World J Surg (2022) 46:1022–1038
https://doi.org/10.1007/s00268-022-06446-8

SCIENTIFIC REVIEW

Efficacy and Safety of Non-Operative Management of Uncomplicated Acute Appendicitis Compared to Appendectomy: An Umbrella Review of Systematic Reviews and Meta-Analyses

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Accepted: 1 January 2022 / Published online: 13 January 2022

Abstract

Background Non-operative management (NOM) of uncomplicated acute appendicitis (AA) has been introduced as an alternative to appendectomy. This umbrella review aimed to provide an overview of the efficacy and safety of NOM of uncomplicated AA in the published systematic reviews.

Methods This umbrella review has been reported in line with the PRISMA guidelines and umbrella review approach. Systematic reviews with and without meta-analyses on the efficacy of NOM of AA were analyzed. The quality of the reviews was assessed with the AMSTAR 2 tool. The main outcomes measures were the treatment failure and complication rates of NOM and hospital stay as compared to appendectomy.

Results Eighteen systematic reviews were included to this umbrella review. Eight reviews documented higher odds of failure with NOM, whereas two reviews revealed similar odds of failure. Six reviews reported lower odds of complications with NOM, six reported similar odds, and one reported lower odds of complications with surgery. Eight reviews reported similar hospital stay between NOM and appendectomy, one reported longer stay with NOM and another reported shorter stay with NOM. Pooled analyses showed that NOM was associated with higher treatment failure overall, in children-only, adults only, and RCTs-only meta-analyses. NOM was associated with lower complications overall, yet children-only and RCTs-only analyses revealed similar complications to surgery. NOM was associated with shorter stay in the overall and adult-only analysis, but not in the children-only analysis.

Conclusions NOM of AA is associated with higher treatment failure, marginally lower rate of complications and shorter stay than appendectomy.

Introduction

Acute appendicitis (AA) is the most common abdominal and surgical emergency and accounts for more than 40,000 hospital admissions in England with an incidence of 1.1 cases per 1000 people annually [1, 2]. AA commonly affects young and middle-age individuals, but no age is exempt. A male preponderance has been noticed, with a male to female ratio of 1.4:1 [3].

The diagnosis of AA can be made on the basis of clinical data; nonetheless the use of laboratory parameters such as total leukocyte count, scoring systems as Alvarado score, and imaging has been widely adopted [4]. To date,

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contrast CT scanning is considered the most accurate modality for the definitive diagnosis of AA with a sensitivity and specificity exceeding 90% [5].

Uncomplicated AA is treated with appendectomy which has been considered the gold standard treatment for such a condition for decades. Yet, non-operative management (NOM) of AA with antibiotics has been devised as a viable alternative to surgery [6]. Interestingly, NOM that involves supportive measures such as intravenous fluids and analgesics without antibiotics was found to yield similar treatment failure rates to NOM involving a 4-day course of antibiotics [7].

Large, multicenter randomized controlled trials that compared the outcome of NOM with appendectomy have concluded promising results after NOM. The CODA trial [8] described NOM with antibiotics as non-inferior to appendectomy on the basis of results of a standard health-status measure. However, about 30% of patients who received NOM had to undergo appendectomy by day 90 after ending treatment.

Although several clinical trials and meta-analyses have assessed the efficacy and safety of NOM of acute appendicitis, no consensus has been reached on the role of NOM in AA. The practice management guideline of the Eastern Association of Surgery for Trauma (EAST) could not make a recommendation for or against NOM as primary treatment for uncomplicated AA and found several limitations of the published literature, which necessitates more research on this topic [9].

Umbrella reviews are considered a tertiary level of research that assesses, cumulates and combines published systematic reviews in both quantitative and qualitative manner [10]. Since umbrella reviews compare the outcomes of systematic reviews relevant to the review question, considering only the highest level of evidence, namely other systematic reviews and meta-analyses for inclusion, the findings of umbrella reviews may be relied upon when developing guidelines and making a consensus [11].

The present work is the first umbrella review of NOM of acute appendicitis that aimed to combine the results of published systematic reviews to provide a broad overview of the efficacy and safety of NOM of uncomplicated AA in terms of the pooled rates of failure, recurrence, complications, and stay after NOM and to assess the level of evidence for clinical practice. The hypothesis and objective of this umbrella review was to provide the surgeons and patients with the risks and benefits of each approach (NOM versus appendectomy) to determine the tradeoffs in order to inform decision-making.

Methods

Reporting and registration

The protocol of this umbrella systematic review has been registered a priori in the International prospective register of systematic reviews (PROSPERO) under special identifier CRD42021255006. The reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12] and Umbrella review approach [11] were followed when reporting this umbrella systematic review.

Strategy of literature search

Databases searched

Two independent investigators (S.E., H.E.) performed an organized literature search of electronic databases including PubMed, Scopus, and Web of Science for published systematic reviews with or without meta-analysis on the outcome of NOM of uncomplicated AA. The databases were searched from their inception through April 2021. To increase the sensitivity of the search process, an Internet-based search using Google Scholar service was conducted.

Search keywords

Keywords used in the search process comprised "appendicitis," "appendix," "Uncomplicated," "treatment," "management," "non-operative," "conservative," antibiotics," "systematic review," "meta-analysis." In addition, the following medical subject headings (MeSH) terms were included in the literature search: (appendicitis), (conservative treatment), (meta-analysis).

Search strategy

The PubMed function "related articles" was activated to search for other relevant studies. In addition, we hand-searched the reference sections of the studies initially retrieved. A preliminary screening by title and abstract was performed then full-text screening of the studies was followed. The full text of the selected articles was reviewed by two independent investigators to check for eligibility.

Eligibility for inclusion

Studies deemed eligible for inclusion had to fulfill the following PICOS criteria:

- P (population): patients with established diagnosis of uncomplicated AA, whether children only, adults only, or both (mixed population).
- I (intervention): NOM of AA.
- C (comparator): appendectomy, whether by open or laparoscopic approach.
- O (outcome): treatment failure, complications, and length of hospital stay.
- S (study design): systematic reviews with or without concurrent meta-analysis.

We excluded irrelevant articles, articles of other designs, editorials, and narrative reviews. Only articles published in English were included to this review.

Assessment of methodologic quality and risk of BIAS

The quality of each study was assessed by two authors independently using the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) tool [13]. The AMSTAR 2 tool is a 16-item checklist used to critically rate the quality of an individual systematic review as critically low, low, moderate, or high. (https://amstar.ca/Amstar_Checklist.php). Discrepancies in outcome interpretation were resolved by consensus and adjudication by a third reviewer.

Grading the evidence

The following criteria [14] were used to assess the grade of evidence of the included meta-analyses:

- Convincing evidence (class I): > 1000 cases, significant combined associations for random-effects calculation ($p < 10^{-6}$), no evidence of small-study effects, no evidence of excess of significance, and no large between-study heterogeneity ($I^2 < 50\%$)
- Highly suggestive evidence (class II): > 1000 cases, significant combined associations for random-effects calculation ($p < 10^{-6}$), and the largest study with 95%CI excluding the null value.
- Suggestive evidence (class III): > 1000 cases and significant combined associations for random-effects calculation ($p < 10^{-3}$).
- Weak evidence (class IV): Other associations with $p < 0.05$; non-significant associations with $p > 0.05$.

Data extraction

Two authors reviewed the full-text of the studies included independently and extracted the following data points from each systematic review into a standardized form for data extraction:

- Authors and year of publication.
- Databases searched and inclusion criteria.
- Number and type of studies included in each systematic review.
- Total number of patients, number who had NOM, and number who had appendectomy.
- Failure rate of NOM.
- Complications after NOM and appendectomy.
- Length of hospital stay in days.
- Effect estimates for failure, complications, and hospital stay.

Outcomes

The primary outcome of this umbrella review was the failure rate of NOM defined as the need for appendectomy either within the index admission or after discharge for increasing or persistent symptoms or development of serious complications such as perforation warranting surgery. Recurrence of AA was defined as an episode of appendicitis being diagnosed again after completion of the initial NOM and discharge of patient. Secondary outcomes were the complication rate of NOM and of appendectomy and length of hospital stay.

Data analysis

Continuous variables were expressed as mean ± standard deviation (SD), or median and normal range. Categorical variables were expressed as numbers and proportions. Review Manager 5.4 was used for pooling of the effect estimate of treatment failure, complications, and hospital stay in the published meta-analyses. The summary (pooled) effect estimates and 95%confidence interval (CI) for each outcome were calculated by combining the effect estimates reported in previously published meta-analyses using the DerSimonian–Laird random-effect model. The summary effect estimates were expressed as risk ratio (RR) for failure and complications and standardized mean difference (SMD) for hospital stay.

Stratified and subgroup analyses were performed, with estimates summarized by patient population (adults only, children only, mixed population) and type of studies included (meta-analyses of RCTs).

Statistical heterogeneity was assessed by the p value of the Higgins inconsistency (I^2) statistics and the χ2-based Cochran's Q test. Heterogeneity was considered low if $I^2 < 25\%$, moderate if I^2 was 25–75%, and high if $I^2 > 75\%$. P values less than 0.05 were considered significant.

Excess statistical significance was assessed using The Ioannidis' excess significance test [15]. The number of the

observed (O) positive studies ($p < 0.05$) in each meta-analysis was compared to the expected number of studies with significant results (E). The expected number of studies with significant results (E) was calculated by summation of the statistical power estimates for each study in a meta-analysis. To estimate the statistical power of each individual study, we used the effect size of the largest study that had the smallest standard error in each included meta-analysis [16]. Excess statistical significance was determined for each meta-analysis when O was greater than E with a two-sided $p < 0.10$.

Publication bias and small-study effect were assessed using a funnel plot of the standard error of each outcome against the rate of the outcome in the studies reviewed. A straight vertical line in the plot indicates the zone in which 95% of studies should be if there were no publication biases. Furthermore, Egger's regression test was used to investigate for small-study effect where smaller studies tend to provide larger effect estimates than larger studies. In random-effects meta-analysis, $p < 0.1$ indicated the presence of small-study effects.

A random-effect meta-regression model was used weighing the studies by their within-study variance and the degree of heterogeneity. The inter-study heterogeneity was assessed in terms of differences in patients' age, sex, type of population (children vs adult vs mixed), total leucocyte count, follow-up duration, and quality of the study. The statistical significance of each examined variable was expressed using slope coefficient (SE) and p value. P value < 0.1 was considered statistically significant.

Results

Characteristics of the reviews included

After screening of 487 non-duplicate articles, 18 systematic reviews with or without meta-analysis [17–34] published between 2011 and 2021 were included to the present umbrella review. The PRISMA flowchart for study selection is shown in Fig. 1.

Databases searched: PubMed/MEDLINE were searched in all (100%) systematic reviews, Embase in 13 (72.2%) reviews, Cochrane central register/library in 11 (61.1%) reviews, Scopus in three reviews (16.7%), and Web of Science in three reviews (16.7%).

Number and type of studies included: The median number of studies included in each review was 6 (range, 4–21). Eight systematic reviews included RCTs only and ten included both RCTs and cohort studies.

Patient population: Six (33.3%) systematic reviews involved adults only, four (22.2%) involved children only, and eight (44.4%) included both adults and children. The median number of patients included to the reviews was 1430 (range, 320–67,688) patients. The median percentage of patients who had NOM was 48.2% (range, 8.5%–69.5%).

Appraisal of quality and level of evidence: Overall, ten systematic reviews were of low quality, five of moderate quality, two of high quality and one of critically low quality. Regarding the level of evidence, 10 studies entailed weak evidence, six entailed suggestive evidence, and two entailed highly suggestive evidence.

The databases searched, inclusion criteria, number and types of studies included, patient population, and quality of the published systematic reviews are summarized in Tables 1 and 2.

Outcome of NOM

Efficacy of treatment: The median failure rate of NOM across the systematic reviews was 25% (range, 6.9%–37.4%). Recurrence of symptoms within one year after NOM occurred in a median of 18.3% of patients (range, 10.8–26.5%). Eight reviews documented higher odds of failure with NOM as compared to appendectomy, whereas two systematic reviews revealed similar odds of failure. The median follow-up across the systematic reviews ranged from 12 to 48 months.

Complications: The median complication rate after NOM was 6.9% (range, 1–32.6%) and the median complication rate after appendectomy was 10.5% (range, 2–27%). Six reviews reported lower odds of complications with NOM as compared to surgery, six reported similar odds, and one reported lower odds of complications with surgery.

Hospital stay: Eight reviews reported similar hospital stay between NOM and appendectomy, one reported longer stay with NOM and another reported shorter stay with NOM.

A summary of the effect estimates used for treatment failure, complications, and hospital stay in each systematic review is shown in Table 3. The quantitative outcomes of the systematic reviews that compared NOM with appendectomy are summarized in Table 4. Figure 2 shows a visual representation of the outcome of the published systematic reviews.

Summary effect estimates for the published meta-analyses with subgroup analyses

NOM was associated with higher treatment failure on pooling the effect estimates of all published meta-analyses and on subgroup analysis of meta-analyses that included children only, adults only, and RCTs only. (Fig. 3).

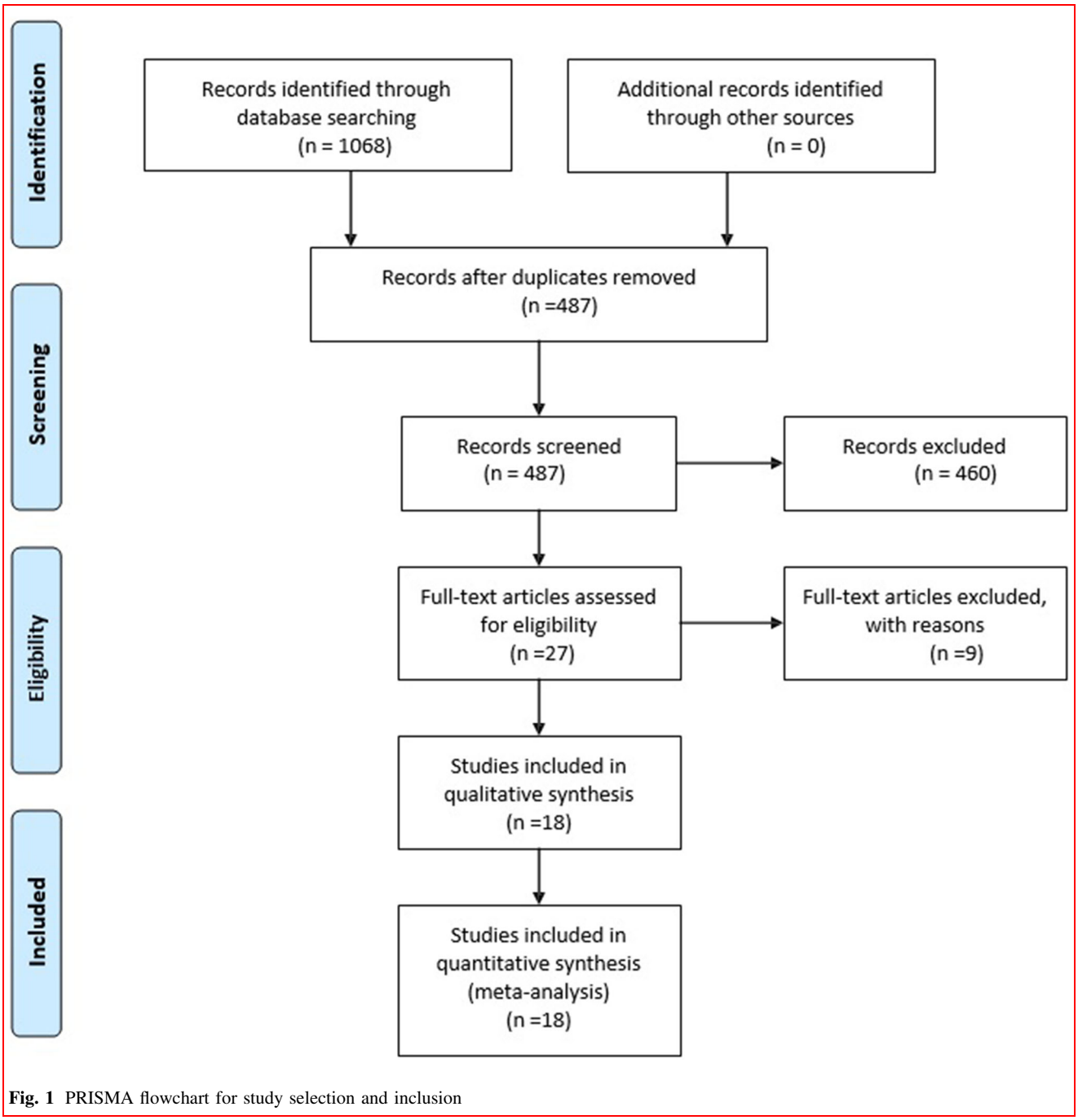

Fig. 1 PRISMA flowchart for study selection and inclusion

NOM was associated with lower complications on pooling the effect estimates of all published meta-analyses. However, subgroup pooling of meta-analyses including children only and RCTs only revealed similar risk of complications between NOM and appendectomy. (Fig. 4).

NOM was associated with shorter stay in the overall analysis and subgroup analyses of adults and RCTs, however; the length of stay was similar in the subgroup analysis of children only. (Fig. 5).

The inclusion of both children and adult population in the same study or meta-analysis may not be precise. Therefore, we reported the outcomes in terms of the population included, in addition to the overall analysis. As for treatment failure, all analyses showed a lower risk of failure with surgery, however; the degree of heterogeneity was high in the adult-only and overall analyses, whereas the children-only analysis included only one meta-analysis, and thus did not exhibit heterogeneity. While the overall analysis implied a lower risk of complications with NOM,

Table 1 Inclusion period, databases searched, inclusion criteria, and quality of the published systematic reviews

Studies	Inclusion period	Databases searched	Inclusion criteria	AMSTAR2	Level of evidence
Emile SH et al. [17]	Inception-Nov 2020	PubMed, Scopus, EMBASE, and Web of Science	Single-arm case series, cohort, and comparative studies that compared the outcome of NOM with appendectomy with at least five patients, in the setting of COVID-19	Low	Suggestive
Maita S et al. [18]	Inception-May 2019	PubMed, Embase, Cochrane and Web of Science	All studies focusing on the initial NOM and comparing antibiotic treatment with appendectomy for acute nonperforated appendicitis in children	Critically low	Weak
Prechal et al. [19]	Nov 1965 to Jan 2016	PubMed, Cochrane Library, Web of Science, trial registries	RCTs including patients $\geq$ 18 years with acute uncomplicated appendicitis which compared NOM with any form of appendectomy	Low	Suggestive
Podda et al. [20]	Inception-Aug 2018	MEDLINE (via PubMed), the Cochrane, EMBASE	RCTs, prospective and retrospective cohort studies comparing NOM and appendectomy for acute uncomplicated appendicitis in adults and children	Moderate	Suggestive
Poprom et al. [21]	Inception-July 2017	Medline and Scopus	RCTs comparing NOM and appendectomy for acute uncomplicated appendicitis in adults and children reporting one of: success, complications, recurrence, and length of stay	Moderate	Suggestive
Kessler et al. [22]	1950–2017	MEDLINE (via PubMed), Ovid Embase, the Cochrane library	Studies that assessed both appendicectomy and the NOM of acute uncomplicated appendicitis in children of less than 18 years of age	Low	Weak
Talutis et al. [23]	1996–2017	PubMed	Prospective studies and trials that compared operative and antibiotic management of acute appendicitis in adults and pediatric populations	Low	Weak
Xu et al. [24]	1946–2016	MEDLINE, Embase	All studies focusing on the NOM of acute uncomplicated appendicitis in children	Low	Weak
Gorter et al. [25]	Inception-Jan 2017	MEDLINE, Embase	All studies investigating initial nonoperative treatment strategy for Uncomplicated appendicitis in patients younger than eighteen years (children)	Low	Weak
Sakran et al. [26]	Inception-Jan 2017	PubMed, Cochrane, and Scopus	RCTs that compared NOM and appendectomy in adult patients with uncomplicated acute appendicitis	Low	Highly suggestive
Podda et al. [27]	Inception-May 2016	PubMed, EMBASE, Medline, Google Scholar and Cochrane Central Register	RCTs comparing NOM and surgical treatment as primary treatment for uncomplicated acute appendicitis in adults irrespective of language and publication status	Low	Suggestive
Findlay et al. [28]	Inception-May 2016	PubMed, EMBASE, Cochrane Central Register of Controlled Trials	RCTs randomizing patients > 16 years to NOM or appendectomy for uncomplicated acute appendicitis	Low	Weak
Harnoss et al. [29]	Inception-Jan 2015	MEDLINE (via PubMed), EMBASE, the Cochrane Library	RCTs and nonrandomized cohort studies assessing NOM versus surgical treatment for uncomplicated acute appendicitis in adults	High	Highly suggestive
Ehlers et al. [30]	Inception-June 2015	PubMed (Medline) and EMBASE	RCTs that compared antibiotics with appendectomy for acute appendicitis	Moderate	Weak
Sallinen et al. [31]	Jan 2011-Dec 2015	MEDLINE, Embase and the Cochrane Central Register of Controlled Trials	RCTs that compared antibiotic treatment with appendicectomy in patients with suspected acute non-perforated appendicitis	Moderate	Weak
Wilms et al. [32]	Inception-June 2011	MEDLINE, Embase and the Cochrane Central Register of Controlled Trials, Prospective trial registries	RCTs and Quasi RCT that compared NOM antibiotic treatment with appendectomy in patients with suspected acute appendicitis	High	Weak

Table 1 continued

Studies	Inclusion period	Databases searched	Inclusion criteria	AMSTAR2	Level of evidence
Liu et al. [33]	1970–2009	MEDLINE	Studies that compared NOM with appendectomy in patients with acute uncomplicated appendicitis	Low	Suggestive
Ansaloni et al. [34]	1966–2009	MEDLINE, Embase and the Cochrane Central Register of Controlled Trials, Cochrane Library	RCTs comparing surgery with NOM antibiotic therapies for the treatment of adult patients with acute appendicitis	Moderate	Weak

*NOM = non-operative management *RCTs = randomized controlled trials

Table 2 Number and type of studies and patient population in the published systematic reviews

Studies	Number of studies	Type of studies	Population	Total number of patients	% NOM	Follow up in months
Emile SH et al. [17]	14	8 Retrospective and 6 Prospective	Mixed	2140	44.8	30
Maita S et al. [18]	21	8 Retrospective and 13 Prospective	Children	67,688	8.5	14
Prechal et al. [19]	5	5 RCTs	Adults	1430	50.8	13.2
Podda et al. [20]	20	8 RCT, 4 Retrospective, 8 Prospective	Mixed	3618	48.2	12
Poprom et al. [21]	9	9 RCTs	Mixed	2108	Not reported	12
Kessler et al. [22]	5	1 RCT, 1 Retrospective, 3 Prospective	Children	442	42.8	12–48
Talutis et al. [23]	11	4 RCTs, 7 Prospective	Mixed	2422	50.4	12–24
Xu et al. [24]	15	1 RCT, 4 Retrospective, 8 Prospective	Children	1163	69.4	12
Gorter et al. [25]	5	1 RCT, 2 Retrospective, 2 Prospective	Children	320	45.9	12
Sakran et al. [26]	5	5 RCTs	Adults	1430	50.8	12
Podda et al. [27]	5	5 RCTs	Adults	1351	46.8	18.5
Findlay et al. [28]	6	6 RCTs	Adults	1724	48.5	12
Harnoss et al. [29]	8	4 RCTs, 4 Cohort	Adults	2551	51.4	12
Ehlers et al. [30]	6	6 RCTs	Mixed	1720	48.5	12
Sallinen et al. [31]	5	5 RCTs	Mixed	1072	47.6	12
Wilms et al. [32]	5	5 RCTS and Quasi RCTs	Mixed	901	46.1	1–12
Liu et al. [33]	6	4 RCTs, 1 Prospective, 1 Retrospective	Mixed	1201	36.1	14.5
Ansaloni et al. [34]	4	4 RCTs	Adults	741	52.6	12

*NOM = non-operative management *RCTs = randomized controlled trials

Table 3 Effect estimates of treatment failure, complications, and hospital stay in the published systematic reviews

Studies	Treatment failure	Complications	Hospital stay
Emile SH et al. [17]	NA	Lower with NOM (OR = 0.36, 95%CI: 0.14–0.93, p = 0.03, I2 = 57.9%)	NA
Maita S et al. [18]	NA	Similar (OR = 0.64, 95%CI: 0.29- 1.39)	Similar (MD = 0.07, 95%CI:—0.8–0.66)
Prechal et al. [19]	Lower failure with surgery (RR = 0.65, 0.55–0.76, I2 = 85%)	Similar (RR = 0.98, 0.82–1.18, I2 = 82%)	Similar (MD = 0.11, 95%CI: -0.22–0.43, I2 = 68%)
Podda et al. [20]	Lower failure with surgery (OR = 0.12, 0.06–0.24, I2 = 81%)	Lower after NOM (OR = 0.41; 95% CI 0.22–0.77; P = 0.006; I2 = 68%)	Similar (SMD = 0.55; 95%CI:1.49–0.39; P: 0.25; I2: 99%)
Poprom et al. [21]	Similar (OR = 0.70; 95%CI: 0.49–1.01)	Lower with NOM 0.39 (95%CI: 0.22, 0.70)	Similar (MD = 0.17, 95%CI: -0.23, 0.56)
Kessler et al. [22]	Lower with surgery (RR = 0.77, 95% CI: 0.71- 0.84; p < 0.001)	Similar (RR 1.07, 95% CI 0.26—4.46)	NA
Xu et al. [24]	Similar (OR = 1.5; 95%CI = 0.38–5.9, p = 0.56, I2 = 39.2%)	NA	NA
Sakran et al. [26]	Lower with surgery (RR = 0.68; 95% CI: 0.60–0.77; p < 0.001, I2 = 77.5%)	Lower with NOM (RR = 0.32; 95% CI: 0.24–0.43; p < 0.001, I2 = 34%)	Similar (WMD = 0.20; 95% CI: − 0.16–0.56; p = 0.285, I2 = 70.5%)
Podda et al. [27]	Lower with surgery (OR = 0.07, 95% CI: 0.02–0.24, P < 0.0001, I2 = 70%	Similar (RR = 0.51, 95% CI: 0.13–1.95, p = 0.32; I2 = 84%)	Similar (SMD = 1.54, 95% CI: 0.47–3.54; P = 0.13, I2 = 99%)
Findlay et al. [28]	Lower with surgery (RR = 0.92; 95% CI 0.87- 0.97; p = 0.002, I2 = 30%)	Similar (RR = 0.41, 95%CI: 0.13–1.3%, p = 0.13, I2 = 76%)	Longer with NOM (MD = 0.48, 95%CI: 0.1–0.85, p = 0.01, I2 = 52%)
Harnoss et al. [29]	Lower with surgery (RR 0.75; 95% CI 0.70–0.79; P = 0.00001; I2: 62%)	Lower with surgery (RR: 0.78; 95% CI 0.72–0.83; P < 0.00001; I2:16.2%)	Similar (RR-0.73; 95% CI-2.69–1.23; P = 0.47; I2 = 0%)
Sallinen et al. [31]	NA	Similar (RD = – 2·6; 95%CI: 6·3, 1·1, p = 0.16, I2 = 26%)	Similar (MD = –3·58; 95%CI: 8·27, 1·11, p = 0.13, I2 = 95%)
Wilms et al. [32]	NA	NA	Shorter with NOM (OR = 0.66; 95% CI: 0.44–0.87, p < 0.001, I2 = 33%)
Liu et al. [33]	NA	Lower with NOM (OR = 0.31, 95%CI:0.19- 0.49, p = 0.001)	NA
Ansaloni et al. [34]	Higher with NOM (OR = 6.01, 95% CI = 4.2–8.4)	Higher with surgery (OR = 1.92; 95%CI: 1.30–2.85)	NA

*RR = risk ratio *OR = odds ratio *MD = mean difference *NOM = non-operative management

the children-only and adult-only analyses showed similar risk. Again, there was high degree of heterogeneity in the adult-only and overall analysis, while the children-only analysis had no heterogeneity. The overall and adult-only analysis showed shorter stay with NOM, yet the children-only analysis showed similar stay. The degree of heterogeneity of hospital stay was generally moderate, and was not present in the children-only analysis (Table 5).

Meta-regression of factors associated with failure and recurrence after NOM

Younger age (SE = 0.198, p = 0.037), male sex (SE = 0.0001, p = 0.06), mixed patient population (SE = 0.172, p < 0.001), and longer follow-up (SE = 0.01, p = 0.07) were associated with higher failure rates, whereas higher leucocyte count (SE = 0.04, p = 0.34) was not associated with failure.

Higher leucocyte count (SE = 0.219, p = 0.019) and male sex (SE = 0.0001, p = 0.004) were associated with

Table 4 Tabular representation of the quantitative outcomes of the systematic reviews

Outcome	Systematic review	Studies/patients	Findings	ES	Upper CI	Lower CI	P value	Heterogeneity
Treatment failure	Prechal et al. [19]	5/1430	Lower with surgery	RR = 0.65	0.55	0.76	*< 0.0001*	I^2 = 85%
	Podda et al. [20]	30/3618	Lower with surgery	OR = 0.12	0.06	0.24	*< 0.0001*	I^2 = 81%
	Poprom et al. [21]	9/2108	Similar	OR = 0.70	0.49	1.01	NA	NA
	Kessler et al. [22]	5/422	Lower with surgery	RR = 0.77	0.71	0.84	*< 0.0001*	NA
	Xu et al. [24]	15/1163	Similar	OR = 1.5	0.38	5.9	*0.56*	39.2%
	Sakran et al. [26]	5/1430	Lower with surgery	RR = 0.68	0.60	0.77	*< 0.0001*	I^2 = 77.5%
	Podda et al. [27]	5/1351	Lower with surgery	OR = 0.07	0.02	0.24	*< 0.0001*	I^2 = 70%
	Findlay et al. [28]	6/1724	Lower with surgery	RR = 0.92	0.87	0.97	*0.002*	I^2 = 30%
	Harnoss et al. [29]	8/2551	Lower with surgery	RR 0.75	0.70	0.79	*0.00001*	I^2 = 62%
	Ansaloni et al. [34]	4/741	Higher with NOM	OR = 6.01	4.2	8.4	NA	NA
Complications	Emile SH et al. [17]	14/2140	Lower with NOM	OR = 0.36	0.14	0.93	*0.03*	I^2 = 57.9%
	Maita S et al. [18]	21/67688	Similar	OR = 0.64	0.29	1.39	NA	NA
	Prechal et al. [19]	5/1430	Similar	RR = 0.98	0.82	1.18	0.16	I^2 = 82%
	Podda et al. [20]	30/3618	Lower with NOM	OR = 0.41	0.22	0.77	*0.006*	I^2 = 68%
	Poprom et al. [21]	9/2108	Lower with NOM	OR = 0.39	0.22	0.7	NA	NA
	Kessler et al. [22]	5/422	Similar	RR 1.07	0.26	4.46	NA	NA
	Sakran et al. [26]	5/1430	Lower with NOM	RR = 0.32	0.24	0.43	*< 0.0001*	I^2 = 34%
	Podda et al. [27]	5/1351	Similar	RR = 0.51	0.13	1.95	0.32	I^2 = 84%
	Findlay et al. [28]	6/1724	Similar	RR = 0.41	0.13	1.3	0.13	I^2 = 76%)
	Harnoss et al. [29]	8/2551	Lower with surgery	RR: 0.78	0.72	0.83	*< 0.0001*	I^2:16.2%
	Sallinen et al. [31]	5/1072	Similar	RD = –2.6	6.3	1.1	0.16	I^2 = 26%
	Liu et al. [33]	6/1201	Lower with NOM	OR = 0.31	0.19	0.49	0.001	NA
	Ansaloni et al. [34]	4/741	Higher with surgery	OR = 1.9	1.30	2.85	NA	NA

Table 4 continued

Outcome	Systematic review	Studies/patients	Findings	ES	Upper CI	Lower CI	P value	Heterogeneity
Hospital stay	Maita S et al. [18]	21/67688	Similar	MD = 0.07	.8	0.66	NA	
	Prechal et al. [19]	5/1430	Similar	MD = 0.11	0.22	0.43	0.53	I^2 = 68%
	Podda et al. [20]	30/3618	Similar	MD = 0.55	1.49	0.39	0.25	I^2 = 99%
	Poprom et al. [21]	9/2108	Similar	MD = 0.17	0.23	0.56	NA	NA
	Sakran et al. [26]	5/1430	Similar	SMD = 0.20	0.16	0.56	0.285	I^2 = 70.5%
	Podda et al. [27]	5/1351	Similar	SMD = 1.54	0.47	3.54	0.13	I^2 = 99%
	Findlay et al. [28]	6/1724	Shorter with surgery	MD = 0.48	0.10	0.85	*0.01*	I^2 = 52%
	Harnoss et al. [29]	8/2551	Similar	RR = 0.73	2.69	1.23	0.47	I^2 = 0%
	Sallinen et al. [31]	5/1072	Similar	MD = 3.58	8.27	1.11	0.13	I^2 = 95%
	Wilms et al. [32]	5/901	Shorter with NOM	OR = 0.66	0.44	0.87	*< 0.0001*	I^2 = 33%

*RR = risk ratio *OR = odds ratio *MD = mean difference *NOM = non-operative management *ES = effect estimate *CI = confidence interval

higher recurrence rates, whereas younger age (SE = 0.004, $p = 0.136$), and mixed population (SE = 0.053, $p = 0.211$) were not associated with recurrence.

Publication bias and small-study effect

As shown in Fig. 6, there was significant publication bias in regards to "Treatment failure" (Egger's intercept = 1.34, 95%CI: 1.91– 0.77, $p = 0.001$), whereas there was no publication bias in regards to the outcomes "Hospital stay" (Egger's intercept = 0.76, 95%CI: 0.22–1.74, $p = 0.11$) and "Complications" (Egger's intercept = 25, 95%CI: 1.9– 1.39, $p = 0.73$).

Table 6 illustrates the results of the test for excess significance for each outcome. Overall, 18 out of 31 total associations had a greater number of observed positive studies than the number of expected positive studies, yet only one association (complication, Emile et al.) had statistical evidence ($p < 0.1$) of excess statistical significance.

Discussion

The present umbrella review aimed to provide an overview of the current evidence on the efficacy and safety of NOM for uncomplicated AA. Over the span of 10 years, 18 systematic reviews were published with a median of six studies per review. This observation reflects the increasing interest in NOM as an alternative to appendectomy, perhaps to avoid the adverse effects of surgery and to preserve the immune function of the appendix [35]. It was notable that PubMed/MEDLINE and Embase were the most commonly searched databases in the systematic reviews included, whereas a few reviews searched Scopus, despite being the largest abstract and citation database of peer-reviewed literature [36].

Less than half of the systematic reviews included level I evidence of RCTs only, whereas 10 systematic reviews included both RCTs and cohort studies which may not be statistically reliable. Overall, more than 50% of the systematic reviews on NOM for AA were of low quality and entailed weak evidence. Only two reviews were of high quality and two were credible and entailed highly suggestive evidence. This calls for higher quality future trials on the role of NOM of AA to avoid the shortcomings of the present trials.

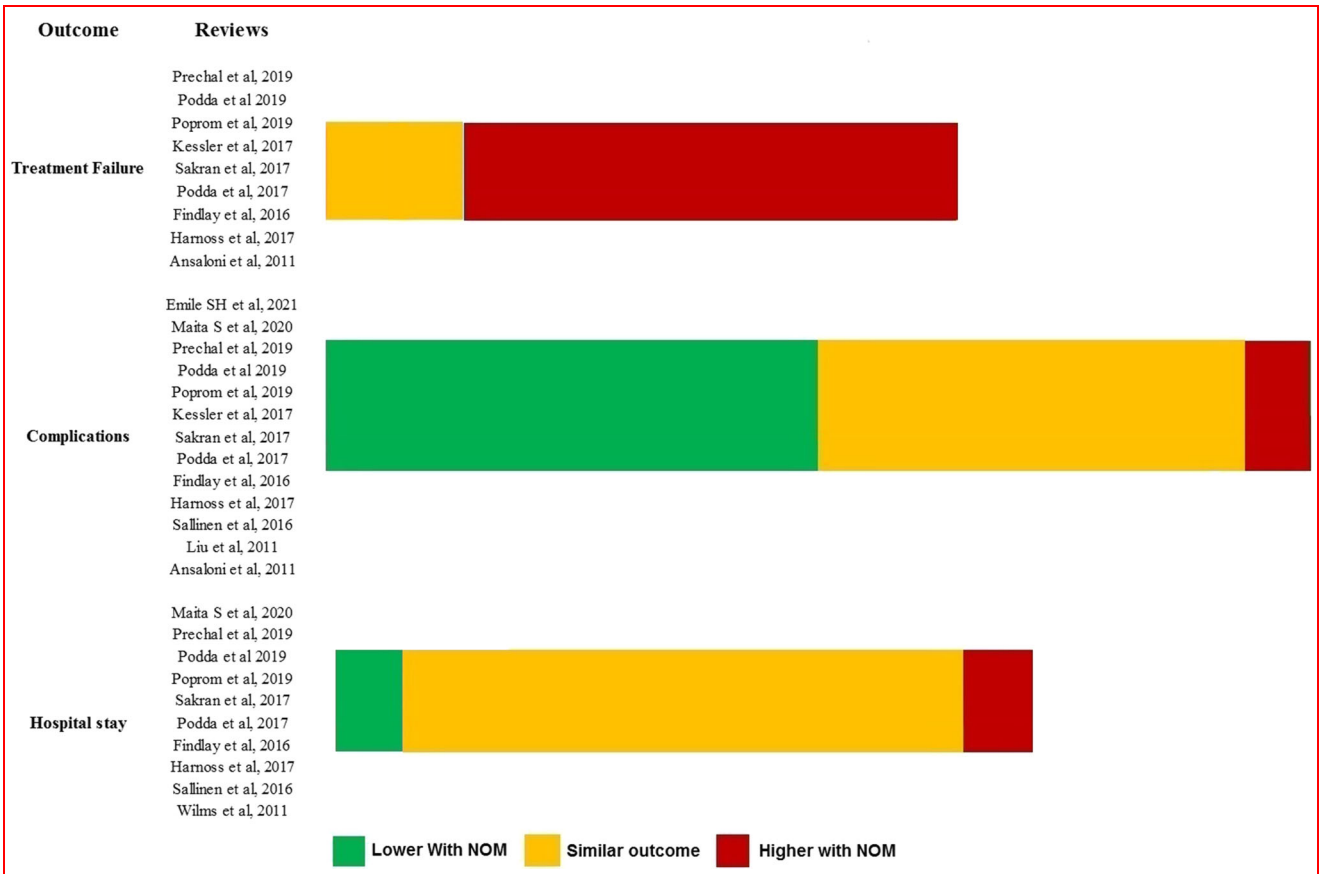

Fig. 2 Visual representation of the qualitative outcome of the umbrella review; the longer the colored part of each bar, the higher the number of studies supporting the conclusion

NOM of AA is suggested as an alternative to appendectomy that can be similarly effective in controlling the symptoms, yet associated with less complications [37]. Therefore, the main outcomes of this umbrella review were treatment effectiveness and complications of NOM. The median rate of treatment failure of NOM was 25% and can reach up to 37.4% [19]. Almost all meta-analyses documented a higher likelihood of failure with NOM, as compared to appendectomy. The exception was a network meta-analysis [21] that reported similar odds of failure between NOM and surgery and this difference may be explained by the small number of studies included in the direct meta-analysis of failure of NOM (n = 3).

The higher likelihood of failure of NOM compared to surgery was further ascertained on subgroup analyses of meta-analyses that included pediatric population only, adult population only, and RCTs alone. This finding does make sense, because surgery effectively removes the inflamed appendix altogether, and thus eradicates the source of symptoms. On the other hand, NOM tends to resolve the acute inflammation in the appendix, however; the retained appendix may still exhibit some degree of inflammation and thus symptoms may persist or recur and moreover some complications such as appendicular mass may develop.

Having a median treatment failure rate of 25% and a median recurrence of symptoms rate of 18%, NOM may not be the optimal definitive treatment of AA. Nonetheless, NOM can be considered as a short-term treatment of AA in certain conditions where access to well-equipped operation theaters is not feasible or when the patient is not considered fit for surgery. Recently, another setting where NOM of AA may be a feasible treatment option has emerged, the COVID-19 pandemic. The role of NOM of AA during the pandemic was discussed in one meta-analysis [17] that concluded that NOM of AA may be a safe, short-term alternative to surgery in the setting of COVID-19.

As regards to the complication rates, the median complication rate of NOM was approximately 7% as compared to 10.5% after appendectomy. While some meta-analyses concluded lower complications after NOM, an equal number concluded similar odds of complications after both treatment modalities. One novel finding of this umbrella review is that while the risk ratio of complications in the

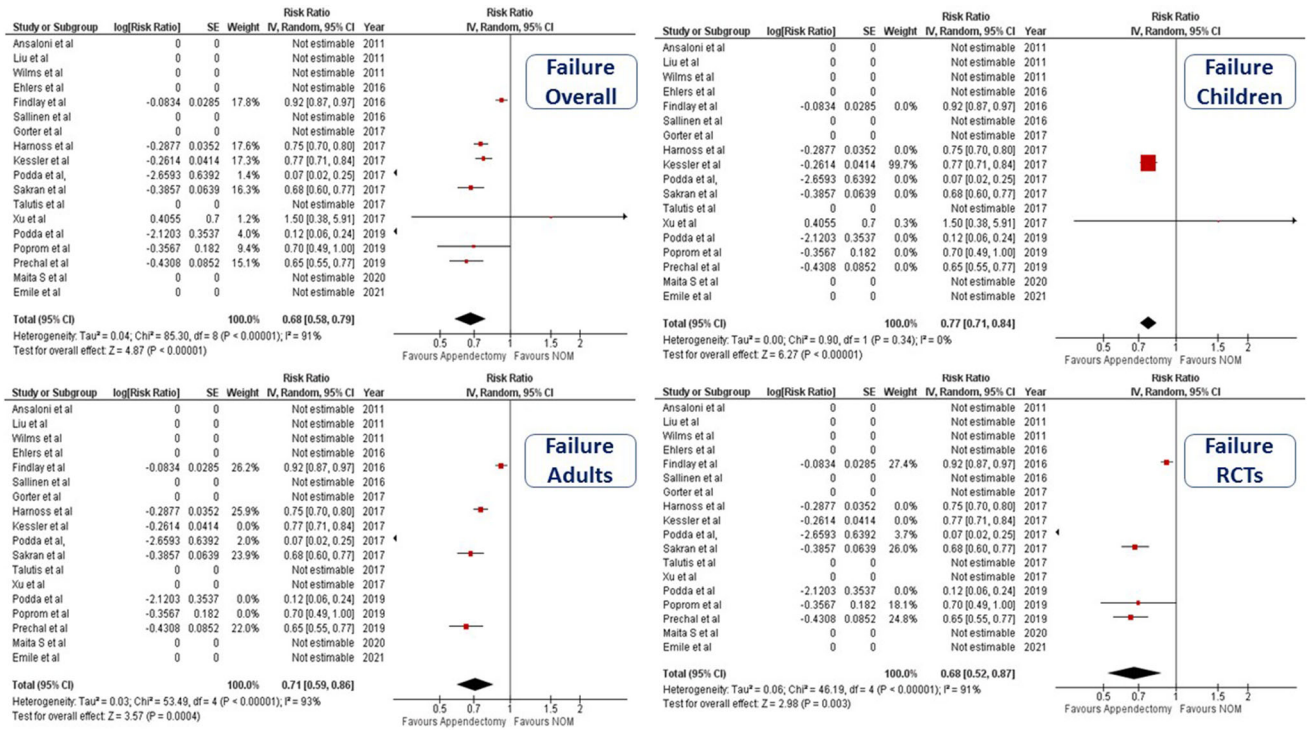

Fig. 3 Forest plot illustrating the risk ratio of treatment failure along with 95% confidence interval and degree of heterogeneity (Overall analysis and subgroup analyses of children-only, adults-only, and RCTs only meta-analyses)

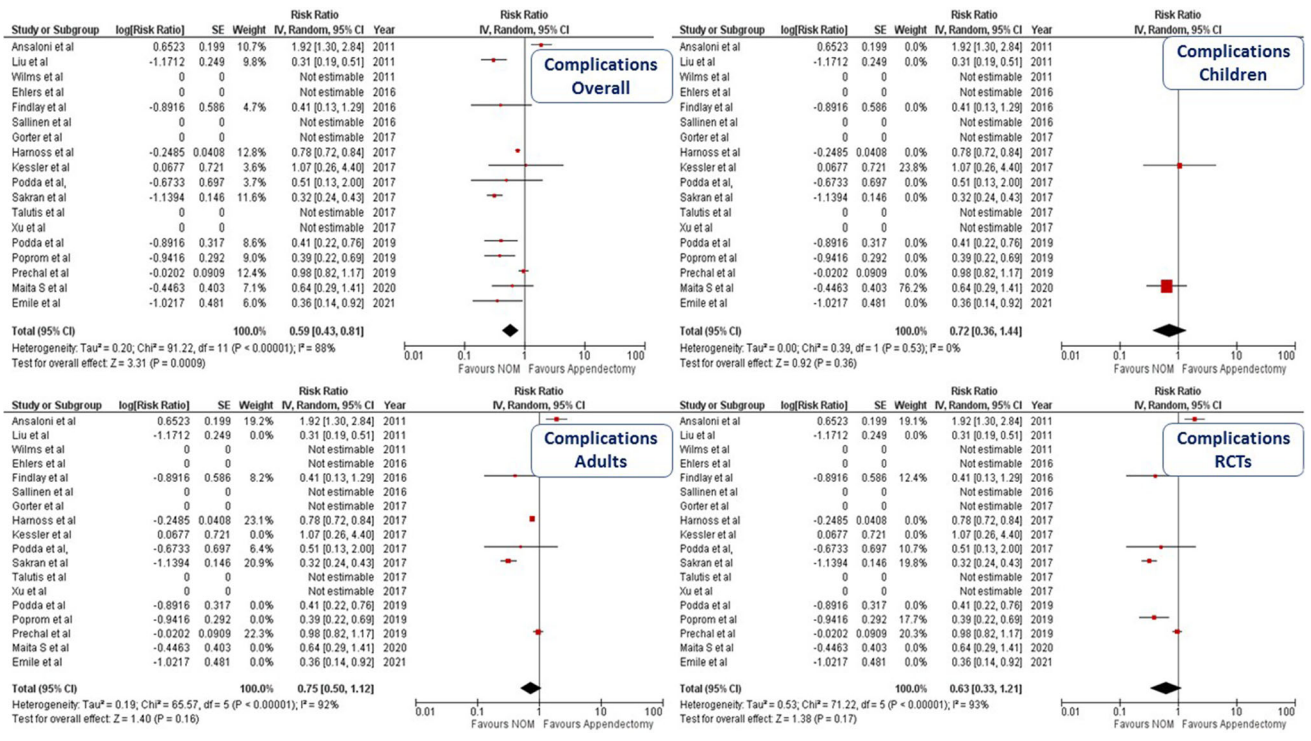

Fig. 4 Forest plot illustrating the risk ratio of complications along with 95% confidence interval and degree of heterogeneity (Overall analysis and subgroup analyses of children-only, adults-only, and RCTs only meta-analyses)

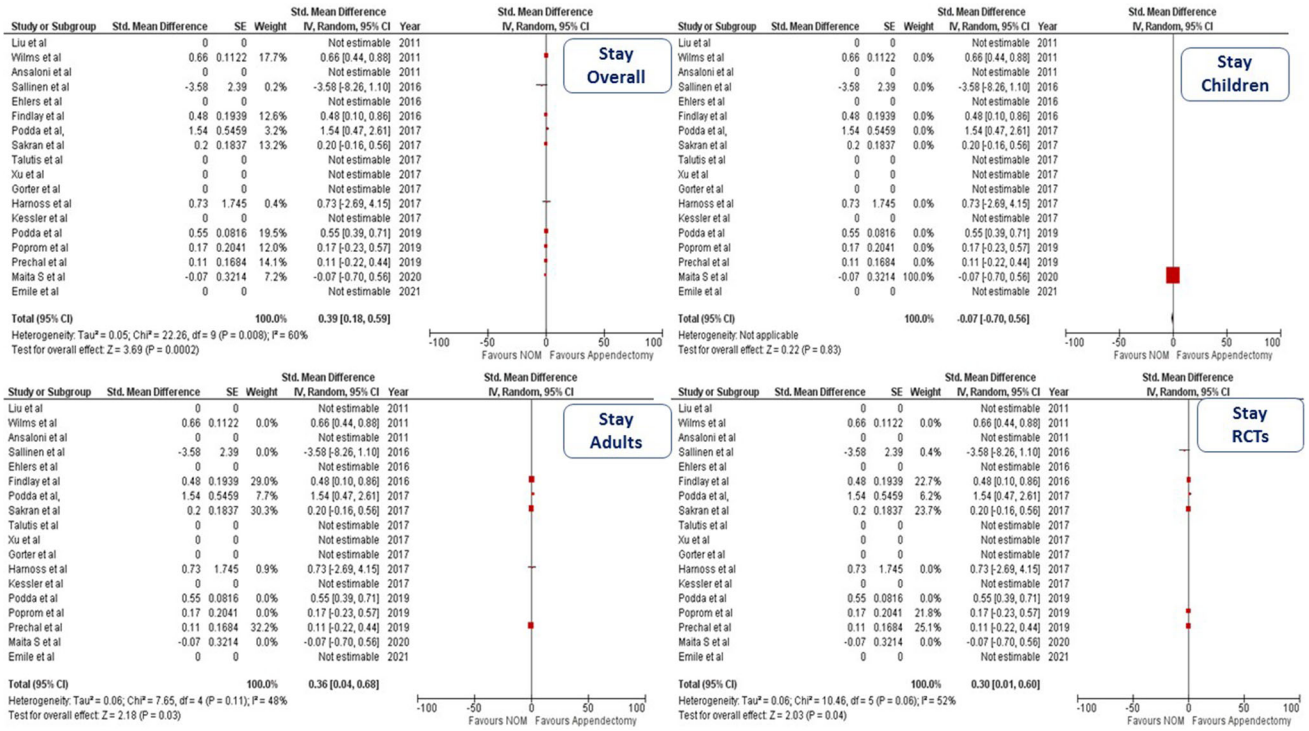

Fig. 5 Forest plot illustrating the standard mean difference in hospital stay along with 95% confidence interval and degree of heterogeneity (Overall analysis and subgroup analyses of children-only, adults-only, and RCTs only meta-analyses)

Table 5 Overall and subgroup analysis of summary effect estimates of treatment failure, complications, and hospital stay

Variable	Overall analysis	Children only	Adults only	RCTs only
Treatment failure	Lower with surgery (RR = 0.68, 95%CI: 0.58–0.79, $p < 0.0001$, $I^2 = 91\%$)	Lower with surgery (RR = 0.77, 95%CI: 0.71–0.84, $p < 0.0001$)	Lower with surgery (RR = 0.71, 95%CI: 0.59-0.86, $p = 0.0004$, $I^2 = 93\%$)	Lower with surgery (RR = 0.68, 95%CI: 0.52–0.87, $p = 0.003$, $I^2 = 91\%$)
Complications	Lower with NOM (RR = 0.59, 95%CI: 0.43–0.81, $p < 0.0001$, $I^2 = 88\%$)	Similar (RR = 0.72, 95%CI: 0.36–1.44, $p = 0.36$, $I^2 = 0$)	Similar (RR = 0.75, 95%CI: 0.5–1.12, $p = 0.16$, $I^2 = 92$)	Similar (RR = 0.63, 95%CI: 0.33–1.21, $p = 0.17$, $I^2 = 93$)
Hospital stay	Shorter with NOM (SMD = 0.39, 95%CI = 0.18-0.59, $P = 0.0002$, $I^2 = 60\%$)	Similar (SMD = 0.07, 95%CI: 0.7–0.56, $p = 0.83$)	Shorter with NOM (SMD = 0.36, 95%CI = 0.04–0.68, P = 0.03, $I^2 = 48\%$)	Shorter with NOM (SMD = 0.3, 95%CI = 0.01–0.6, P = 0.04, $I^2 = 52\%$)

*RR = risk ratio *SMD = standardized mean difference *NOM = non-operative management *RCTs = randomized controlled trials

overall analysis of all meta-analyses was lower with NOM, the subgroup analyses of children-only, adults-only, and RCTs-only meta-analyses found similar risk of complications. This interesting finding may be explained that the lower complication risk in the overall analysis was only marginal and thus when specifically analyzed for each population this marginal effect disappeared and the risk was similar between NOM and surgery. However, this finding should be interpreted with caution given the high level of statistical heterogeneity among the reviews included.

It should be noted that even when the complication rate of NOM is similar or lower than appendectomy, the type and severity of complications may quite differ. Complications of surgery usually involve mild morbidities such as wound-related complications (infection, seroma, dehiscence), ileus, and pelvic collection. On the other hand, complications of NOM may involve formation of

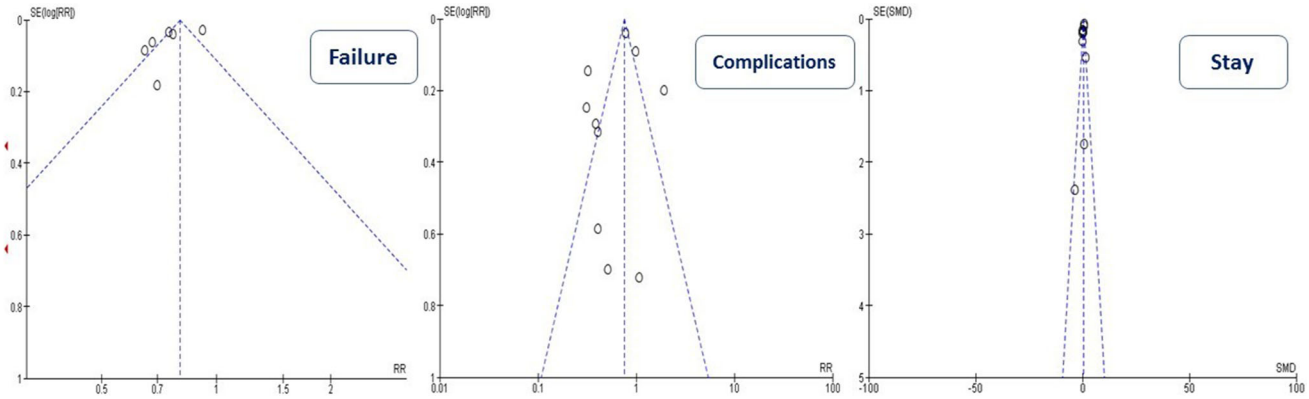

Fig. 6 Funnel plot for assessment of publication bias in the three study outcomes

appendicular mass or abscess or sometimes perforation and peritonitis which is more serious and warrants interventional or surgical management. However, it should be noted that NOM for uncomplicated AA does not statistically increase the perforation rate in adult patients [37].

Another outcome of interest is hospital stay after NOM and surgery. It may be expected that NOM is associated with longer stay than appendectomy owing to the time required for the antibiotic treatment and for frequent observation of the patient to document improvement in symptoms with NOM. However, most meta-analyses documented similar stay with both treatment methods, except one [29] that concluded longer stay with NOM and another [32] that found longer stay with surgery. Interestingly, the summary effect estimate of hospital stay was significantly shorter with NOM overall, in adult-only population and in meta-analyses of RCTs alone, whereas meta-analyses entailing children only showed similar stay. Nevertheless, it is noteworthy that the difference in hospital stay between NOM and surgery groups was only a few hours which may not be clinically important.

Despite the high degree of heterogeneity observed in the present umbrella review, some findings may aid in the clinical decision-making on AA. Given the higher failure rate of NOM, it should be reserved for the cases when appendectomy cannot be performed either due to lack of operative facilities or with patients at high risk for anesthesia and surgery. The potential advantages offered by NOM by having lower complication rate and shorter stay do not seem consistent among the published meta-analyses. Given the low heterogeneity of all outcomes in the children-only population, the conclusions on the outcome of NOM may be more reliable. With similar complication and stay, yet higher failure of NOM in children, surgery might be the optimal treatment option for children presenting with AA.

The primary findings of this umbrella review that can help advance the understanding of the role of NOM of AA can be summarized as: (1) NOM was followed by a significantly higher failure rate (median rate 25%) than appendectomy and this was consistent on subgroup analysis of children only, adults only, RCTs only; (2) Studies that entailed younger patients, more male patients, mixed population, and had longer follow-up were more likely to report higher failure/recurrence rates of NOM; (3) The complication rate of NOM (median 6.9%) was similar to surgery on analysis of meta-analyses of RCTs only to exclude selection bias; (4) Although stay of NOM was shorter than that after surgery in adults, this was not reproduced in children; (5) There was significant publication bias of the outcome "failure of NOM" implying that some negative studies reporting high failure of NOM were not published. Therefore, the actual failure rate of NOM might be higher than that reported.

Some systematic reviews included to this umbrella review may have included similar set of primary studies. However, each meta-analysis was handled and analyzed separately, knowing that some meta-analyses may have included similar set of primary studies, yet the study protocol, inclusion criteria, and statistical analysis methods of each meta-analysis would differ, and thus may lead to different conclusions. For example, using fixed-effect and random-effect models may yield different results. That is why the systematic reviews included had different weight and risk ratios as demonstrated in the forest plots, even if some included similar primary studies.

Limitations of the present study include the remarkable heterogeneity of the systematic reviews included. About half of the reviews entailed a mixed population of adults and children which did not allow for separate analysis of each subgroup. Moreover, 55% of the systematic reviews included both RCTs and observational studies in the same analysis which may compromise the accuracy of the final

Table 6 Test for excess significance and small-study effect in each meta-analysis

Outcome	Systematic review	Total number of studies	Observed positive studies	Expected positive studies	P for TES	Small Study
Treatment failure	Prechal et al. [19]	5	5	4.21	0.99	No
	Podda et al. [20]	30	10	4.82	0.23	No
	Poprom et al. [21]	9	3	2.13	0.99	No
	Kessler et al. [22]	5	4	2.99	0.99	Yes
	Sakran et al. [26]	5	4	2.69	0.5	No
	Podda et al. [27]	5	4	0.33	0.2	No
	Findlay et al. [28]	6	6	4.09	0.45	Yes
	Harnoss et al. [29]	8	8	5.85	0.47	Yes
	Ansaloni et al. [34]	4	3	1.77	0.99	No
Complications	Emile SH et al. [17]	14	6	0.39	0.07	No
	Maita S et al. [18]	21	0	6.1	NP	No
	Prechal et al. [19]	5	3	5.45	NP	No
	Podda et al. [20]	30	4	4.82	NP	No
	Poprom et al. [21]	9	1	1.07	NP	No
	Kessler et al. [22]	5	0	7.62	NP	No
	Sakran et al. [26]	5	3	1.98	0.99	Yes
	Findlay et al. [28]	6	2	3.27	NP	No
	Harnoss et al. [29]	8	8	6.08	0.47	No
	Sallinen et al. [31]	5	0	17.8	NP	No
	Liu et al. [33]	6	NA	NA	NA	No
	Ansaloni et al. [34]	4	1	1.2	NP	Yes
Hospital stay	Maita S et al. [18]	21	1	5	NP	No
	Prechal et al. [19]	5	1	0.7	0.99	No
	Podda et al. [20]	30	3	0.91	0.61	No
	Poprom et al. [21]	9	1	0.1	0.99	No
	Sakran et al. [26]	5	1	1.02	NP	No
	Podda et al. [27]	5	2	6.16	NP	No
	Findlay et al. [28]	6	1	1.72	NP	No
	Harnoss et al. [29]	8	6	5.04	NP	No
	Sallinen et al. [31]	5	4	1.97	0.52	No
	Wilms et al. [32]	6	2	1.76	0.99	No

*TES = test for excess significance

outcomes. That is why we conducted dedicated subgroup analyses of the pediatric population, adult population, and RCTs separately. Finally, most systematic reviews were of low quality and the level of evidence inferred was rather weak.

Conclusions

Based on the umbrella review and collective analysis of systematic reviews and meta-analyses, NOM of AA is associated with higher treatment failure, marginally lower rate of complications, and shorter hospital stay to appendectomy. The potential benefits of NOM of AA were not apparent on subgroup analysis of the meta-analyses that included pediatric population only. These results reinforce the concept that the success of the NOM approach requires careful patient selection and close observation.

Authors' contribution Sameh Emile designed the study. Sameh Emile, Ahmad Sakr, Mostafa Shalaby and Hossam Elfeki contributed to data collection and interpretation. Sameh Emile wrote the manuscript. Ahmad Sakr, Mostafa Shalaby and Hossam Elfeki reviewed and edited the final manuscript.

Declarations

Conflict of interest None to be disclosed by the authors.

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