Endoscopic retrograde appendicitis therapy in adults with uncomplicated acute appendicitis: a systematic review and meta-analysis

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Background and Aims: Endoscopic retrograde appendicitis therapy (ERAT) has emerged as a minimally invasive endoscopic alternative to laparoscopic appendectomy in the treatment of acute appendicitis. In this systematic review and meta-analysis, we evaluated the efficacy and safety of ERAT in treating uncomplicated acute appendicitis.

Methods: A systematic review of studies in the PubMed/MEDLINE and Cochrane databases was performed through June 2023. Primary outcomes were clinical success rate (defined as resolution in signs and symptoms of appendicitis) and technical success rate (defined as successful placement of a drain or stent within the appendicular orifice or irrigation to relieve appendiceal obstruction). Secondary outcomes were adverse event rates and rates of intestinal perforation, procedure time, hospital length of stay, duration of follow-up, and rates of appendicitis recurrence after ERAT.

Results: Eight studies were considered eligible for analysis (326 patients, average age of 36.4 years old, 55.4% men). The rate of technical success was 98% (95% confidence interval [CI], 97-100; $I^2 = 2.2\%$), and the rate of clinical success was 99% (95% CI, 97-100; $I^2 = 0\%$). The total pooled adverse event rate was 1.8% (95% CI, .4-3.2; $I^2 = 0\%$) with a pooled intestinal perforation rate of 1.5% (95% CI, .02-2.8; $I^2 = 0\%$). The average procedure time was 44.9 minutes. The average hospital length of stay after ERAT was 3.22 days. The aggregate rate of appendicitis recurrence after ERAT was 6% (95% CI, 3-9; $I^2 = 16.5\%$) after an average follow-up of 17.7 months.

Conclusions: ERAT demonstrated excellent technical and clinical success rates with minimal adverse events. Additional randomized controlled studies are needed to refine inclusion criteria and to standardize the approach to appendiceal stent placement during ERAT to minimize rates of intestinal perforation. (iGIE 2023;2:522-8.)

Acute appendicitis (AA) is the most common abdominal surgical emergency in the world, with a lifetime risk of 8.6% in male patients and 6.9% in female patients.[1] The pathogenesis of AA stems from obstruction of the appendiceal orifice, most often caused by a wedge of impacted stool ("fecalith"), but can also have other etiologies, including infections, tumors, or hyperplasia of lymphatic tissue.[2] For many years, open appendectomy was the only treatment available for AA; however, the current standard of therapy for AA is laparoscopic appendectomy.[3] Recent studies have incorporated the use of antibiotics as an alternative treatment, but a meta-analysis in 2019 of 9 randomized control trials revealed a high rate of recurrent appendicitis of 18.2%, suggesting inferiority to laparoscopic intervention.[4] Moreover, other studies have suggested the role of the appendix in the immune function and preservation of colonic floral diversity as potential reasons against appendectomy.[5,6] Additionally, the rates of negative appendectomy, defined as the absence of inflammation on pathology on removal of the appendix, vary widely but generally range from 10% to 30%, with a higher incidence in female patients compared with male patients.[7]

Endoscopic retrograde appendicitis therapy (ERAT), a minimally invasive endoscopic alternative to laparoscopic appendectomy, has recently emerged. First described in 2012, ERAT consists of advancement of a colonoscope to the appendiceal orifice for fecalith extraction, luminal irrigation, and optional placement of a drain or stent to relieve the appendiceal orifice obstruction. This minimally invasive approach allows for preservation of the appendix and, based on individual studies, is an alternative therapeutic option for patients with AA deemed too high risk for surgical intervention due to comorbidities or other factors. This technique can also serve as a bridge to laparoscopic appendectomy in acutely ill patients. In our study, we performed an updated systematic review and meta-analysis to determine the safety and efficacy of ERAT for the treatment of AA in the adult population.

METHODS

Our study protocol adhered to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Supplementary Table 1, available online at www.igiejournal.org).[8]

Eligibility criteria

The patient, intervention, comparison, and outcome framework was used to guide inclusion and exclusion criteria in this study.[9] The patient population included adult patients aged >18 years undergoing ERAT for uncomplicated AA (appendicitis without signs of perforation or necrosis). A comparison group was not selected for this study. The primary outcomes assessed in this study were clinical success rate (defined as resolution in signs and symptoms of appendicitis, including fever and abdominal pain) and technical success rate (defined as successful placement of a drain or stent within the appendiceal orifice or successful saline solution or water irrigation to relieve appendiceal obstruction). Secondary outcomes were adverse event rates (perforation, bleeding, infection, or obstruction), procedure time, hospital length of stay, duration of follow-up, and recurrent appendicitis after ERAT. Exclusion criteria were pediatric populations (patients aged <18 years) and patients with complicated appendicitis (periappendiceal abscesses and appendiceal necrosis or perforation), a suspected appendiceal tumor, contraindications to colonoscopy, and an allergy to contrast solution.

No current expert consensus is available regarding exclusion criteria for the upper limit of appendicolith size in ERAT; thus, all sizes were included provided other criteria were met as outlined above. In selecting manuscripts for analysis, manuscripts in languages other than English, unpublished manuscripts, oral and poster presentations, and case series with ≤5 patients were excluded.

ERAT procedure description

The ERAT technique has been previously described by Liu et al.[10] In brief, after colonic preparation with an oral polyethylene glycol–containing solution or an enema, a colonoscope with a transparent cap was inserted to the level of the cecum at Gerlach's valve. The appendix was intubated by displacement of Gerlach's valve by the colonoscope and subsequent insertion of a catheter and guidewire. The guidewire was further inserted under fluoroscopy with water-soluble contrast to assess for the general morphology and diameter of the appendiceal lumen, appendiceal stones, filling defects, or contrast extravasation into the abdominal cavity. The appendiceal lumen was then flushed with saline solution; if stones or fecaliths were present, the stones were retrieved using an extraction basket or a retrieval balloon. If pus or luminal stenosis was noted, a plastic stent was placed, with repeat abdominal imaging in 2 to 4 weeks to determine the need for stent extraction.

Search strategy and quality assessment

The search strategy involved using PubMed/MEDLINE and Cochrane databases from their inception through June 13, 2023. Search terms included "endoscopic retrograde appendicitis therapy." Two authors (A.P. and J.L.) independently reviewed and extracted studies, with 1 author (R.A.) serving as arbitrator. Quality assessment was performed by 2 authors (P.S. and J.L.) using the U.S. National Heart, Lung, and Blood Institute for controlled intervention and cohort studies (Supplementary Table 2, available online at www.igiejournal.org).[11]

Statistical analysis

Forest plots for pooled-effect sizes and 95% confidence intervals (CIs) were determined by the DerSimonian and Laird random-effects model.[12] To assess heterogeneity, the inconsistency index (I^2) was used, with the standard distinctions of <30%, between 30 and 59%, between 60 and 75%, and >75% to indicate low, moderate, substantial, and considerable heterogeneity, respectively. Given that fewer than 10 studies were included in this meta-analysis, Egger test for publication bias and funnel plots were not included because of lower statistical power with a small study sample size.[13] The cutoff for statistical significance was $P \leq .05$. Statistical analyses were conducted using the "metaphor" package in the R statistics program.[14,15]

RESULTS

Study selection and characteristics

Of 67 studies and records located using the PubMed and Cochrane databases, 8 studies were included as demonstrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig. 1). One study by Chen et al,[16] which included a retrospective cohort of 101 patients, was retracted (for an undisclosed reason) and was therefore not included in this study. Of the 8 studies, 2 were randomized controlled trials, 3 were retrospective observational studies, and 3 were prospective observational studies (Table 1).[17-24] Two studies were multicenter. All studies were conducted in China between 2015 and 2023. Of the 8 studies, 326 patients were included, with an average age of 36.4 years old, and most patients in the studies were men (55.4%).

Quality assessment

Study quality was assessed using the U.S. National Heart, Lung, and Blood Institute for controlled intervention and cohort studies.[11] No significant methodologic issues were identified, and all studies were assessed as good quality. Minor inconsistencies were noted regarding reporting of sample size justification and power analysis and dropout and follow-up rates (Supplementary Table 2).

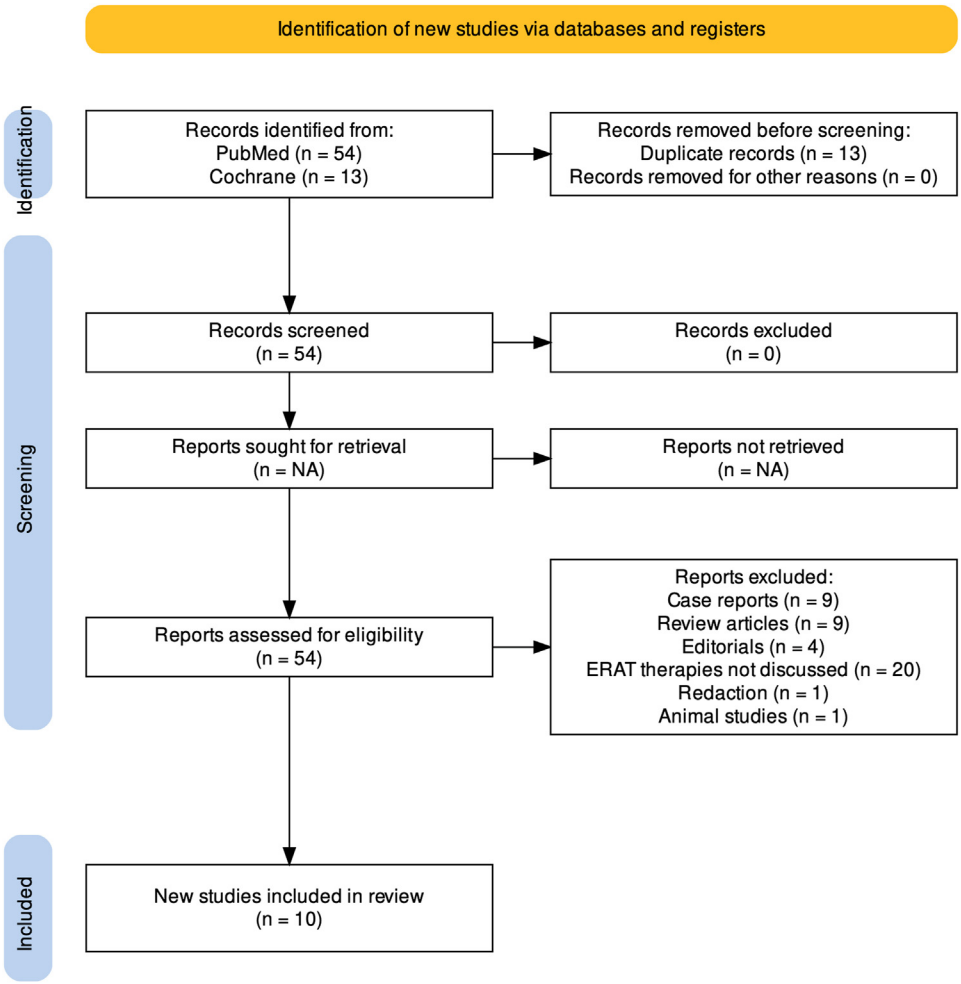

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses study flowchart. *NA*, not applicable; *ERAT*, endoscopic retrograde appendicitis therapy.

Primary outcome

The rate of technical success was 98% (95% CI, 97-100; I^2 = 2.2%) (Fig. 2). The rate of clinical success was 99% (95% CI, 97-100; I^2 = 0%) (Fig. 3).

Secondary outcomes

The total pooled adverse event rate was 1.8% (95% CI, .4-3.2; I^2 = 0%), with a pooled perforation rate of 1.5% (95% CI, .02-2.8; I^2 = 0%) (Table 2). The aggregate rate of appendicitis recurrence after ERAT was 6% (95% CI, 3-9; I^2 = 16.5%) after an average follow-up of 17.7 months. The average procedure time was 44.9 minutes. The average hospital length of stay after ERAT was 3.22 days.

Sensitivity analysis

Given the low heterogeneity across the included studies and relatively similar sample sizes, sensitivity analyses did not reveal an effect size for technical or clinical success that was significantly different from the cumulative rate.

DISCUSSION

AA remains one of the most common abdominal surgical emergencies, with an incidence of 80 to 90 cases per 100,000 people per year.[25,26] In those who present with uncomplicated AA, ERAT is a compelling alternative to laparoscopic appendectomy. Although comparing short- and long-term adverse outcomes between these modalities is challenging given the paucity of data (only 2 randomized controlled trials have been conducted at the time of our literature review), these randomized controlled trials support lower postoperative pain, lower median hospital length of stay, shorter procedural time, and lower overall adverse event rates in those who received ERAT.[22,24] One disadvantage of appendectomy is the rate of not seeing inflammation on excised specimens—the so-called negative appendectomy—which is generally reported to be between 10% and 30% of appendectomy cases,[7] with a recent meta-analysis of 76,688 patients demonstrating a 13% pooled rate of no histopathologic inflammation on the removed specimens.[27]

TABLE 1. Baseline characteristics of included endoscopic retrograde appendicitis therapy studies

Author, Year	Country	Study design	No. of patients	Average age (y)	No. of men	No. of women
Liu, 2015[17]	China	Retrospective observational single center	33	45.9	24	17
Li, 2016[18]	China	Prospective observational single center	21	36	9	12
Ye, 2018[19]	China	Prospective observational single center	22	39.5	9	13
Kong, 2021[20]	China	Prospective observational multicenter	14	32.9	5	9
Ding, 2022[21]	China	Retrospective observational single center	70	39.9	42	38
Yang, 2021[23]	China	Retrospective observational single center	78	30	40	38
Shen, 2022[22]	China	Randomized control trial single center	33	44.1	18	15
Liu, 2022[24]	China	Randomized control trial multicenter	55	39	33	22

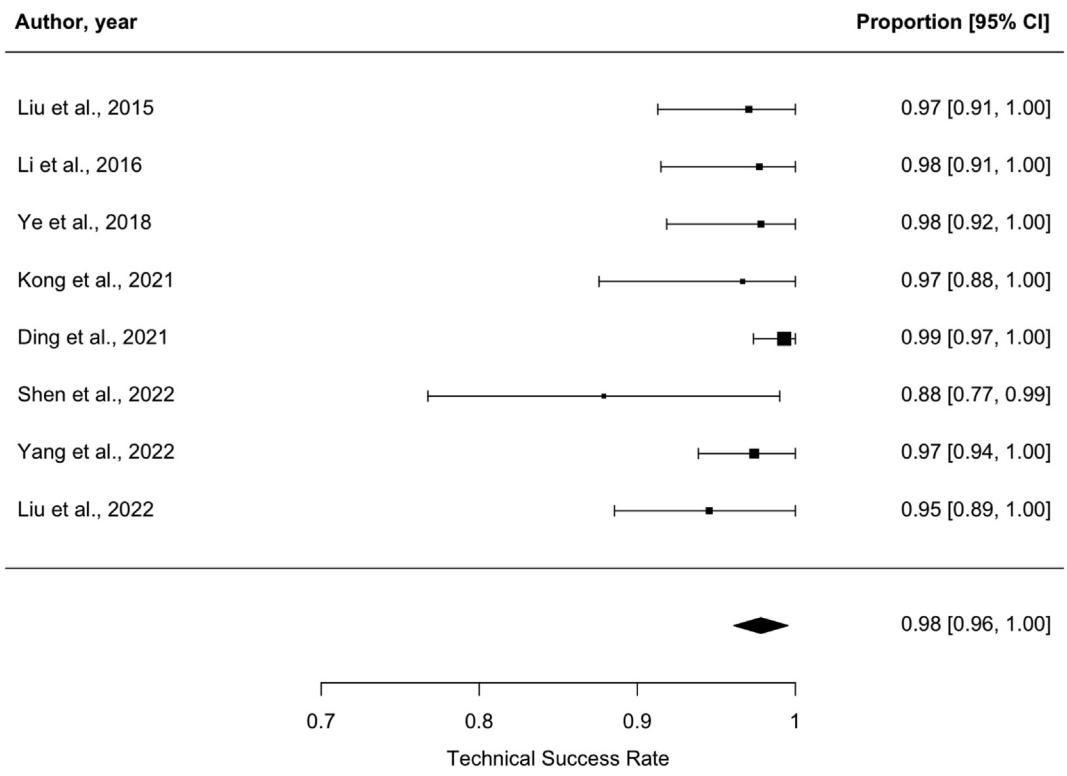

Figure 2. Technical success rates after endoscopic retrograde appendicitis therapy. *CI*, Confidence interval.

Additionally, the rates of negative appendectomy in female patients has been reported to be higher than those in male patients, in part because of the diagnostic uncertainty in differentiating abdominal pain from GI and gynecologic causes.[28-30] It is suggested that ERAT may obviate the need for unnecessary surgery because of the advantage of direct appendiceal visualization. Endoscopic retrograde appendicography (similar to fluoroscopic cholangiography obtained during ERCP) has been reported to outperform US and CT in the diagnosis of appendicitis, with sensitivities and specificities approaching 100%.[31,32]

Our meta-analysis demonstrated that ERAT is a safe, effective, and minimally invasive alternative to surgery that can be used to diagnose and treat adults with uncomplicated AA. In this meta-analysis, 98% technical and 99% clinical success rates were reported, which are similar to those seen with appendectomy.[24,33] Additionally, rates of adverse outcomes were low, with an aggregate adverse outcome rate including perforation, bleeding, infection, or obstruction of 1.8%; a perforation rate of 1.5%; and an appendicitis recurrence rate of 6%. Other metrics, including an average procedural duration of 44.9 minutes and average hospital length of stay of 3.22 days, were favorable.

One concern with ERAT involves appendiceal perforation because of the need for enema administration or colonic preparation (to enhance intraprocedural visualization) and colonic

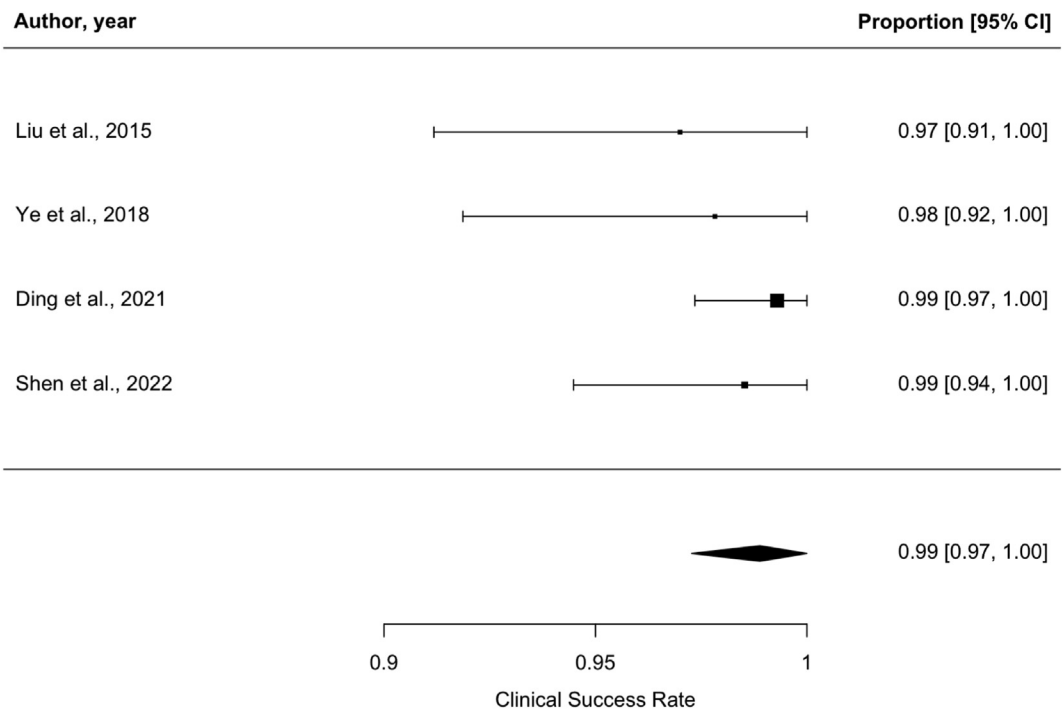

Figure 3. Clinical success rates after endoscopic retrograde appendicitis therapy. *CI*, Confidence interval.

TABLE 2. Adverse events after endoscopic retrograde appendicitis therapy

Author, year	No. of patients	Total adverse events	Perforation	Bleeding	Obstruction	Infection
Liu, 2015[17]	33	1	1	0	0	0
Li, 2016[18]	21	1	1	0	0	0
Ye, 2018[19]	22	0	0	0	0	0
Kong, 2021[20]	14	0	0	0	0	0
Ding, 2022[21]	70	1	1	0	0	0
Yang, 2021[23]	78	3*	1	0	0	0
Shen, 2022[22]	33	0	0	0	0	0
Liu, 2022[24]	55	0	0	0	0	0

*Two of 3 participants experienced fever.

insufflation during the procedure. In this meta-analysis, the pooled perforation rate was 1.5%, with 4 perforation events. The first perforation event[17] occurred in the context of an appendiceal base orifice occlusion by a large calcified fecalith (>1 cm). However, it was unclear if the perforation was because of stent placement as the site of perforation was at the level of the mid-stent rather than at the tip, which might suggest the perforation may have been unrelated to stent placement. This perforation required emergent conversion to an appendectomy, which proceeded without short- or long-term adverse events. The second instance[18] of perforation occurred during appendicolith removal using an extraction basket. The perforation was managed conservatively with stent placement without appendicitis recurrence in a 12-month follow-up period. In the third instance of perforation,[21] a patient was noted to have a large bezoar in the appendix (size unspecified) during appendicography. An extraction basket was used for bezoar retrieval, but the patient subsequently developed abdominal distension, prompting abdominal radiography, which demonstrated subdiaphragmatic air. This was also managed conservatively without long-term adverse events. In the last instance of perforation,[23] appendicography demonstrated a fecal stone in the distal appendiceal cavity, with contrast extravasation into the abdominal cavity, confirming appendiceal perforation. The perforation was managed with abdominal drain placement and a repeat ERAT procedure 1 month later

for stone removal with long-term resolution of symptoms. Of these 4 cases of perforation, only 1 required conversion to appendectomy, whereas the other instances were successfully managed conservatively. Additionally, none of these cases had evidence of long-term morbidity. Taken together, these data suggest that perforation in ERAT can be successfully managed conservatively in most cases with good long-term outcomes. Perforation rates could theoretically be minimized with refinement of inclusion criteria, such as favoring those earlier in the appendicitis disease course, consideration of fecalith size, and further endoscopic experience with ERAT given its relatively recent implementation; however, this would need to be studied specifically to draw or ascertain optimal timing for ERAT.

Additionally, the rate of recurrence of appendicitis after ERAT was favorable, with pooled data demonstrating a 6% recurrence in this meta-analysis. Although greater than the published rates of recurrence with appendectomy, this represents an improvement compared with those treated with antibiotics, which has been reported to be as high as 24.7% at 120 days and 39.1% at 5 years in 2 retrospective analyses.[34,35] However, it is important to note that for the purposes of our study, comparisons of outcomes of ERAT and antibiotics alone or ERAT with laparoscopic appendectomy were not assessed, so further studies are needed to ascertain direct comparative outcomes between ERAT and other conventional approaches of treatment for AA. Additionally, rates of recurrence in ERAT may be driven in part because of the lack of standardization regarding appendiceal stent placement during treatment and variability in endoscopic implementation; this would be an interesting area for further studies to delineate the role of stent placement. Studies have supported a functional role for the appendix, such as defense against enteric bacteria such as *Clostridioides difficile* (with a higher rate of occurrence in patients who underwent an appendectomy) and as an important reservoir for the gut microbiome.[36,37] The benefits of organ preservation versus the risks of appendicitis recurrence remain to be evaluated.

There are some limitations to our study. Most studies included in the meta-analysis have smaller population sizes. In addition, all studies included originated in China, and only 2 were multicentered. Furthermore, studies including children were excluded in the statistical analysis to avoid confounding and make our search more targeted to adult populations, which thereby incorporates some degree of selection bias. Finally, most studies were performed by advanced endoscopists, which raises the question of how generalizable this procedure is to other medical providers performing endoscopies.

In conclusion, ERAT is a minimally invasive technique that can be implemented for the treatment of uncomplicated AA with excellent success rates and minimal adverse events. Additional studies are needed to ascertain methods to reduce rates of recurrent appendicitis and differences in outcomes as compared with laparoscopic appendectomy and antibiotic therapy alone.

DISCLOSURE

All authors disclosed no financial relationships.

Abbreviations: AA, acute appendicitis; CI, confidence interval; ERAT, endoscopic retrograde appendicitis therapy.

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SUPPLEMENTARY TABLE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Checklist for systematic reviews

Section and topic	Item no.	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	Abstract
Abstract			
Abstract	2	See the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 for Abstracts checklist.[8]	Abstract
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2, paragraph 1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2, paragraph 1
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped. for the syntheses.	Page 2, paragraph 3
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3, paragraph 1
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	Page 3, paragraph 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process.	Page 3, paragraph 1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process.	Page 3, paragraph 1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses), and, if not, the methods used to decide which results to collect.	Page 3, paragraph 2
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 2, paragraph 3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process.	Page 3, paragraph 2
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	Page 3, paragraph 2
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item no. 5).	Figure 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Figure 1
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3, paragraph 2

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

Section and topic	Item no.	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3, paragraph 2
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, meta-regression).	Page 3, paragraph 2
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 4, paragraph 2
Reporting bias assessment	14	Describe any methods used to assess risk of bias because of missing results in a synthesis (arising from reporting biases).	Page 4, paragraph 2
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 3, paragraph 2
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 4, paragraph 2
Results of individual studies	19	For all outcomes, present, for each study, (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	Page 3, paragraphs 5-6
Results of syntheses	20a	For each synthesis, briefly summaries the characteristics and risk of bias among contributing studies.	Page 3, paragraphs 5-6
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 3, paragraphs 5-6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 3, paragraphs 5-6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 4, paragraph 2
Reporting biases	21	Present assessments of risk of bias because of missing results (arising from reporting biases) for each synthesis assessed.	Page 4, paragraph 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 3, paragraphs 5-6
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 4, paragraph 3
	23b	Discuss any limitations of the evidence included in the review.	Page 5, paragraph 2
	23c	Discuss any limitations of the review processes used.	Page 5, paragraph 2
	23d	Discuss implications of the results for practice, policy, and future research.	Page 5, paragraph 3
Other Information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not completed
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not completed
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

Section and topic	Item no.	Checklist item	Location where item is reported
Support	25	Describe sources of financial or nonfinancial support for the review and the role of the funders or sponsors in the review.	Disclosure statement
Competing interests	26	Page 3, paragraph 1	Disclosure statement
Availability of data, code, and other material	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 3, paragraph 2

NA, Not applicable.

SUPPLEMENTARY TABLE 2. Quality assessment by the U.S. National Heart, Lung, and Blood Institute for included studies*

Author, year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Rating
Controlled intervention studies															
Shen, 2022	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	N	Good
Liu, 2023	Y	Y	NR	NR	NR	Y	Y	Y	Y	Y	Y	N	Y	NR	Good
Observational cohort studies															
Liu, 2015	Y	Y	NR	Y	N	Y	Y	NA	Y	NA	Y	NA	Y	Y	Good
Li, 2016	Y	Y	NR	Y	N	Y	Y	NA	Y	NA	Y	NA	Y	Y	Good
Ye, 2018	Y	Y	NR	Y	CD	CD	Y	NA	Y	NA	Y	NA	CD	Y	Good
Kong, 2021	Y	Y	NR	Y	N	Y	Y	NA	Y	NA	Y	NA	Y	Y	Good
Ding, 2021	Y	Y	NR	Y	N	Y	Y	NA	Y	NA	Y	NA	NR	Y	Good
Yang, 2022	Y	Y	N	Y	Y	Y	Y	NA	Y	NA	Y	NA	CD	Y	Good

Y, Yes; *N,* no; *NA,* not applicable; *CD,* cannot determine; *NR,* not reported.
*Numbered criteria per the U.S. National Heart, Lung, and Blood Institute study quality assessment tool.[11]