 6.50	29.50 ± 6.17	30	30	Adhesive intestinal obstruction; hospitalization time; operating time; appendix stump inflammation; abdominal pain; hospitalization expense
15 Xiaotian Y	2016	China	Laparoscopy	27/29	26/30	45.0 ± 1.5	45.2 ± 8.5	56	56	Adhesive intestinal obstruction; hospitalization time; hospitalization expense
16 Hongxia C	2015	China	Laparoscopy	31/14	30/15	35.2 ± 2.3	34.6 ± 3.1	45	45	Adhesive intestinal obstruction; hospitalization time; hospitalization expense; abdominal pain; appendix stump inflammation
17 Zhiqiang Z	2015	China	Open	40/20		38.23		30	30	Operating time; amount of bleeding; the time of anal exsufflation; temperature recovery time after operation
18 Zhiyong Y	2013	China	Open	94/74		32.5 ± 3.4		84	84	Adhesive intestinal obstruction; hospitalization time; wound infection; the time of anal exsufflation; white blood cell count; temperature recovery time after operation; abdominal pain
19 Caiyang L	2014	China	Open	20/19	22/17	42.9 ± 6.6	41.8 ± 7.2	39	39	Adhesive intestinal obstruction; hospitalization time; wound infection; temperature recovery time after operation; the time of anal exsufflation; white blood cell count
20 Zhongli W	2013	China	Open	65/35		32		50	50	Adhesive intestinal obstruction; hospitalization time; wound infection; abdominal abscess; the time of anal exsufflation
21 Mugou Hu	2012	China	Open	29/31	26/34	32 ± 4.75		60	60	Adhesive intestinal obstruction; wound infection; abdominal abscess; operating time; white blood cell count; the time of anal exsufflation
22 Hongcai Z	2004	China	Open	60/36	62/43	37.2	41.7	96	105	Adhesive intestinal obstruction; wound infection

NA, not available; SL, simple ligation; SI, stump invagination.

Table 2. Quality assessment of bias in the included studies

Study	Risk of bias							
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blind outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias	Grades*
3	High	Unclear	Unclear	Unclear	Low	Low	Unclear	B
4	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
5	High	Unclear	Unclear	Unclear	Low	Low	Unclear	B
6	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
7	Low	Low	Unclear	Unclear	Low	Low	Unclear	A
8	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
9	Low	Low	Unclear	Unclear	Low	Low	Unclear	A
10	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
11	Low	Unclear	Unclear	Unclear	Low	Low	Unclear	B
12	Low	Unclear	Unclear	Unclear	Low	Low	Unclear	B
13	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
14	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
15	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
16	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
17	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
18	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
19	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
20	Low	Unclear	Unclear	Unclear	Low	Low	Unclear	B
21	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B
22	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear	B

*Cochrane risk of bias tool (version 5.0), Level A: low bias, four or more items are low risk. Level B: moderate bias, two or three items were low risk.

Study characteristics

This meta-analysis included twenty RCTs [3-22] with a total of 3677 patients. The SL group contained 1866 patients, while the SI group contained 1811 patients. Thirteen [10-22] of the RCTs were conducted in China, and the others were conducted in Sweden [3], England [4], Oman [5], Nepal [6], Tanzania [7], Pakistan [8], and India [9]. The publication dates ranged from 1984 to 2016. Sixteen RCTs [3-12, 17-22] adopted open surgery, and the remainder [13-16] performed laparoscopic surgery. There was no significant difference between the two groups regarding the age and sex of the patients. **Table 1** shows the specific characteristics of the studies.

Quality assessment

All the studies mentioned were randomized. Four studies [7, 11, 12, 20] used the random number table method, one study used a lottery method [9], and the rest of the studies did not mention the randomization and allocation concealment methods. With regard to random sequence generation, five studies [7, 9, 11, 12, 20] were low risk and two studies [3, 5] were high risk; in the other studies, the risk was unclear. With regard to allocation concealment, two studies [7, 9] were low risk, and in the other studies, the risk was unclear. All studies are unclear regarding the blinding of participants and personnel, blinding the outcome assessment, and other potential sources of bias. All studies were low risk in terms of incomplete outcome data and selective outcome reporting. We graded them according to the Cochrane risk of bias tool (version 5.0), Level A: low bias, four or more items are low risk. Level B: moderate bias, two or three items were low risk. Level C: High bias, less than or equal to one items were of low risk. After quality evaluation, we found that two [7, 9] studies were type A, and the others were type B. **Table 2** shows the quality assessment of bias in the included studies.

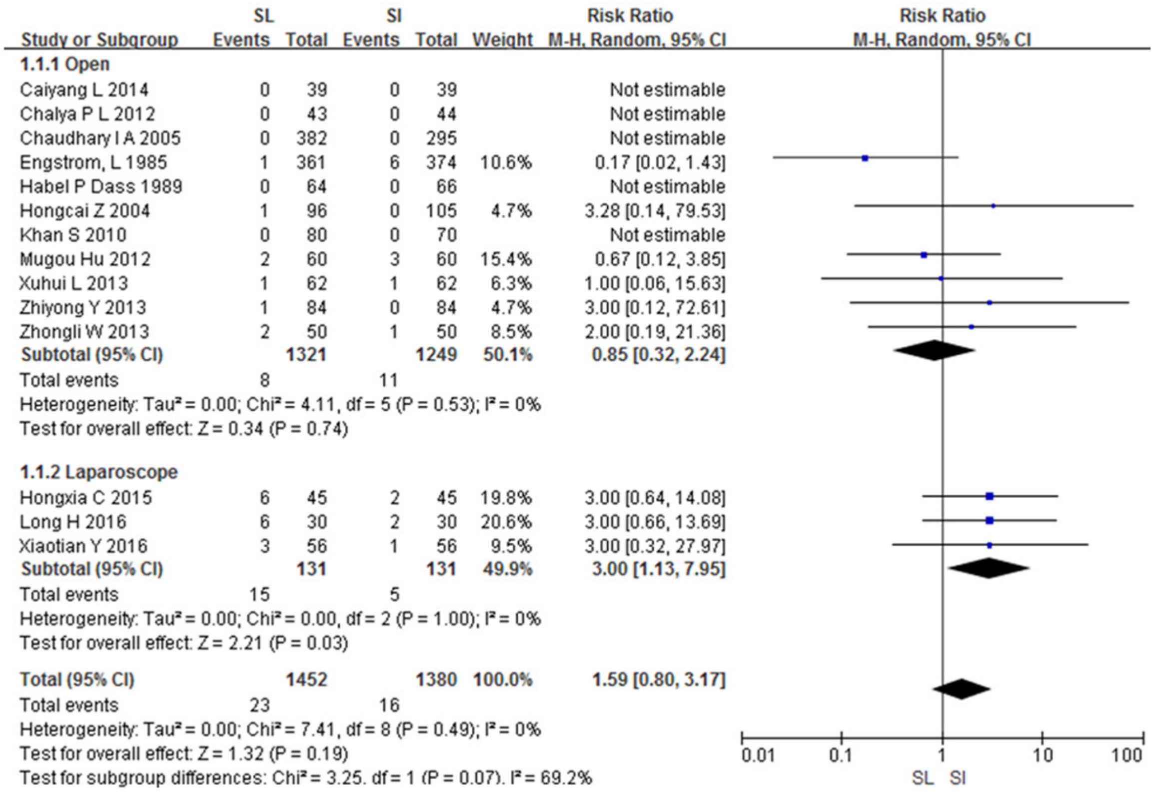
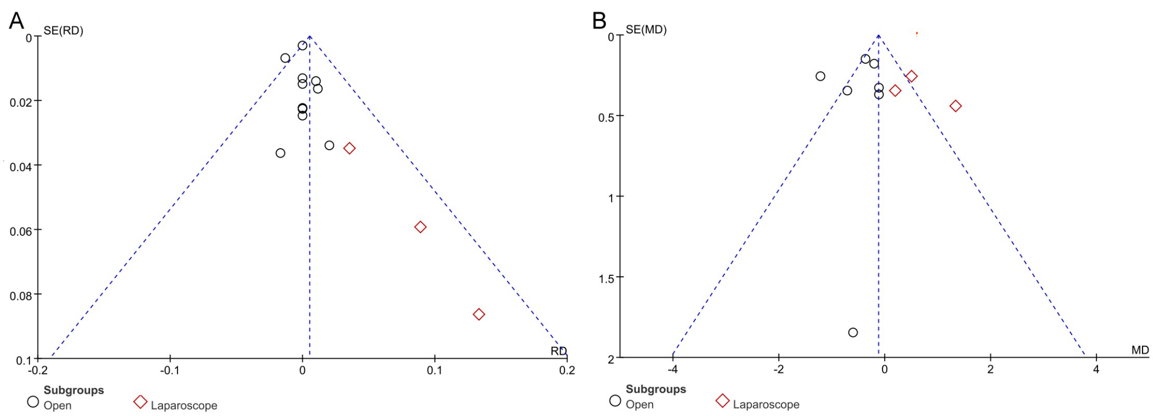


Figure 2. Forest plot of the rate of adhesive intestinal obstruction.



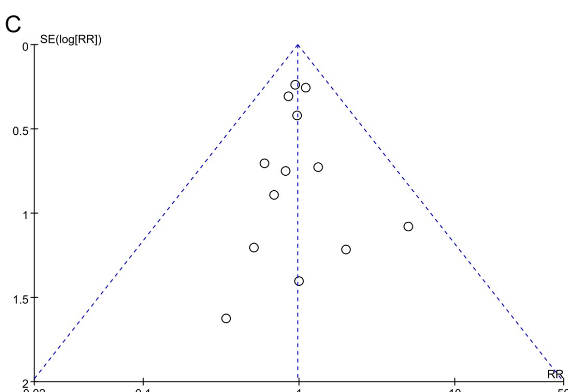


Figure 3. Funnel plot. Adhesive intestinal obstruction (A), hospitalization time (B), wound infection (C).

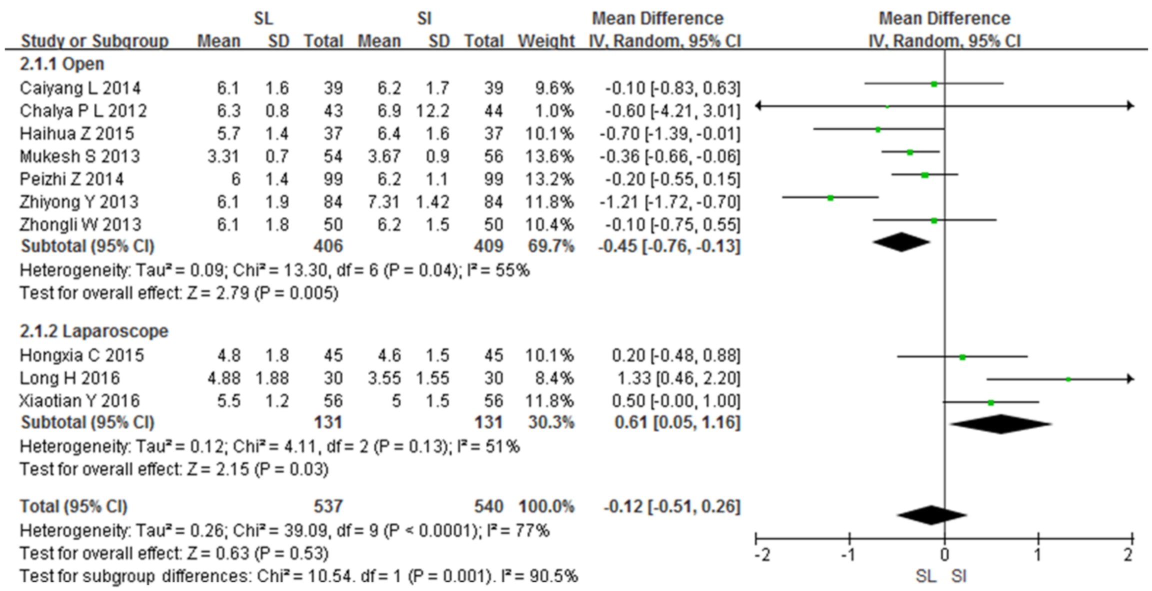


Figure 4. Forest plot of hospitalization time.

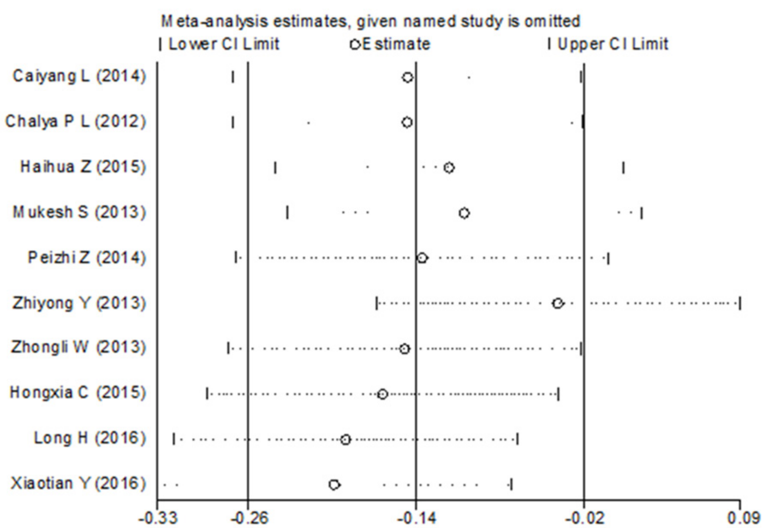


Figure 5. Sensitivity analysis of hospitalization time.

Meta analysis

The frequency of adhesive intestinal obstruction: Fourteen studies (2832 patients) [3, 5-8, 12, 14-16, 18-22] investigated the frequency of adhesive intestinal obstruction. There was statistical heterogeneity among the studies (P = 0.07, I^2 = 69.2%); therefore, the random effects model was chosen. The overall analysis showed that there was no statistically significant difference between the SL and SI groups (RR = 1.59, 95% CI: [0.80, 3.17]). We performed subgroup analysis based on different operation methods (open or laparoscopy). The meta-analysis results showed that the heterogeneity decreased significantly when analyzing the open surgery group [3, 5-8, 12, 18-22] (P = 0.53, I^2 = 0%) and the laparoscopy group [14-16] (P = 0.49, I^2 = 0%)). In the open surgery group, the frequency of adhesive intestinal obstruction was almost the same between the SI and SL groups (risk ratio (RR) = 0.85, 95% confidence interval (CI): 0.32-2.24). In the subgroup analysis, for the laparoscopy subgroup, the frequency of adhesive intestinal obstruction was higher in the SL group than in the SI group (RR = 3.00, 95% CI: 1.13-7.95) (**Figure 2**). A funnel plot to test the publication bias showed that publication bias existed (**Figure 3A**).

Hospitalization time: Ten studies (1077 patients) [7, 9-11, 14-16, 18-20] reported the hospitalization time for the two different surgical procedures. The overall analysis showed that statistical heterogeneity existed among these studies (P < 0.001, I^2 = 77%); therefore, the random effects model was chosen. We found no statistically significant difference in hospitaliza-

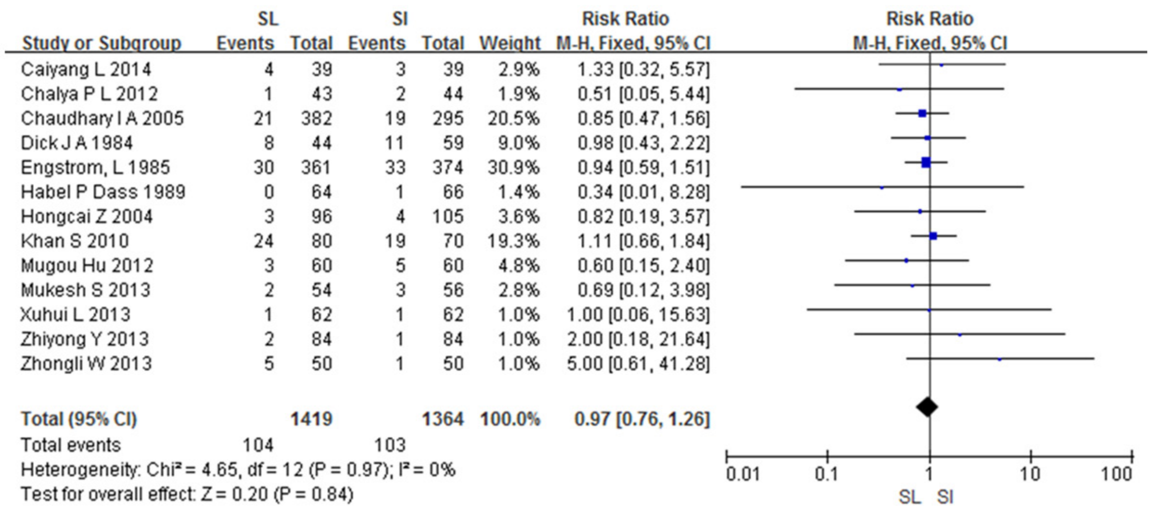


Figure 6. Forest plot of the rate of wound infection.

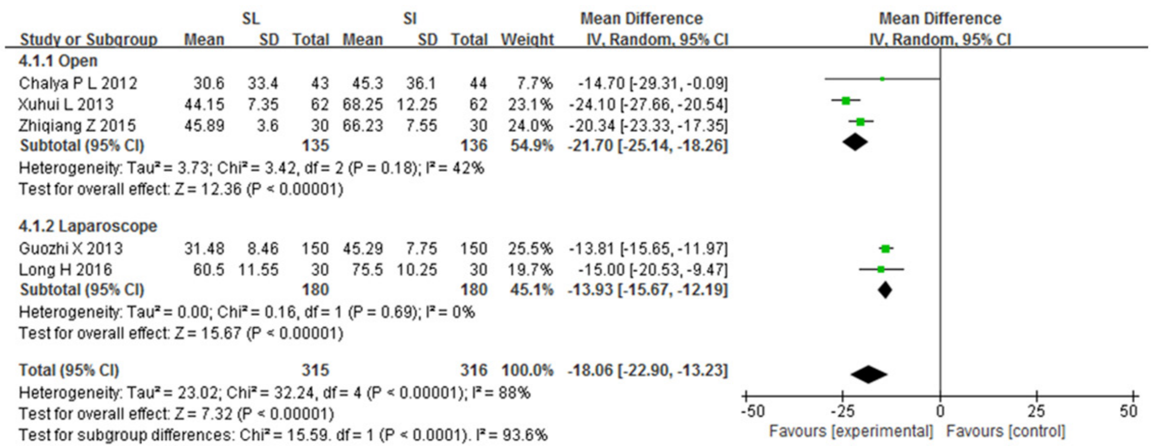


Figure 7. Forest plot of operating time.

tion time between the SL and SI groups (MD = -0.12, 95% CI: -0.51-0.26). We then performed subgroup analysis between the open and laparoscopic surgery subgroups. The meta-analysis results showed that the heterogeneity among the studies decreased for the analysis of the open subgroup [7, 9-11, 18-20] (P = 0.04, I^2 = 55%) and the laparoscopy subgroup [14-16] (P = 0.13, I^2 = 51%). In the open subgroup, the hospitalization time of the SL group was shorter than that of the SI group. However, in the laparoscopy group, the hospitalization time was longer in the SL group than in the SI group (**Figure 4**). We conducted a funnel plot to test the publication bias (**Figure 3B**). The plot was basically symmetrical, indicating little publication bias. We also conducted sensitivity analysis (**Figure 5**) and found no significant source of sensitivity.

The frequency of wound infection: Thirteen studies (2783 patients) [3-9, 12, 18-22] reported the frequency of wound infection. No heterogeneity was found among these studies (P = 0.97, I^2 = 0%); therefore, the fixed effects model was chosen. We found no statistically significant difference between the SL and SI groups in terms of the frequency of wound infection (RR = 0.97, 95% CI: 0.76-1.26). Both groups had similar frequencies of wound infection (**Figure 6**). A funnel plot to test showed that publication bias existed among these studies (**Figure 3C**).

Surgery time: Five studies (631 patients) [7, 12-14, 17] reported the surgery time, including three open surgery studies [7, 12, 17] and two laparoscopic surgery studies [13, 14]. The overall analysis showed that the there was signifi-

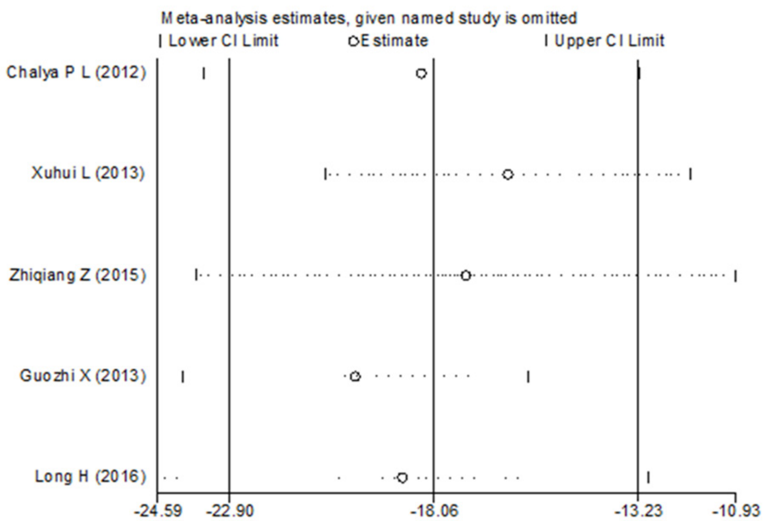


Figure 8. Sensitivity analysis of operating time.

cant heterogeneity (P < 0.00001, I^2 = 88%) among these studies; therefore, the random effects model was chosen. The surgery time of the SL group was statistically significantly shorter than that of the SI group (MD = -18.06, 95% CI: -22.90 to -13.23). We then performed a subgroup analysis. The meta-analysis results showed that the heterogeneity decreased in the analyses of the open surgery group [7, 12, 17] (P = 0.18, I^2 = 42%) and the laparoscopy group [13, 14] (P = 0.69, I^2 = 0%). In the open surgery group, the surgery time of the SL group was shorter than that of the SI group (MD = -21.70, 95% CI: -25.14 to -18.26), and in the laparoscopy group, the surgery time of the SL group was longer than that the SI group (MD = -13.93, 95% CI: -15.67 to -12.19) (**Figure 7**). Sensitivity analysis showed no significant source of sensitivity (**Figure 8**).

Post-operative fever: Four studies (1082 patients) [3, 6, 7, 9] mentioned post-operative fever. There was no statistical heterogeneity among the studies (P = 0.88, I^2 = 0%); therefore, the fixed effects model was chosen. There was no statistically significant difference in the frequency of post-operative fever between the two groups (RR = 1.00, 95% CI: 0.76-1.33) (**Figure 9**).

The frequency of paralytic ileus (24 to 48 hours after surgery): Four studies (1021 patients) [6-9] mentioned paralytic ileus (at 24 to 48 hours after surgery). There was no statistical heterogeneity among the studies (P = 0.48, I^2 = 0%); therefore, the fixed effects model was chosen. The frequency of paralytic ileus in the SL group was significantly lower than that in the SI group (RR = 0.48, 95% CI: 0.27-0.85) (**Figure 10**).

Temperature recovery time after operation: Four studies (444 patients) [11, 12, 18, 19] reported the temperature recovery time after surgery. There was no statistical heterogeneity among the studies (P = 0.60, I^2 = 0%); therefore, we choose the fixed effects model. The temperature recovery time after surgery of the SL group was statistically significantly shorter than that of SI group (MD = -0.18, 95% CI: -0.24 to -0.12) (**Figure 11**).

Discussion

Twenty studies comprising a total of 3677 patients were included in this meta-analysis. This study mainly concentrated on the frequency of adhesive intestinal obstruction, hospitalization time, wound infection, surgery time, post-operative fever, paralytic ileus (at 24 to 48 hours after surgery), and temperature recovery time after operation.

For adhesive intestinal obstructions, the meta-analysis found that there was no statistically significant between the studies in the open surgery subgroup; however, in the laparoscopy subgroup, the SL group showed more frequent adhesive intestinal obstructions than in the SI group. The wound surface of the stump invagination is smooth, which can reduce the possibility of the residual stump entering the abdominal cavity, thus preventing postoperative intestinal adhesion [23], which is consistent with the results of in the laparoscopy subgroup. Watters et al, [24] showed that there was no significant difference in terms of the ileus between the SL and SI groups, which was consistent with the results of the open surgery subgroup reported here. The open surgery and laparoscopy group showed opposite results. The reasons may be as follows: firstly, in laparoscopic surgery, the view of the abdomen is clear; damage to abdominal tissues and organs

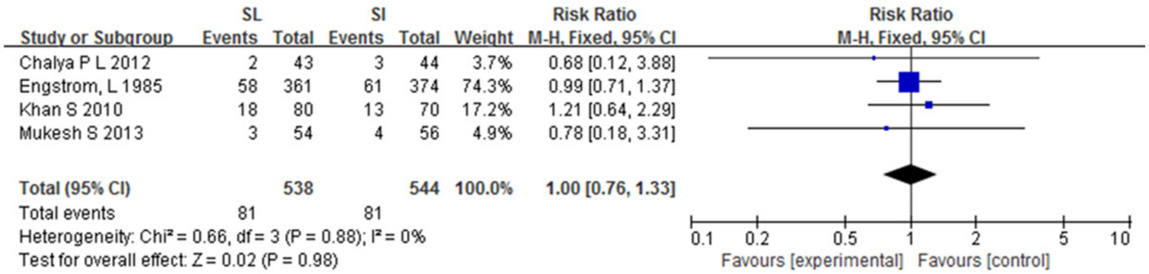


Figure 9. Forest plot of post-operative fever.

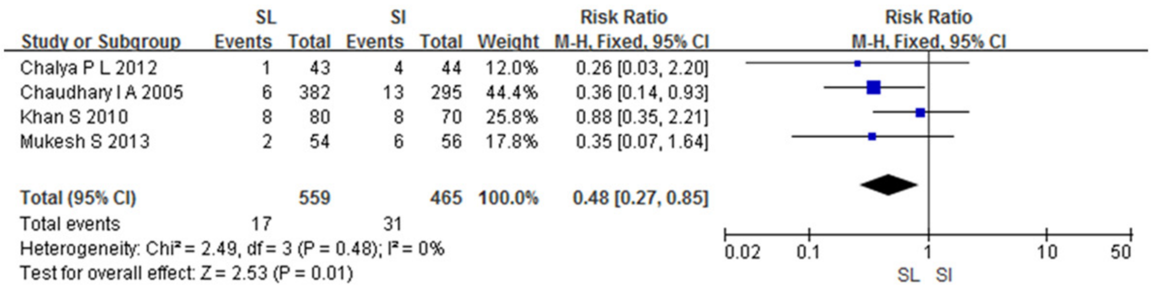


Figure 10. Forest plot of the rate of paralytic ileus (24 to 48 hours after surgery).

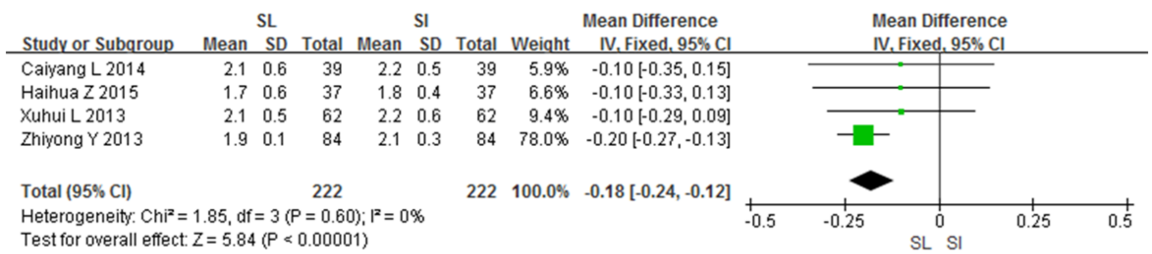


Figure 11. Forest plot of temperature recovery time after operation.

is reduced and excessive extrusion of the intestinal wall are avoided. As a result, the incidence of adhesive intestinal obstruction is reduced compared with laparotomy. Secondly, because of the limited number of samples in laparoscopic group, there is a possibility of bias.

SI is a more complicated procedure than SL; therefore the surgery time of the SI group was longer than that of the SL group. For wound infection, our meta-analysis found that there was no statistically significant difference between SL and SI groups. SI can avoid the exposure of the appendix stump to the abdominal cavity, reducing the infection rate. For inflammatory appendicitis with severe edema, SI might separate the bowel wall, increasing the likelihood of infection. Therefore, the results of the meta-analysis in terms of wound infection are understandable. Postoperative fever is closely related to infection; however, there was no statistically significant difference between the SL group and SI group in terms of postoperative infection.

In the SI group, the incidence of paralytic ileus was higher, which could have occurred for several reasons. First, the appendix is required to be buried in the serosa, which could result in deformation and ischemia in the distal cecum during surgery. Secondly, the tightness of the pouch suture also affects ischemia of the cecum, and surgeons, particularly younger or inexperienced surgeons, find it difficult to complete a modest string suture. Both of these factors might increase the incidence of paralytic ileus [25]. In addition, the absorption time of the inflammation of the appendiceal stump was shortened significantly because of the lack of a string suture in the SL group. The temperature recovery time after surgery is closely related to inflammation, and as a result, the temperature recovery time in the SL group was shorter.

For hospitalization time, our meta-analysis showed that in the open surgery subgroup, the hospitalization time for the SL group was shorter than that of the SI group, but longer in laparoscopy surgery. Street [26] showed that compared with the SL group, the SI group had little difference in postoperative complications, length of hospital stay, or may even be better in some respects. This conflicts with the results of our meta-analysis. During laparoscopic surgery, there are fewer invasions into the abdomen, and the surface of the cecum wall is smoother than that after in SI, which leads to a faster recovery and shorter hospital stay.

Our study has some limitations. First, the common types of appendicitis are acute simple appendicitis, acute purulent appendicitis, and acute perforative appendicitis, and this meta-analysis has not carried out based on these classifications. Second, there were fewer RCTs concerning laparoscopic appendectomy; we only identified four RCTs. Third, although we identified 20 RCTs, we found that high-quality studies were still lacking after quality evaluation. Finally, twelve of the 20 studies were from China, thus there is a possibility of regional bias.

Simple ligation and stump invagination are the most common surgical methods to treat the appendix stump, and are chosen by many general surgeons when performing an appendectomy. There are few meta-analyses in this field currently. We believe that this meta-analysis provides feasible options for physicians when treating a patient with appendicitis.

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Disclosure of conflict of interest

None.

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