Surgery 174 (2023) 1292–1301

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Endoscopic retrograde appendicitis therapy versus appendectomy or antibiotics in the modern approach to uncomplicated acute appendicitis: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Accepted 16 August 2023
Available online 6 October 2023

ABSTRACT

Introduction: Endoscopic retrograde appendicitis therapy has been proposed as an alternative strategy for treating appendicitis, but debate exists on its role compared with conventional treatment.
Methods: This systematic review was performed on MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE. The last search was in April of 2023. The risk ratio with a 95% confidence interval was calculated for dichotomous variables, and the mean difference with a 95% confidence interval for continuous variables. The risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool (randomized controlled trials) and the Risk of Bias in Non-Randomized Studies of Intervention tool (non-randomized controlled trials).
Results: Six studies met the eligibility criteria. Four studies compared endoscopic retrograde appendicitis therapy ($n = 236$ patients) and appendectomy ($n = 339$) and found no differences in technical success during index admission (risk ratio 0.97, 95% confidence interval [0.92,1.02]). Appendectomy showed superior outcomes for recurrence at 1-year follow-up (risk ratio 11.28, 95% confidence interval [2.61,48.73]). Endoscopic retrograde appendicitis therapy required shorter procedural time (mean difference −14.38, 95% confidence interval [−20.17, −8.59]) and length of hospital stay (mean difference −1.19, 95% confidence interval [−2.37, −0.01]), with lower post-intervention abdominal pain (risk ratio 0.21, 95% confidence interval [0.14,0.32]). Two studies compared endoscopic retrograde appendicitis therapy ($n = 269$) and antibiotic treatment ($n = 280$). Technical success during admission (risk ratio 1.11, 95% confidence interval [0.91,1.35]) and appendicitis recurrence (risk ratio 1.07, 95% confidence interval [0.08,14.87]) did not differ, but endoscopic retrograde appendicitis therapy decreased the length of hospitalization (mean difference −1.91, 95% confidence interval [−3.18, −0.64]).
Conclusion: This meta-analysis did not identify significant differences between endoscopic retrograde appendicitis therapy and appendectomy or antibiotics regarding technical success during index admission and treatment efficacy at 1-year follow-up. However, a high risk of imprecision limits these results. The advantages of endoscopic retrograde appendicitis therapy in terms of reduced procedural times and

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https://doi.org/10.1016/j.surg.2023.08.029

shorter lengths of stay must be balanced against the increased risk of having an appendicitis recurrence at one year.

Introduction

Acute appendicitis is a common surgical emergency, with 7% to 12% of the population experiencing the disease at some point in life.[1,2] Laparoscopic appendectomy remains the standard treatment but carries the risk of negative appendectomy, which is experienced by up to 28% of patients,[3] as well as the risk of postoperative complications, which affect 8.2% to 31.4% of patients.[4,5] Increasing evidence supports that uncomplicated acute appendicitis can be safely treated with antibiotics,[6,7] which yields a recurrence rate of approximately 39% at 5-year follow-up.[8,9] Moreover, recent studies have argued against appendectomy based on the concept that the appendix has secretory and immune functions.[10]

Inspired by the clinical use of endoscopic retrograde cholangiopancreatography, Liu et al introduced endoscopic retrograde appendicitis therapy (ERAT) in 2012.[11] This minimally invasive alternative treatment uses a flexible endoscope to access and treat the inflamed appendix from the cecum and can be performed under conscious or local anesthesia. Endoscopic retrograde appendicitis therapy has been reported to have several advantages over appendectomy[12] and comparable efficacy, with studies reporting that up to 95% of cases of uncomplicated acute appendicitis did not experience recurrence after ERAT.[13]

To date, 2 systematic reviews of studies investigating the results of ERAT have been conducted,[14,15] which reported low to moderate confidence in the results. Although no pooled analyses have compared ERAT with appendectomy and antibiotics for uncomplicated acute appendicitis, 5 studies have been published since the last systematic review.[12,16–19] Aiming to address the existing controversies, we conducted a systematic review and meta-analysis to compare the outcomes of ERAT with appendectomy and with antibiotic therapy alone in the management of uncomplicated acute appendicitis. The findings of this review will assist in guiding future research and clinical practice.

Methods

Ethical approval was not required for this study. We conducted this systematic review and meta-analysis according to the recommendations of the 2020 update of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[20] Meta-analysis of Observational Studies in Epidemiology guidelines,[21] the Cochrane Handbook for Systematic Reviews of Interventions guidelines,[22] and A Measurement Tool to Assess systematic Reviews criteria.[23] Two reviewers (F.P. and M.P.) independently conducted all stages of study identification, selection, quality assessment, and data extraction. After using kappa statistics to determine the consistency between their results, the reviewers resolved any inconsistencies through discussion until they reached a consensus.

The reviewers identified studies by reviewing the title and abstract, followed by a full-text review using the Rayyan web app for systematic reviews (https://www.rayyan.ai/). They considered all studies comparing ERAT with appendectomy or comparing ERAT with conservative antibiotic therapy as a treatment for uncomplicated acute appendicitis eligible for inclusion. When there was an overlap in patient cohorts of 2 or more studies and no difference in study interval was reported, they included the most recent report in the pooled analysis. Using the results yielded by this strategy, we performed 2 separate meta-analyses, 1 comparing ERAT with appendectomy and 1 comparing ERAT with antibiotic treatment.

Inclusion and exclusion criteria

We adopted the Patient/Problem, Intervention, Comparison, and Outcome (PICO) structure for the meta-analyses (Supplementary Table S1). To be included in the sample, the studies must have compared ERAT and laparoscopic or open appendectomy with conservative treatment with antibiotic therapy for uncomplicated acute appendicitis between 2012 and 2023. We excluded studies comparing ERAT with appendectomy and antibiotic therapy for purposes other than uncomplicated appendicitis, such as appendiceal phlegmons; studies that did not report data on the selected outcomes of interest did not specify patient selection criteria or did not use a control group; and publications that were expert opinions, review articles without original data, editorials, case series, or case reports.

Study identification

We systematically searched MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE to identify relevant studies. We manually searched the reference lists of relevant studies using the “related articles” function in PubMed. Our search strategy combined text words and medical subject heading terms related to ERAT versus appendectomy or conservative management with antibiotics for treating uncomplicated acute appendicitis in several logical combinations (Supplementary Table S1). We also conducted a search for grey literature using Google Scholar, ClinicalTrials.gov, and Open Grey. Our detailed search strategy is freely accessible in the protocol (PROSPERO 2023 CRD42023395277).

Risk of bias and quality of evidence assessment

Two authors (F.P. and M.P.) independently assessed the risk of bias using the Cochrane Risk of Bias 2.0 tool[24] and assessed the risk of bias in observational studies using the Risk of Bias in Non-Randomized Studies of Intervention tool.[25] Using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach, 2 authors (M.P. and A.P.) independently evaluated the quality of evidence for imprecision, inconsistency, indirectness, and publication bias and classified the quality of evidence as very low, low, moderate, or high.[26] Using their results, we created a summary table of their findings using GRADEpro version 3.6.1 software (https://www.gradepro.org/).

Outcomes of interest and data extraction

We assessed 2 primary efficacy and safety outcomes. The first primary outcome was the technical success rate during the index admission, with success defined as entirely performing a technique without the need for interruption or switching to another intervention during admission. The second primary outcome was treatment efficacy at 1-year follow-up, with efficacy defined as the absence of new episodes of acute appendicitis or recurrent symptoms suggestive of acute appendicitis, including right iliac fossa pain alone or with fever. The secondary outcomes we assessed were procedural duration, postintervention abdominal pain, length of hospital stay, short-term postintervention complications, other complications (intra-abdominal abscess, incisional pain, obstructive symptoms, enterocolitis, or enterocutaneous fistula), and appendicitis recurrence (confirmed at surgery). Two authors (F.P. and M.P.) independently reviewed each included article using a double-blinded procedure to increase the accuracy of the data extracted.

Statistical Analysis

We performed all statistical analyses using ReviewManager version 5.4.1 software and the RevMan Web (https://revman.cochrane.org/info). We included variables for meta-analysis if they had been reported by at least 2 studies. We calculated the risk ratio (RR) with a 95% CI for dichotomous variables and the weighted mean difference (MD) with a 95% CI for continuous variables. When continuous data were reported as the median and range, we used Hozo's[27] method to estimate the respective mean and SD. We assessed the statistical heterogeneity of the results across studies using the Higgins' I^2 and χ^2 test, evaluating the results at an I^2 value exceeding 50% as an indication of substantial heterogeneity.

Besides the results for statistical heterogeneity, we reviewed the clinical and methodological heterogeneity results to inform our decision whether to use a fixed or random-effects model. Given the intrinsic heterogeneity of interventions, populations, study designs, methods, and statistical heterogeneity, we exclusively applied the random-effects model for our meta-analyses. Our subgroup analyses focused on relevant outcomes of ERAT compared with laparoscopic appendectomy and ERAT compared with open appendectomy. We performed sensitivity analyses of clinically relevant outcomes using the leave-one-out method depending on the weight of each study included in the pooled analysis and based on the qualitative evaluation of the included studies.

Results

Of the 224 records we identified by searching MEDLINE, the Cochrane Central Register of Controlled Trials, and EMBASE (we identified no relevant grey literature), 217 met the criteria for full-text reading. The reviewers determined that 6 studies met the inclusion for meta-analysis (inter-rater reliability $\kappa > 0.90$), all of which had been conducted in China (Figure 1).[12,16–19,28] Regarding the focus of the study, 4 studies compared ERAT with appendectomy,[12,16–18] and 2 compared ERAT with antibiotic therapy.[19,28] Regarding the type of study, 3 studies were randomized controlled trials (RCTs)[12,17,28] and 3 were retrospective cohort studies.[16,18,19] The 2 studies comparing ERAT with appendectomy analyzed data from 575 patients, of whom 236 had undergone ERAT and 339 appendectomies. In the meta-analysis of studies that compared ERAT with antibiotic treatment, 269 patients had undergone ERAT and 280 antibiotic therapies.

Study characteristics

The study characteristics are summarized in Tables I and II. Overall, we found similar exclusion criteria for the studies that compared ERAT with appendectomy. The standard exclusion criteria were age under 18 years; pregnancy or lactation; history of inflammatory bowel disease; computed tomography (CT) findings of complicated appendicitis; and colonoscopy showing involuted mass-like protrusion, mucus, or polyp-like tissue at the opening of the appendix. Yang et al[16] excluded patients with filling defects in the appendiceal lumen that remained after repeated flushing during appendicography with confirmed absence of fecal stone, whereas Shen et al[17] excluded patients with appendiceal diameter >15 mm on CT scan. Ding et al[18] included periappendiceal abscesses.

Regarding the trials that compared ERAT with antibiotic therapy, the exclusion criteria were complicated appendicitis, abdominal

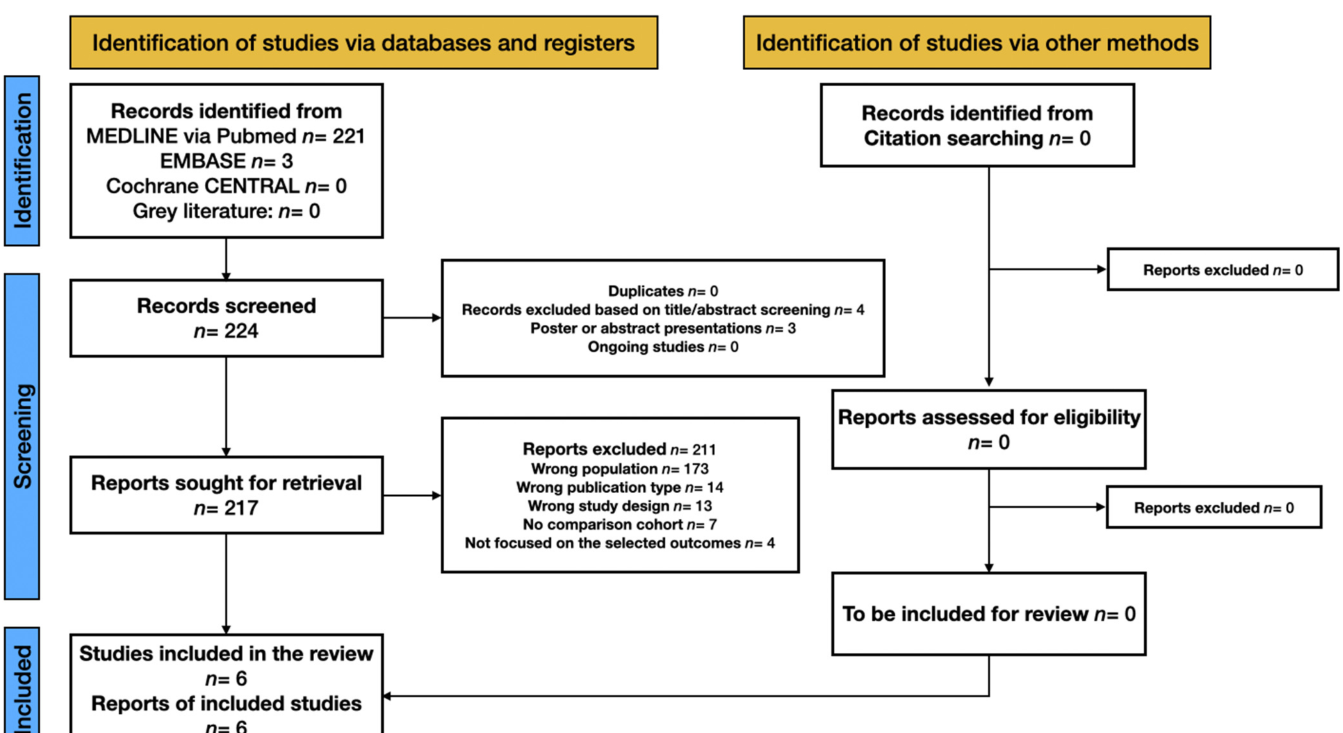

Figure 1. Flow chart of the study selection process according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Table I
General characteristics of patients enrolled in studies included in meta-analysis comparing endoscopic retrograde appendicitis therapy and appendectomy

		Liu et al (2022)	Yang et al (2022)	Shen et al (2022)	Ding et al (2022)
Study type		RCT	*n*-RCT (retrospective)	RCT	*n*-RCT (retrospective)
Study duration (mo)		28	35	19	35
Study period		August 2013–December 2015	April 2017–March 2020	January 2018–August 2019	January 2017–December 2019
Study location		3 Chinese hospitals	1 Chinese hospital	1 Chinese hospital	1 Chinese hospital
Patients randomized or allocated, *n* (%)	ERAT	55 (50)	78 (50)	33 (33.3)	70 (33.3)
	Appendectomy	55 (50)	78 (50)	66 (66.7) (33 lap, 33 open)	140 (66.7) (68 lap, 72 open)
Sex (M:F)	ERAT	33:22	40:38	18:15	42:28
	Appendectomy	33:22	41:37	36:30	88:52
Age (y)	ERAT	39 (49) (median (IQR])	30 (21–35.3) (median [IQR])	44.1 ± 16.9	39.9 ± 12.0
Mean ± SD/median (range)	Appendectomy	39 (48) (median [IQR])	30 (22.8–34.3) (median [IQR])	43.2 ± 15.4 (lap) 45.4 ± 18.1 (open)	39.1 ± 12.2 (lap) 38.4 ± 10.7 (open)
WBC count ($\times 10^9$/L) at admission	ERAT	13.3 (22.8) (mean [IQR])	NR	11.8 ± 3.8	NR
Mean ± SD/median (range)	Appendectomy	13.7 (23.1) (mean [IQR])	NR	11.9 ± 3.8 (lap) 13.6 ± 3.8 (open)	NR
Body temperature at admission	ERAT	NR	NR	37.4 ± 0.8	NR
Mean ± SD	Appendectomy	NR	NR	37.13 ± 0.5 (lap) 37.22 ± 0.5 (open)	NR
Mean CRP concentration (mg/L) at admission	ERAT	28.2 (219.9) (median [IQR])	NR	NR	13.6 (5.5–20)
Median (range)	Appendectomy	50 (259.6) (median [IQR])	NR	NR	11.4 (7.5–20.2) 11.7 (5.3–21.5)
Mean/median Alvarado score	ERAT	8 (7) (median (IQR])	NR	8 (7–9)	NR
Median (range)	Appendectomy	8 (8.5) (median [IQR])	NR	8 (6–9) (lap) 8 (7–9) (open)	NR
AIR score	ERAT	NR	NR	NR	7 (5–10)
Median (range)	Appendectomy	NR	NR	NR	7 (5–10) (lap) 8 (5–11) (open)
Appendectomy (open:laparoscopic)		NR	0:78	33:33	72:68
Follow-up (mo)	ERAT	36	12	22	6
Median	Appendectomy	36	12	22	6
Patients lost to follow-up, *n* (%)	ERAT	–	NR	–	NR
	Appendectomy	–	NR	–	NR

RCT, randomized controlled trial; *n-RCT*, non-randomized controlled trial; *ERAT*, endoscopic retrograde appendicitis therapy; *lap*, laparoscopic; *WBC*, white blood cell; *CRP*, C-reactive protein; *NR*, not reported; *AIR*, appendicitis inflammatory response.

Table II
General characteristics of patients enrolled in studies included in meta-analysis comparing endoscopic retrograde appendicitis therapy and antibiotic therapy

		Kang et al (2021)	Li. et al (2023)
Study type		RCT	*n*-RCT (retrospective)
Study duration (mo)		16	23
Study period		October 2018–February 2020	May 2018–June 2020
Study location		1 Chinese hospital	5 Chinese hospitals
Patients randomized or allocated, *n* (%)	ERAT	36 (43.4)	233 (50.0)
	AT	47 (56.6)	233 (50.0)
Sex (M:F)	ERAT	22:14	135:98
	AT	23:24	138:95
Age (y)	ERAT	6.7 ± 3.0	23 (21–25) (median [IQR])
Mean ± SD/median (range)	AT	6.5 ± 3.3	25 (22–27) (median [IQR])
WBC count at admission ($\times 10^9$/L)	ERAT	11.0 ± 7.3	NR
Mean ± SD	AT	8.7 ± 3.4	NR
Body temperature at admission	ERAT	37.4 ± 0.9	NR
Mean ± SD	AT	37.5 ± 1.1	NR
CRP concentration at admission (mg/L)	ERAT	NR	NR
	AT	NR	NR
Alvarado score	ERAT	NR	NR
	AT	NR	NR
AIR score	ERAT	NR	NR
	AT	NR	NR
Follow-up (mo)	ERAT	9.1 ± 4.5	12
Mean ± SD	AT	8.6 ± 3.1	12
Patients lost to follow-up, *n* (%)	ERAT	2 (5.5)	NR
	AT	NR	NR

RCT, randomized controlled trial; *n-RCT*, non-randomized controlled trial; *ERAT*, endoscopic retrograde appendicitis therapy; *AT*, antibiotic therapy; *WBC*, white blood cell; *CRP*, C-reactive protein; *AIR*, appendicitis inflammatory response; *NR*, not reported.

free air, other causes of acute abdomen on abdominal X-ray, contraindication for colonoscopy, or allergy to contrast media. Li et al[19] excluded patients younger than 18 or older than 60 years, whereas Ding et al[18] included only children aged 1 to 13 years diagnosed with acute uncomplicated appendicitis based on CT or ultrasound criteria refusing surgery. ERAT had been performed with the standard technique[11] in all studies except 1 study,[28] and the surgical technique for appendectomy was not specified in 3 studies.[12,16,18] Different antibiotic regimens were used to treat patients selected for conservative treatment, and different outcome measures were adopted within the ERAT, appendectomy, and antibiotic treatment groups (Supplementary Tables S1 and S2).

Risk of bias

Figures 2 and 3 present the risk-of-bias analysis results. Outcomes might have been influenced by bias in allocation concealment, as methods of patient allocation showed substantial variability amongst different studies and were not specified in Liu et al[12] or Kang et al.[28] None of the studies performed blinding of participants, personnel, or outcome assessors. The 3 retrospective cohort studies[16,18,19] were considered at low risk of bias, and 2 studies[16,19] were considered at moderate risk of bias for missing data.

GRADE quality of evidence assessment

Systematic review and meta-analysis of studies comparing ERAT with appendectomy revealed that the overall quality of evidence was low for technical success during the index admission and for length of hospital stay, short-term postintervention complications, and postintervention complications, and it was very low for treatment efficacy at 1-year follow-up and postintervention complications. The certainty of the evidence was moderate for procedural duration, whereas it was high for postintervention abdominal pain, appendicitis recurrence at 1-year follow-up, and wound infection (Supplementary Figure S1). Systematic review and meta-analysis of studies comparing ERAT with antibiotic therapy revealed that the certainty of evidence was low for technical success during the index admission and for postintervention pain duration, postintervention duration of clinical symptoms, pain relief at 24 hours post-treatment, appendicitis recurrence at 1-year follow-up, and length of hospital stay, and it was very low for treatment efficacy at 1-year follow-up (Supplementary Figure S2).

Patient characteristics

The results of both meta-analyses revealed that the patients did not significantly differ in terms of sex or age among the treatment groups (Tables I and II). The mean follow-up was 19 ± 11 months in the ERAT, 16.1 ± 10.1 months in the appendectomy, and 10.3 ± 1.7 in the antibiotics group.

Meta-analysis of clinical outcomes

Supplementary Table S3 summarizes the main results of the meta-analyses. Figure 4 shows the results of the comparison of ERAT with appendectomy, and Figure 5 shows the results of the comparison of ERAT and antibiotic therapy. Supplementary Table S4 shows the results of the analysis of the comparison of the outcomes of ERAT with appendectomy. Supplementary Table S5 shows the results of the analysis of the comparison of the outcomes of ERAT and antibiotic therapy.

Comparison of ERAT and appendectomy

In the analysis of primary outcomes, comparison of ERAT and appendectomy regarding technical success during index admission revealed no statistically significant differences (RR = 0.97, 95% CI = 0.92–1.02; test for subgroup differences: $\chi^2 = 3.08$; $P = .08$) or treatment efficacy at 1-year follow-up (RR = 1.43, 95% CI = 0.69–2.95; test for subgroup differences: $\chi^2 = 0.36$; $P = .55$), whereas appendectomy showed superior outcomes compared with ERAT for recurrence at 1-year follow-up (RR = 11.28, 95% CI = 2.61–48.73; test for subgroup differences: $\chi^2 = 0.00$; $P = .98$). In the analysis of secondary outcomes, ERAT was associated with a significantly shorter procedural duration (MD = −14.38, 95% CI = −20.17 to −8.59; test for subgroup differences: $\chi^2 = 2.34$; $P = .13$), less postintervention abdominal pain (RR = 0.21, 95%

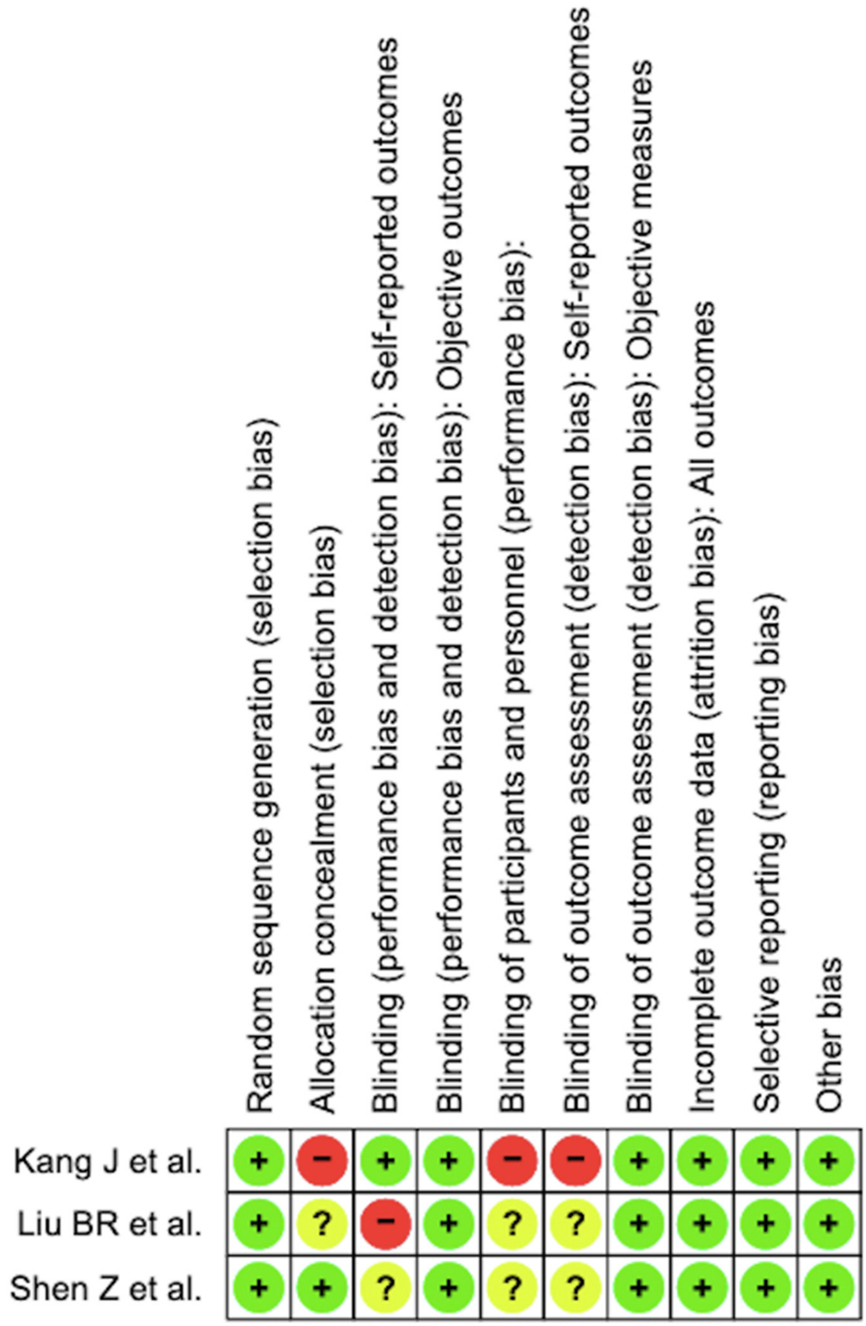

Figure 2. Cochrane risk-of-bias 2.0 chart showing the evaluation of the risk of bias of the randomized controlled trials included in the systematic review and meta-analysis.

CI = 0.14–0.32; test for subgroup differences: $\chi^2 = 0.14$; $P = .71$), and shorter hospital length of stay (MD = −1.19, 95% CI = −2.37 to −0.01; test for subgroup differences: $\chi^2 = 0.73$; $P = .39$) compared with appendectomy. There were no significant differences between ERAT and appendectomy regarding short-term postintervention complications (RR = 0.40, 95% CI = 0.09–1.82; test for subgroup differences: $\chi^2 = 0.06$; $P = .81$) or other postintervention complications (RR = 0.34, 95% CI = 0.05–2.20; test for subgroup differences: $\chi^2 = 0.29$; $P = .59$).

Comparison of ERAT with antibiotic therapy

In the analysis of primary outcomes, comparison of ERAT with antibiotic therapy revealed no statistically significant differences regarding technical success during index admission (RR = 1.11, 95% CI = 0.91–1.35; test for subgroup differences: $\chi^2 = 5.89$; $P = .02$, ERAT superior in RCTs), treatment efficacy (RR = 1.06, 95% CI = 0.81–1.40; test for subgroup differences: $\chi^2 = 14.37$; $P = .0002$, ERAT superior in observational studies) and 1-year appendicitis recurrence (RR = 1.07, 95% CI 0.08 = 14.87; test for subgroup differences: $\chi^2 = 3.2$; $P = .07$). In the analysis of secondary outcomes, ERAT was associated with a significantly shorter hospital length of stay (MD = −1.91, 95% CI = −3.18 to −0.64; test for subgroup differences: $\chi^2 = 10.44$; $P = .001$, ERAT highly superior in RCTs). There were no significant differences regarding postintervention duration of pain and clinical symptoms, pain relief 24 hours after treatment, and postintervention complications.

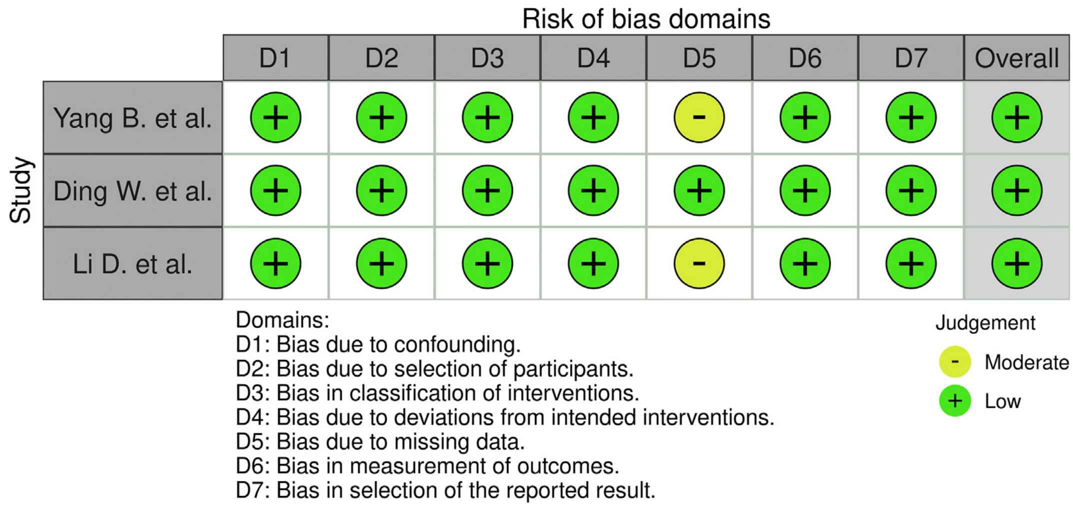

Figure 3. Risk of bias in non-randomized studies of interventions chart showing the evaluation of the risk of bias of the randomized controlled trials included in the systematic review and meta-analysis.

Subgroup and sensitivity analyses

Subgroup meta-analysis comparing ERAT with open appendectomy and with laparoscopic appendectomy revealed superior results for ERAT in terms of postintervention abdominal pain compared with open appendectomy but not with laparoscopic appendectomy and revealed superior results for ERAT compared with both laparoscopic and open appendectomy regarding procedural duration (outcomes reported only in 1 study[18]). Sensitivity analysis comparing ERAT with appendectomy revealed superior results for appendectomy regarding technical success during index admission when the study by Ding et al[18] (weight = 35.6%) was excluded (RR = 0.96, 95% CI = 0.91–0.99). The benefit of ERAT for the procedural time was lost when Yang et al[16] (weight = 34.5%) were excluded (MD = −16.30, 95% CI = −34.04–1.44). Length of primary hospital stay was comparable between the 2 study groups when Yang et al[16] was excluded (weight = 25.5%, MD = −1.03, 95% CI = −3.28–1.22). The short-term postintervention complication rate for ERAT was significantly lower when Shen et al[17] was excluded (weight = 30.5%, RR = 0.14, 95% CI = 0.03–0.60). When Liu et al[12] was excluded

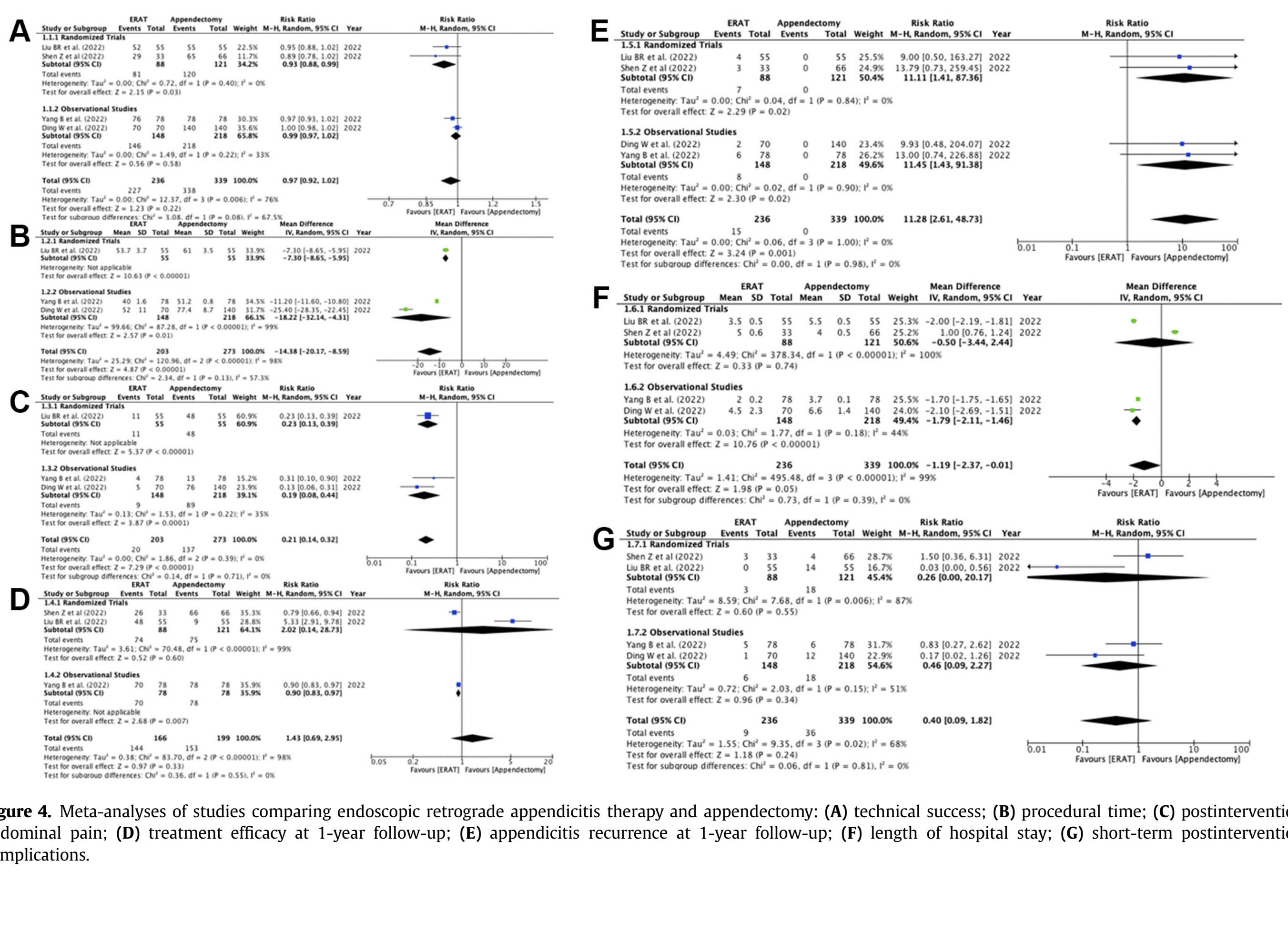

Figure 4. Meta-analyses of studies comparing endoscopic retrograde appendicitis therapy and appendectomy: **(A)** technical success; **(B)** procedural time; **(C)** postintervention abdominal pain; **(D)** treatment efficacy at 1-year follow-up; **(E)** appendicitis recurrence at 1-year follow-up; **(F)** length of hospital stay; **(G)** short-term postintervention complications.

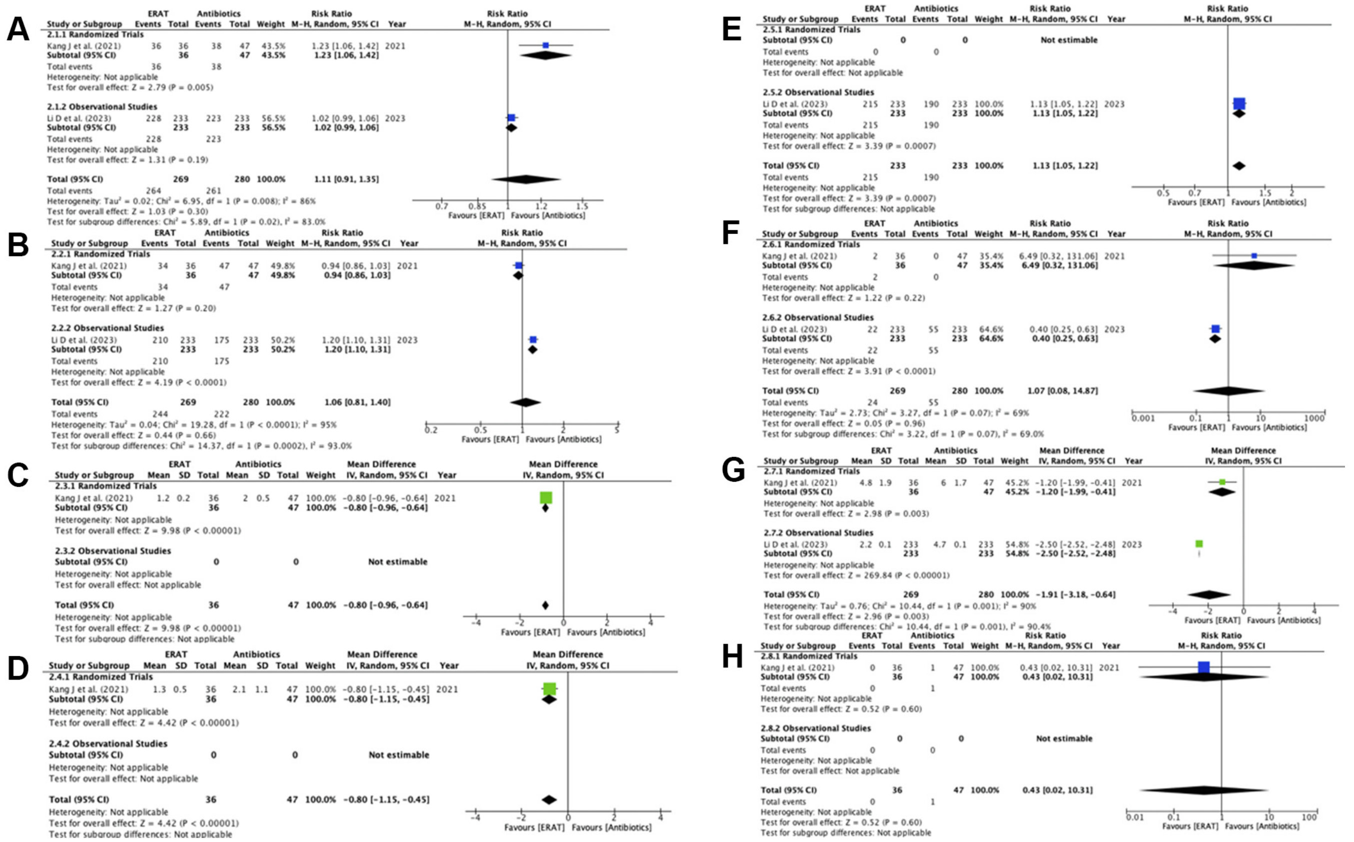

Figure 5. Meta-analyses of studies comparing endoscopic retrograde appendicitis therapy and conservative treatment with antibiotics: **(A)** technical success; **(B)** treatment efficacy at 1-year follow-up; **(C)** postintervention pain duration; **(D)** postintervention duration of clinical symptoms; **(E)** pain relief at 24 hours after treatment; **(F)** appendicitis recurrence; **(G)** length of hospital stay; **(H)** short-term postintervention complications.

(weight = 28.8%), appendectomy was associated with higher treatment efficacy at 1-year follow-up (RR = 0.86, 95% CI = 0.74–0.99).

Discussion

The results of our meta-analyses indicate that current data cannot prove the superiority of ERAT or appendectomy in the technical success rate of patients with uncomplicated acute appendicitis. However, notwithstanding that a high risk of imprecision and inconsistency might impact the final synthesis of evidence, ERAT proved superior to appendectomy in terms of procedural duration and postintervention abdominal pain. This finding accords with the recent literature, which reports that the most evident benefit of ERAT is the shorter duration of postintervention pain and hospital stay.[12,13,28] However, previous studies have also found that the immediate post-intervention rate after ERAT was significantly higher than that of appendectomy.[18] Nevertheless, taken together, these findings indicate that integration of ERAT into daily clinical practice is a sustainable strategy that can save a significant amount of medical and social resources in terms of time and cost.

Compared with non-operative treatment with antibiotics, which treat symptoms and stop bacterial growth, ERAT can remove the appendiceal obstruction responsible for the inflammatory process.[29] Many surgical bodies, including the American College of Surgeons and the World Society of Emergency Surgery, have described antibiotic treatment as an acceptable first-line therapy for uncomplicated acute appendicitis.[4,30] However, several RCTs and subsequent meta-analyses[9] have demonstrated that antibiotic therapy as a primary non-operative management strategy fails within 24 to 48 hours in approximately 10 % of cases and is associated with a 27.7 % recurrence rate within 1 year.

Lack of long-term follow-up was one of the main limitations to the widespread adoption of an antibiotic-first strategy until 2018, when Salminen et al published the 5-year follow-up results of the Appendicitis Acuta trial, which reported a 39.1 % recurrence rate within 5 years in patients initially treated with antibiotics.[8] Similarly, the Comparison of Outcomes of Antibiotic Drugs and Appendectomy Collaborative reported that 40 % of patients with uncomplicated appendicitis who had received initial antibiotic treatment required appendectomy within 1 year and 46 % within 2 years.[31]

These long-term follow-up studies support the feasibility of non-operative management with antibiotics as an alternative to surgery for uncomplicated appendicitis but raise concerns related to the high rates of appendicitis recurrence at long-term follow-up. However, the so-called "antibiotic-first" treatment strategy for uncomplicated acute appendicitis is associated with a higher risk of complicated appendicitis and a significant recurrence rate after antibiotic treatment in patients with appendicoliths.[32] In this context, ERAT is helpful for patients with appendicoliths, as it can flush them out of the appendiceal lumen and remove the obstruction, thus relieving symptoms and considerably reducing the recurrence rate of appendicitis.

Appendicitis is a common and severe situation during pregnancy because of the increased risk of fetal loss and perforation in the third trimester. Although laparoscopic appendectomy appears to be a relatively safe therapeutic option in pregnancy, it poses the risk of fetal loss and preterm delivery. In this regard, ERAT performed with contrast-enhanced ultrasound instead of endoscopic retrograde appendiceal radiography or using an intraductal cholangioscope is a promising alternative.[33]

In our pooled analysis, the rate of curative treatment within 1 year of follow-up after ERAT was 93.6%, which, to the best of our knowledge, is among the highest efficacy rates achieved by a nonsurgical treatment to date. In keeping with our results, previous analyses reported that up to 94 % of patients treated with ERAT experienced no recurrence during follow-up.[13,16] Another advantage of ERAT over antibiotic therapy is that ERAT rapidly eliminates painful symptoms, whereas patients experience variable pain levels during antibiotic treatment and after appendectomy. Compared to conservative therapy with antibiotics, ERAT has proven superior in reducing the duration of postintervention pain symptoms and length of hospital stay. Moreover, treatment efficacy outcomes, such as treatment efficacy at 1-year follow-up, appendicitis recurrence, and short-term complications, were comparable for ERAT and appendectomy.

A recent study exploring the general population's preference regarding operative or antibiotic treatment of uncomplicated appendicitis found that 49.2% of 254 participants preferred antibiotic treatment for uncomplicated appendicitis, and approximately 50% would accept a >50% recurrence risk within 1 year.[34] Since the publication of a previous sensitivity analysis survey of 1,728 respondents, which reported that 85.8% would have chosen laparoscopic appendectomy, 4.9% open appendectomy, and only 9.4% antibiotics alone,[35] the percentage of those who opt for a strategy of saving the appendix has been increasing. This increase makes it important for researchers to place increasing attention on alternative techniques to appendectomy.

Similarly, emerging evidence shows that an increasing number of parents prefer conservative management of uncomplicated appendicitis over surgical management for their children owing to fears of surgical risks and complications. Considering that the appendix plays an essential role in regulating immunity and the composition of the intestinal microbiome, all efforts should be made to preserve the organ in children during their period of development until solid evidence on the long-term consequences of appendectomy on the potentially increased risk of colorectal cancer and cardiovascular diseases has accumulated.[5] In this context, ERAT could produce the best outcomes for children.

Study Limitations

To our knowledge, our study was the first systematic review and meta-analysis to directly compare the ERAT technique with appendectomy and conservative therapy with antibiotics to treat uncomplicated acute appendicitis. Furthermore, it was the first analysis of the efficacy and safety outcomes of ERAT in the context of the therapeutic spectrum available for treating uncomplicated acute appendicitis performed in compliance with the GRADE methodology. As the first of its kind, our study faced several limitations that should be considered when reviewing our findings. One limitation is that the results are limited by a high risk of inconsistency due to the high statistical heterogeneity for several outcomes, such as procedural duration, treatment efficacy at 1-year follow-up, length of primary hospital stay, and postintervention abdominal pain, and risk of imprecision due to the small sample size for all the outcomes analyzed. However, the enrollment criteria in all studies we examined were similar except for the exclusion of patients with acute appendicitis complicated by an abscess on preoperative diagnostic imaging.

Another limitation was that 1 of the studies we analyzed enrolled only pediatric patients aged 1 to 13 years, preventing subgroup analysis based on population type (adult vs pediatric). However, we were able to perform a subgroup analysis comparing ERAT with laparoscopic and open appendectomy, which confirmed the clear advantage of ERAT compared with open appendectomy and the limited advantage of ERAT compared with laparoscopic appendectomy as the only advantage of ERAT over laparoscopic appendectomy was less postintervention pain.

A third disadvantage was that all ERAT studies were conducted in China, which may limit the generalizability of the findings to other populations or regions. As populations vary in patient characteristics, health care practices, and disease patterns, the results from a single country may not reflect the experience or applicability of ERAT globally. Moreover, depending on the research environment and funding sources, studies conducted in a single country may be influenced by that country's research priorities, funding availability, and clinical practices, which may introduce bias in study design, methodology, patient selection, and interpretation of results.

In conclusion, our systematic review and meta-analyses were the first attempt to summarize the scientific evidence on ERAT compared with appendectomy and conservative antibiotic therapy in uncomplicated acute appendicitis. With high treatment success, rapid postintervention abdominal pain relief, preservation of the appendix, and fast recovery, ERAT appears to be a novel, efficacious management strategy. However, further exploration of its efficacy is required using appropriately powered and designed RCTs. Until further evidence is accumulated, the advantages of ERAT in terms of reduced procedural times and shorter length of stay must be balanced with the increased risk of recurrence at 1-year follow-up, and treatment decisions should be made by discussion with patients.

Funding/Support

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

Conflict of interest/Disclosure

The authors have no conflicts of interests or disclosures to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [https://doi.org/10.1016/j.surg.2023.08.029].

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