REVIEW ARTICLE

The Endoscopic Retrograde Appendicitis Therapy for Acute Appendicitis in Children: A Systematic Review and Meta-Analysis

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ABSTRACT

Background • Acute appendicitis (AA) is a prevalent abdominal emergency in children, and there has been growing interest in the use of endoscopic retrograde appendicitis treatment (ERAT) over the past two decades. A meta-analysis of published retrospective studies was conducted to investigate the clinical characteristics and therapeutic efficacy of ERAT for AA in children.

Methods • A systematic review and meta-analysis of retrospective studies were carried out, encompassing data from PUBMED, MEDLINE, Cochrane, China National Knowledge Infrastructure (CNKI), WanFang, and VIP Database. The search was limited to studies published between January 1, 2012, and June 31, 2022, with the final search conducted on October 31, 2022. No restrictions were imposed regarding publication or study design filters. The registration number in PROSPERO was CRD42022377739.

Results • Seven retrospective cohort studies with 423 patients were included. The majority of children who underwent ERAT were male (57.6%, 95% CI 52.8%-62.4%). The ERAT procedure had a high success rate (99.5%, 95% CI 98.2%-100.0%) and averaged around 49 minutes. ERAT's efficacy for treating acute appendicitis was high (99.0%, 95% CI 96.5%-100.0%), with a low recurrence rate (4.2%, 95% CI 2.2%-6.7%). Patients typically stayed in the hospital for about 4.3 days, and the rate of postoperative complications was around 3.9% (95% CI 2.0%-6.2%).

Conclusions • Despite the heterogeneity among studies, ERAT appears to be an effective treatment for acute uncomplicated appendicitis in children. It has a high success rate, a low recurrence rate, preserves the appendix's function, and causes minimal damage. ERAT could be considered a safe and effective treatment option for pediatric appendicitis. (*Altern Ther Health Med.* 2023;29(8):342-346).

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INTRODUCTION

Acute appendicitis (AA) is a prevalent abdominal emergency in children, encompassing both acute uncomplicated and acute complicated cases.[1,2] In children, the symptoms of AA can often manifest atypically and insidiously, leading to severe outcomes due to reduced omental protection and ambiguous presentation. Diagnostic imaging techniques such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are widely employed, with US being the preferred modality due to its rapidity, affordability, and absence of radiation risks.[3] Despite laparoscopic appendectomy being the primary treatment approach, studies have indicated a high rate of negative appendectomies (surgical removal of a normal appendix) in adults, which is even more pronounced in children.[4-6]

In 2012, Liu et al. introduced endoscopic retrograde appendicitis treatment (ERAT), a minimally invasive technique inspired by Endoscopic Retrograde Cholangiopancreatography (ERCP) utilized for acute septic cholangitis. ERAT involves the insertion of a colonoscope into the cecum, insufflation of a small amount of air for visualization, placement of a guidewire through a catheter into the appendix, lavage with saline or antibiotics to remove residual feces or pus, and performance of a retrograde appendiculogram to ensure proper drainage of the appendiceal cavity.[7] Since its inception, the efficacy and safety of ERAT have garnered recognition and exploration.[8,9] Despite the growing interest in ERAT, there remains a lack of consensus regarding its efficacy and safety in treating pediatric acute appendicitis. To address this gap, we conducted a comprehensive meta-analysis of the existing literature.

METHODS

Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[10] We registered the study on PROSPERO, of which the registration number was CRD42022377739.

We conducted a systematic review and meta-analysis of retrospective studies that were carried out, encompassing data from PUBMED, MEDLINE, Cochrane, China National Knowledge Infrastructure (CNKI), WanFang, and VIP Database. The search was limited to studies published between January 1, 2012, and June 31, 2022, with the final search conducted on October 31, 2022. No restrictions were imposed regarding publication or study design filters. The search strategy for these databases was as follows: "Endoscopic retrograde appendicitis therapy" [Title/Abstract] and "((Appendicitis) [all fields]) AND ((Endoscopy) [all fields]) AND ((children) OR (child) [all fields])". Reference lists of related articles were also scanned to broaden the search. Additionally, a hand search was conducted across all six databases. The data were screened by two independent researchers, and disagreements were resolved through discussion or consultation with another researcher.

Inclusion and exclusion criteria were developed following the principles of PICOS (participant, intervention, comparison, outcome, study). The inclusion criteria were as follows: (1) case series that reported Endoscopic Retrograde Appendicitis Therapy (ERAT); (2) study subjects were under 18 years of age; (3) the study reported at least one of the following outcomes: clinical symptoms, appendiceal condition, successful intubation, drainage with a stent, effective interventions, complications, recurrence; (4) the study provided appropriate statistical estimates or counts.

The exclusion criteria were as follows: (1) case reports with less than 5 cases; (2) study subjects over 18 years of age; (3) review articles and meta-analyses; (4) conference abstracts; (5) studies that focused on diseases other than acute appendicitis; (6) studies that involved acute complicated appendicitis combined with other diseases.

The following information was extracted: name of first author, year of publication, study type, mean age, gender, number of participants, main clinical symptoms, appendiceal condition, number of successful intubations, whether drainage with stent was required, effectiveness of treatment, complications, recurrence, time of operation, recovery time of body temperature, hospital stays, and follow-up time. The Newcastle-Ottawa Scale (NOS) score[11] was used to evaluate the quality of the studies, which focuses on three categories: selection, comparability, and outcome. The maximum NOS score is 9 stars. An article that scored ≥6 stars was considered to be of high quality and was included in our study.

Statistical analysis was conducted using STATA version 16.0. The pooled proportions of ERAT were calculated using the DerSimonian and Laird approach.[12] All studies with missing values or zero counts were excluded from the analysis pairwise. First, a chi-squared test for homogeneity of proportions among the different studies was performed using the Cochran method. Then, the pooled proportions of ERAT were estimated along with the corresponding 95% confidence intervals (CI), using the DerSimonian-Laird random effects weighting scheme for the studies included in the analysis.

Some study outcomes were reported as medians with ranges or mid-quartiles with ranges. According to the methods introduced by Luo[13] and Wan,[14] those data were converted to means with deviations. Thus, the results for each group are presented as the mean ± standard deviation ($\bar{x} \pm s$). The I^2 statistic was used to test the degree of heterogeneity, with a $P < .05$ indicating high heterogeneity and vice versa. The random-effects model was applied to pool the high heterogeneity results, and the fixed-effects model was used for low heterogeneity ($P > .05$). Begg's and Egger's tests were performed to assess the risk of bias, with a $P < .05$ considered to have a high risk of publication bias.

RESULTS

We initially identified 303 papers through the article search, and after removing duplicate entries, we proceeded to evaluate the titles and abstracts of 221 records; following a thorough full-text review, 214 papers were excluded as they did not meet the predefined inclusion criteria (Figure 1). Ultimately, our study included 7 retrospective cohort studies involving 423 patients.

Characteristics of included studies

Table 1. summarizes the characteristics of the 7 studies included in the meta-analysis, which enrolled a total of 423 patients.

Figure 1. Flow diagram representing the selection of study

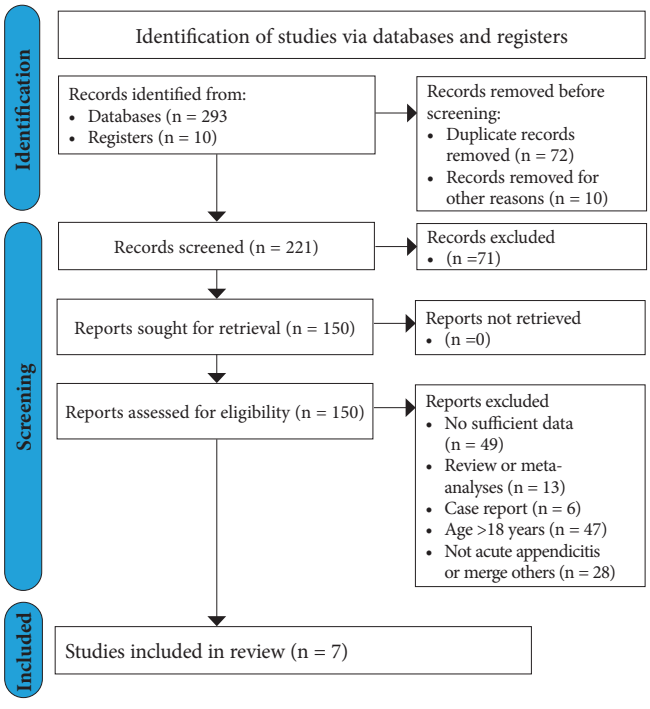


Table1. Summarized characteristics of 7 records included in the meta-analysis

Clinical characteristics	Number of cases (n = 423)
Gender	
male	221
female	202
abdominal pain	
yes	321
no	12
Vomiting	
yes	87
no	165
Fever	
yes	114
no	219
Intubation	
Successful	418
failed	5
Appendiceal thickening	
yes	213
no	39
Appendiceal pus	
yes	46
no	126
Appendiceal fecaliths	
yes	162
no	117
Drainage with stent	
yes	167
no	110
Failed intubation	5
Effective	
yes	412
no	6
Failed intubation	5
Complications[a]	
yes	21
no	397
Failed intubation	5
Recurrence	
yes	17
no	328
Failed intubation	5
loss follow-up	3

[a]gastrointestinal hemorrhage and perforation, spread of abdominal abscesses, contrast allergy and intussusception

Table 2. Baseline characteristics of 7 records included in the meta-analysis

Study (Name, year)	Study type	Number of patients	Gender (M/F)	Age (years)	NOS scores
Kang et al, 2021[15]	R	36	22/14	6.74 ± 3.02	8
Jia et al, 2022[16]	R	30	14/16	11 ± 3	8
Wang et al, 2017[17]	R	42	25/17	7.87 ± 3.31	7
Zheng et al, 2021[18]	R	81	48/33	10 ± 2.01	8
Deng et al, 2021[19]	R	18	10/8	6.01 ± 0.85	8
Xu et al, 2022[20]	R	64	47/17	8.7 ± 2.6	6
Liu et al, 2021[21]	R	152	77/75	6.84 ± 3.09	7

Abbreviations: R, retrospective; M, Male; F, Female; NOS, Newcastle-Ottawa Quality Assessment Scale.

Table 3. Pooled proportions of clinical characteristics (A).

Characteristics	Number of articles	Cases (n)	Total number of cases (N)	Effects Model	Pooled-proportion	95%CI-lb	95%CI-ub	I^2	*P* value
Gender									
male	7	221	423	Fixed	0.576	0.528	0.624	48.44%	<.001
female	7	202	423	Fixed	0.424	0.376	0.472	48.44%	<.001
Clinical symptoms									
abdominal pain	4	321	333	Fixed	0.967	0.943	0.985	0%	<.001
vomiting	3	87	252	Fixed	0.344	0.286	0.405	0%	<.001
fever	4	114	333	Random	0.325	0.146	0.534	92.75%	<.001
Appendiceal condition									
appendiceal thickening	3	213	252	Random	0.848	0.365	1.000	98.25%	<.001
appendiceal pus	4	46	172	Random	0.307	0.035	0.684	95.98%	.007
appendiceal fecaliths	4	162	279	Random	0.543	0.253	0.818	95.33%	<.001
Successful intubation	7	418	423	Fixed	0.995	0.982	1.000	0%	<.001
Drainage with stent	4	167	282	Random	0.502	0.092	0.910	98.14%	<.001
Effective interventions	7	412	423	Random	0.990	0.965	1.000	51.61%	<.001
Complications	7	21	423	Fixed	0.039	0.020	0.062	49.19%	<.001
Recurrence	6	17	353	Fixed	0.042	0.022	0.067	12.29%	<.001

Abbreviations: CI-lb, lower confidence interval bounds; CI-ub, upper confidence interval bounds; Complications, gastrointestinal hemorrhage, perforation, abdominal abscess spread, contrast allergy, or/and intussusception; Appendiceal fecaliths, substances that form when intestinal contents, such as feces, enter the appendiceal cavity.

Table 3. Pooled effects size of clinical characteristics (B)

Characteristics	Number of articles	Total number of cases (N)	Effects Model	Effects size (95%CI)	I^2	*P* value
age(years)	7	423	Random	7.794 (7.577,8.011)	97.50%	<.001
Time of operation(minutes)	6	387	Random	49.006(48.179,49.833)	85.20%	<.001
Recovery time of body temperature(days)	3	141	Fixed	1.292(1.228 ,1.356)	0%	<.001
hospital stays(days)	6	393	Random	4.319(4.254 ,4.385)	95.40%	<.001
Follow-up time(month)	5	317	Random	11.992(11.127,12.858)	92.30%	<.001

Abbreviations: CI, confidence interval.

Meta-Analysis Results

Table 2 presents the baseline characteristics of the 7 studies, with Newcastle-Ottawa scale (NOS) scores ranging from 6 to 8 stars, indicating moderate to high quality of the included cohort studies. Pooled proportions of dichotomous variables are presented in Table 3 (A), while pooled effect sizes of continuous variables are presented in Table 3 (B).

Publication Bias

Table 4 displays the results of Begg's and Egger's tests for publication bias of clinical characteristics, such as gender, age, clinical symptoms, appendiceal conditions, successful intubation, drainage with stent, effective interventions, complications, recurrence, time of operation, recovery time of body temperature, hospital stays, and follow-up time. Egger's funnel plots were also constructed for the enrolled seven studies, with different subgroups classified to evaluate publication bias (Figure 2A, 2B, 2C). Several symmetrical inverted funnels were observed.

Table 4. Begg's and Egger's Test of publication bias of clinical characteristics

	Number of studies	*P* value[a]	
		Begg's test	Egger's test
Gender			
male	423	1.000	.364
female	423	1.000	.876
age(years)	423	.230	.122
Clinical symptoms			
abdominal pain	333	.734	.396
vomiting	252	1.000	.469
fever	333	.734	.781
Appendiceal conditions			
appendiceal thickening	252	1.000	/
appendiceal pus	172	.089	.006[b]
appendiceal fecaliths	279	1.000	.809
Successful intubation	423	1.000	/
Drainage with stent	282	.734	.650
Effective	423	1.000	/
Complications	423	1.000	.905
Recurrence	353	.806	.839
Time of operation(minutes)	387	.452	.030[b]
Recovery time of body temperature(days)	141	1.000	.502
hospital stays(days)	393	.452	.019[b]
Follow-up time(month)	317	.296	.110

[a]*P* value means the value of Pr>|z| (continuity corrected, in Begg's Test) or P>|t| (in Egger's Test).
[b]*P* value < .05 was considered to have a high risk of publication bias.

Figure 2A. Meta-analysis of the prevalence of boys

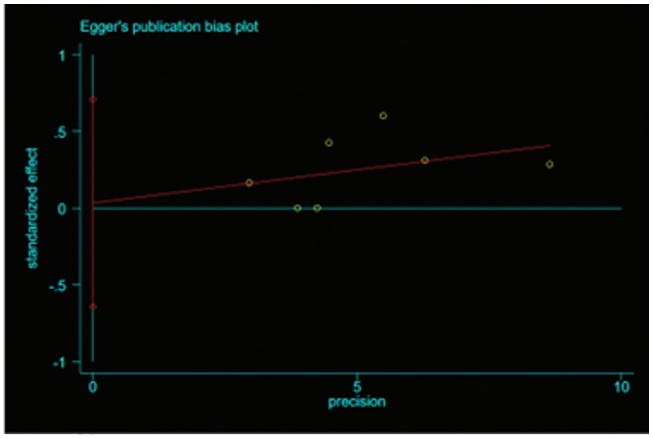


Figure 2B. Meta-analysis of the age of children

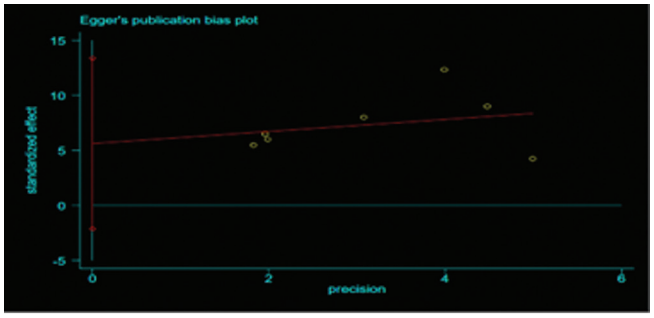
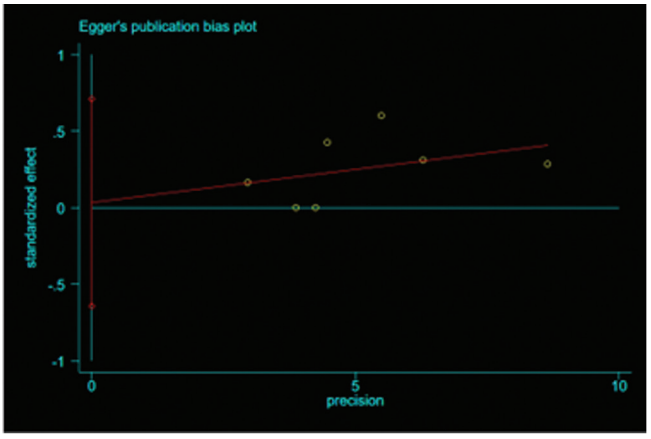


Figure 2C. Meta-analysis of complications



DISCUSSION

In recent years, there has been a renewed interest in the non-surgical treatment of acute appendicitis (AA) without complications, challenging the long-standing belief that the appendix serves no significant purpose. Studies have indicated that the appendix may contribute to immune function and the gut microbiome,[22] prompting a shift towards conservative treatment options for uncomplicated AA over the past two decades.[23] Concerns regarding surgical risks and complications, Such as infection, appendiceal stump fistula, fecal leakage, intestinal obstruction, intraoperative malpractice, have led to an increasing number of parents opting for conservative approaches,[9] resulting in a growing body of research focused on non-surgical treatments for AA. However, the cases involving endoscopic retrograde appendicitis therapy (ERAT) in children remain relatively limited and diverse. This study aimed to analyze the effectiveness of ERAT in the treatment of AA in children and provide guidance on the diagnosis and management of the condition.

Our study initially included 303 articles, from which we identified and analyzed seven retrospective case series. While the typical clinical manifestations of AA include fever, vomiting, and migrating periumbilical pain to the right iliac fossa, pediatric cases often present with nonspecific symptoms, making differential diagnosis challenging.[6,24,25] Among the children who underwent ERAT in our study, approximately 57.6% (95% CI 52.8%-62.4%) were male. We synthesized the clinical manifestations of AA in children, highlighting abdominal pain, vomiting, and fever as the primary symptoms. ERAT enables endoscopic observation and assessment of the appendix, facilitating the diagnosis of AA based on criteria such as appendiceal thickening, pus presence, and appendiceal fecaliths.[7] Successful catheter insertion, a crucial aspect of ERAT, was achieved in 99.5% of cases (95% CI 98.2%-100.0%), demonstrating the feasibility of the procedure in treating AA. The average operation time for ERAT was approximately 49 minutes (95% CI 48.179-49.833), with an overall efficacy rate of 99.0% (95% CI 96.5%-100.0%) for acute appendicitis. The pooled recurrence rate was 4.2% (95% CI 2.2%-6.7%), and the average hospital stay was 4.319 days (95% CI 4.254-4.385). Postoperative complications, defined as gastrointestinal hemorrhage, perforation, abdominal abscess spread, contrast allergy, and intussusception, occurred at a rate of approximately 3.9% (95% CI 2.0%-6.2%).

However, our meta-analysis does have limitations. Firstly, the available data were derived solely from observational or retrospective cohort studies, inevitably introducing selection bias. Secondly, the surgical teams themselves were the authors of the reports, which may introduce a certain level of bias. Thirdly, the analysis was based on limitedlimited studies, resulting in significant heterogeneity in clinical presentations and postoperative outcomes. Fourthly, there were indications of potential publication bias. Furthermore, longer-term follow-up studies are necessary.

Although there is an urgent need for conservative treatment options for acute appendicitis in children, there is a scarcity of studies available. ERAT shows promise as a minimally invasive and organ-preserving approach, and further clinical randomized trials focusing on AA in children should be conducted to enhance our understanding and generate more reliable results.[8] However, it is important to acknowledge that ERAT has its limitations, particularly in treating complicated AA, such as suspected appendiceal perforation, appendiceal gangrene, abdominal abscesses, and diffuse peritonitis. Additionally, most studies were conducted in single centers, making it unclear how generalizable or reproducible the safety and efficacy of ERAT are across different medical institutions.

In conclusion, our study demonstrates that ERAT is a feasible and effective treatment option for AA in children, offering advantages such as shorter operation times, high

efficiency, low recurrence rates, and shorter hospital stays. Further research, including multi-center studies, large-sample randomized controlled studies, is warranted to comprehensively explore the potential and limitations of ERAT.

CONCLUSION

Despite significant heterogeneity observed among the primary studies, our findings demonstrate the substantial morbidity, clinical characteristics, and prognosis associated with ERAT. ERAT proves to be highly effective with a low recurrence rate in children with acute uncomplicated appendicitis, while preserving the appendix's physiological function and minimizing extensive damage. Consequently, ERAT represents a safe and effective treatment option for pediatric appendicitis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

CONSENT FOR PUBLICATION

All of the authors agree to publication in the Journal of "Alternative Therapies in Health and Medicine."

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

COMPETING INTERESTS

The authors reported no proprietary or commercial interest in any product mentioned or the concept discussed in this article.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTES

Lan Liu and Huiping Zeng are co-first authors: systematic search, data extraction, Formal analysis, article writing; Bing Zhang YingYing Yang, Jianxi Bai and Sheng Lin: Formal analysis, quality assessment; Yifan Fang: quality assessment; Siqi Xie is the corresponding author who determined the main idea of the manuscript. All authors reviewed the manuscript.

ACKNOWLEDGEMENTS

Paper editing: Nick Xie

REGISTRATION OF RESEARCH STUDIES

1. Name of the registry: PROSPERO
2. Unique Identifying number or registration ID: CRD42022356262

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