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REVIEW ARTICLE

Rate of Application and Outcome of Non-operative Management of Acute Appendicitis in the Setting of COVID-19: Systematic Review and Meta-analysis

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Abstract

Background Non-operative management (NOM) of acute appendicitis has been assessed in several studies before COVID-19 pandemic. This systematic review aimed to assess the extent of adoption, efficacy, and safety of NOM of acute appendicitis in the setting of COVID-19.

Methods This was a PRISMA-compliant systematic review of the literature. Electronic databases and Google Scholar were queried for studies that applied NOM of acute appendicitis during COVID-19. The main outcome measures were the rates of NOM application during the pandemic as compared to the pre-pandemic period, failure and complication rates of NOM. Failure was defined as the need for appendectomy during NOM and complications included development of appendicular mass or abscess.

Results Fourteen studies (2140 patients) were included. The male to female ratio was 1.44:1 and median age was 34. Nine hundred fifty-nine (44.8%) patients had a trial of NOM. The weighted mean rate of NOM application was 50.1% (95%CI: 29.8–70.5%). The application of NOM during the pandemic was significantly more likely than its application before COVID-19 (OR = 6.7, $p < 0.001$). The weight mean failure rate of NOM was 16.4% (95%CI: 9.4–23.4). NOM failure was more likely in children and patients with complicated appendicitis. The weighted mean complication rate after NOM was 4.5% (95%CI: 1.4–7.7). NOM had significantly lower odds for complications than appendectomy (OR = 0.36, $p = 0.03$). There was no mortality after application of NOM.

Conclusion NOM of acute appendicitis in the setting of COVID-19 may be a safe, short-term alternative to surgery with acceptably low failure and complication rates.

Keywords Non-operative management · Appendicitis · COVID-19 · Outcome · Systematic review · Meta-analysis

Introduction

Acute appendicitis is the most common abdominal emergency that accounts for thousands of emergency department admissions every year.[1] Appendectomy is the gold standard treatment for uncomplicated acute appendicitis. However, recently there has been a growing trend for non-operative management (NOM) of acute appendicitis with antibiotics as an alternative to appendectomy.[2]

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Proponents of NOM of acute appendicitis advocate this line of treatment as it preserves the immune function of the appendix that may represent an essential component of gut immunity.[3] In addition, NOM avoids the adverse effects of surgery that include the risk of organ injury, surgical site infection (SSI), and abdominal adhesions.[4] On the other hand, opponents of NOM emphasize that appendectomy is the definitive treatment of uncomplicated appendicitis because the treatment success of NOM is 18% lower than surgery.[5] According to the collective evidence available,[2] the index admission treatment failure and the rate of recurrence of symptoms within 1 year after NOM of acute appendicitis were 8.5% and 19.2%, respectively.

As coronavirus disease 2019 (COVID-19) struck the world hard with millions of infected people across the world, the surgical practice has been likewise compromised. Millions of elective surgical procedures have been canceled, increasing the ultimate burden on healthcare services and hospitals. Even the practice of emergency surgery has dramatically changed during the current pandemic.[6] However, acute appendicitis remains a surgical priority and does not quarantine.[7]

Owing to the current circumstances, surgeons thought that NOM of acute appendicitis can be a safer alternative to surgery, in order to reduce the exposure of patients to the risk of contracting COVID-19 and the possible adverse effects of surgery on the immune system that may increase the incidence of pulmonary complications in patients with perioperative SARS-COV-2.[8] The present systematic review aimed to assess the extent of adoption, efficacy, and safety of NOM as a main treatment strategy for acute appendicitis during COVID-19 pandemic and how it has altered the outcomes of acute appendicitis.

Methods

Registration

The protocol of this systematic review was registered a priori in the international prospective register of systematic reviews (Prospero) with special identifier CRD42020222126.

Search Strategy

This systematic review is reported in compliance with the screening guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Fig. 1).[9] A systematic literature search for the studies that assessed the role of NOM of acute appendicitis in the setting of COVID-19 pandemic was performed on November 2020, by three independent investigators (S.E., S.K., H.H.).

Electronic databases including PubMed, Scopus, EMBASE, and Web of Science were queried using the following keywords: "COVID-19," "COVID19," "Coronavirus disease," "SARS-COV-2," "Pandemic," "appendicitis," "appendix," "treatment," "management," "non-operative," "conservative," and "antibiotics." In addition, the following medical subject headings (MeSH) terms were included in the literature search: (appendicitis), (COVID-19), and (conservative treatment). A parallel internet-based search using Google Scholar service was performed to increase the sensitivity of the search process. A detailed overview of the literature search is shown in Appendix S1.

To improve the yield of the search process, we activated the PubMed function "related articles" to search for other relevant studies and hand-searched the reference section of each study retrieved. The studies were initially filtered by title and abstract, then subsequently screened by full-text. The full-text of the selected articles was reviewed to check for eligibility.

Eligibility for Inclusion

Studies deemed eligible for inclusion had to include at least five patients who underwent NOM of acute appendicitis in the setting of COVID-19. Single-arm case series or cohort studies and comparative studies that compared the outcome of NOM with appendectomy were included. The outcomes assessed by the studies were the rate of application of NOM of appendicitis during COVID-19 as compared to the pre-COVID-19 period, failure and complication rates of NOM.

In order to increase the level of evidence and reporting of data, only the studies that were published in full-text in peer-reviewed journals were selected whereas non-reviewed preprints and conference abstracts without full-text articles were not eligible for inclusion.

We excluded animal studies, irrelevant articles, editorials, case reports entailing less than five patients, reviews, and meta-analyses. Only articles published in English were included to this review.

Assessment of Methodologic Quality and Risk of Bias

The methodological quality of the studies included was appraised by two authors (S.E. and H.H.) in an independent manner. The tool used for quality assessment was the methodological index for non-randomized studies (MINORS).[10] The MINORS tool can be used for assessment of both single-arm and comparative studies. The maximum scores for single-arm and comparative studies are 16 and 24, respectively. Low risk of bias is indicated by a score ≥ 12 for single-arm studies and ≥ 20 for comparative studies. Discrepancies in interpretation of the results were resolved by consensus and adjudication by a third reviewer (G.D.).

Data Extraction

The full-text of the included studies was reviewed by two authors (S.E. and H.H.) and the following data points were extracted into excel spread sheets:

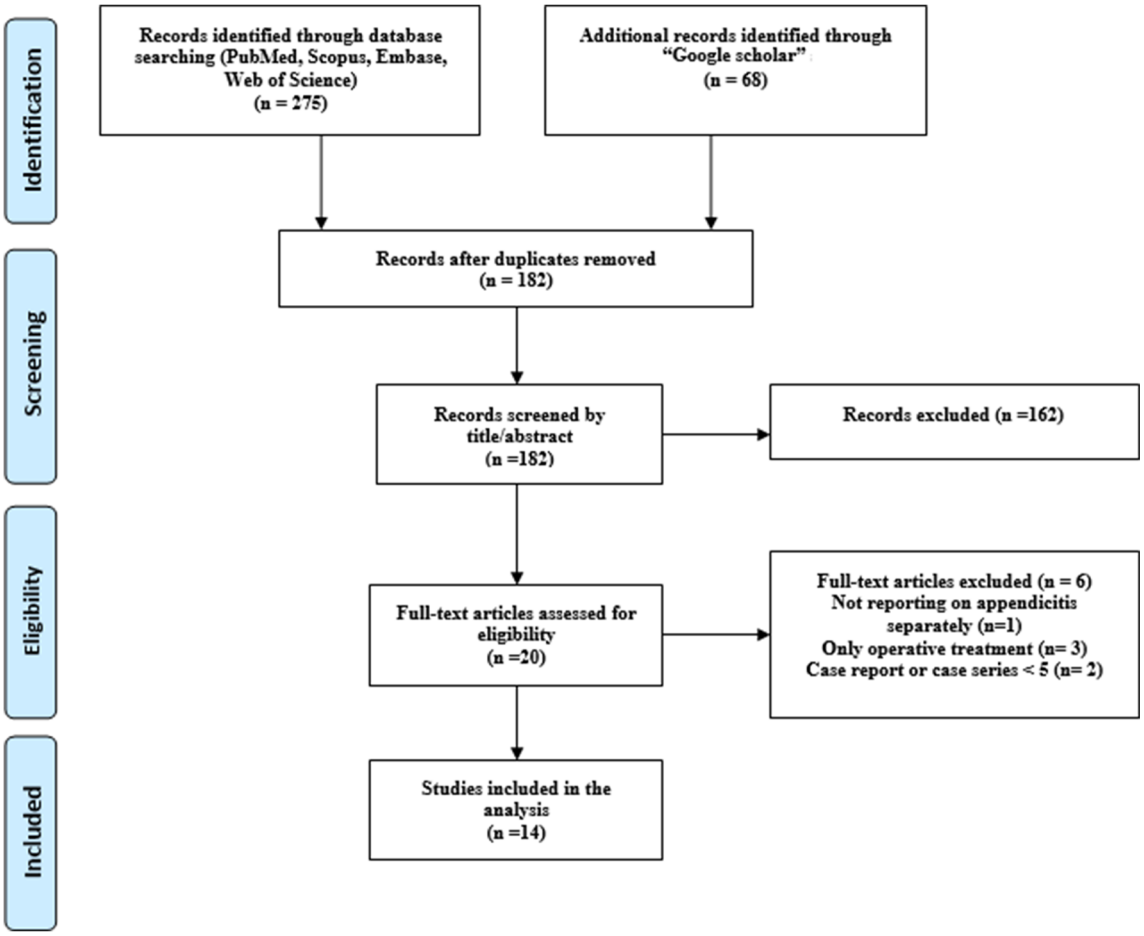

Fig. 1 PRISMA flow chart

- Authors, year of publication, duration, country, and type of the study.
- Patient characteristics including age and sex.
- Number of patients who had NOM during COVID-19 and in the pre-COVID period.
- Number of patients who underwent upfront appendectomy without trial of NOM.
- Percentage of NOM patients who required appendectomy, defined as failure of NOM.
- Complications of NOM and appendectomy.
- 30-day readmission rates after NOM.
- Length of hospital stay and follow-up duration in days.

Outcomes

The primary outcomes of this systematic review were the rate of application of NOM of appendicitis during COVID-19 as compared to the pre-COVID-19 period and failure of NOM. Failure of NOM was defined as the need for appendectomy either within the index admission or after discharge for increasing or persistent symptoms or development of serious sequel warranting surgery such as perforation. Secondary outcomes were the complication rate of NOM as compared to that of appendectomy, length of hospital stay, readmission rate, mortality, and the rate of negative appendectomy. Complications included development of appendicular mass for which NOM was still applied and did not warrant surgery or development of appendicular abscess which required US or CT-guided drainage without the need for surgery. Definitions of the study outcomes are shown in Appendix S2.

Assessment of Publication Bias

We assessed publication bias among the studies by establishing a funnel plot of the standard error of the rates of application and failure of NOM against the application and failure rates reported in the studies reviewed. Absence of publication bias was confirmed by symmetry of the funnel plot and presence of 95% of dots representing the studies near the straight vertical line in the plot. Further assessment of publication bias was made using Egger's regression test.

Statistical Analysis

We used SPSS version 25 (IBM, Chicago, USA) to analyze the data. Continuous variables were expressed as mean ± standard deviation (SD), or median and normal range. Categorical variables were expressed as numbers and proportions. *p* values less than 0.05 were considered significant.

An open source, cross-platform meta-analysis software "openMeta[Analyst]™" version 12.11.14 was used for conducting a meta-analysis of the outcome of NOM of acute appendicitis. Using random-effect meta-analysis model, we calculated the weighted mean rates of application, failure, and complications of NOM. Statistical heterogeneity was assessed by the *p* value of the inconsistency (I^2) statistics. Heterogeneity was considered low if $I^2 < 25\%$ and high if $I^2 > 75\%$.

We applied a random-effect meta-regression model, weighing the studies by their within-study variance and the degree of heterogeneity to determine the risk factors of failure of NOM. The inter-study heterogeneity was investigated as related to differences in patients' age, sex, complicated appendicitis, region of the study, and number of centers participating. The statistical significance of each examined variable was examined using slope regression coefficient (SE) which is the estimated increase in the log odds of the outcome per unit increase in the value of the exposure, 95%CI, and *p* value.

Results

Study and Patients' Characteristics

This systematic review included 14 studies[11–24] published in 2020. Five studies were based in the UK, three in USA, two in China, and one in Ireland, Nepal, Israel, and India. All studies were cohort, eight of which were retrospective analysis of data and six were prospective studies. Four studies were multicentric and ten were single-center studies. The review entailed 2140 patients with acute appendicitis with a male to female ratio of 1.44:1 and median age of 34 (range, 10–44) years. The diagnosis of acute appendicitis was based on clinical examination and adjunct radiologic examination by ultrasound or CT scanning.

Among the 14 studies included, 10 of which had follow-up of 30 days, four had less than 30 days, and none exceeded 30 days of follow-up. Therefore, the median follow-up duration across the studies was 30 (range, 7–30) days. According to the quality assessment, there were 11 studies of high risk of bias and three of low risk of bias. The median MINORS score was 17.5 (range, 12–20) (Table 1).

Table 1 Characteristics of the studies reviewed

Study	Country	Duration	Multicenter	Type	Number	Males	Age	MINORS
English et al.[11]	UK	March–May 2020	Yes	Prospective comparative cohort	79	48	33	18/24 (high risk)
Finkelstein et al.[12]	USA	March–May 2019/2020	No	Retrospective comparative cohort	48	23	44	18/24 (high risk)
Ganesh et al.[13]	UK	Nov 2019–May 2020	No	Retrospective comparative cohort	32	12	37	17/24 (high risk)
Javanmard-Emamghissi et al.[14]	UK	March–May 2020	Yes	Prospective comparative cohort	500	267	35	20/24 (low risk)
Kvasnovsky et al.[15]	USA	March–May 2020	No	Retrospective comparative cohort	55	NA	12.4	12/24 (high risk)
Patel et al.[16]	USA	March–May 2020	No	Retrospective comparative cohort	75	52	32	19/24 (high risk)
Verma et al.[17]	India	March–July 2020	No	Prospective comparative cohort	91	52	NA	16/24 (high risk)
Zhou et al.[18]	China	January–March 2020	No	Retrospective comparative cohort	90	54	40.9	20/24 (high risk)
Kelly et al.[20]	Ireland	March–April 2020	No	Retrospective single-arm cohort	18	NA	NA	13/16 (low risk)
Khanal et al.[20]	Nepal	Jul 20	No	Prospective single-arm cohort	73	44	27	13/16 (low risk)
Bethel et al.[21]	UK	April–May 2020	Yes	Prospective comparative cohort	838	526	10	17/24 (high risk)
Basamh et al.[22]	UK	March–April 2020	No	Prospective single-arm cohort	42	24	41	13/16 (high risk)
Gao et al.[23]	China	June 2019–April 2020	No	Retrospective comparative cohort	58	40	42.8	18/24 (high risk)
Tankel et al.[24]	Israel	Dec 2019–April 2020	Yes	Retrospective comparative cohort	141	77	23.3	19/24 (high risk)

Rate of Application of NOM

Of 2140 patients who presented with acute appendicitis during COVID-19, 959 (44.8%) patients had a trial of NOM. The median age of patients was 33 years. The weighted mean rate of NOM application was 50.1% (95%CI: 29.8–70.5%, $I^2 = 99.5\%$). Only two studies reported the type of antibiotics used for NOM of acute appendicitis; Basamh et al.[22] used co-amoxiclav or meropenem in patients with penicillin allergy and Khanal et al.[20] used a combination of ceftriaxone–metronidazole.

The rate of application of NOM varied by country as it ranged from 38.9 to 100% in the studies conducted in the UK, 10–100% in USA, and 10–29.3% in China whereas it was 69.2% in India, 74% in Nepal, and 7.8% in Israel. The median rate of NOM application in the Western countries (USA, UK, Ireland) was 54.2% versus 29.3% in the Eastern countries (India, China, Nepal).

When compared to similar time periods before the onset of COVID-19, the application of NOM of acute appendicitis during the pandemic was significantly more likely than its application before COVID-19 (OR = 6.7, 95%CI: 2.2–20.2, $p < 0.001$, $I^2 = 89.3\%$) (Table 2, Fig. 2). The rate of increased application of NOM during COVID-19 compared to before the onset of the pandemic ranged from 6.5 to 100%.

Outcome of NOM

Failure

Twelve studies including 931 patients reported failure of NOM in 171 (18.3%) patients who required appendectomy during index admission or on 30-day follow-up. The weight mean rate of failure of NOM was 16.4% (95%CI: 9.4–23.4, $I^2 = 88.9\%$) (Table 3, Fig. 3). The indications for appendectomy included ongoing or increasing symptoms in seven studies and development of complicated appendicitis in six studies. Three studies entailing 28 patients did not report failure of NOM.

The rate of NOM failure varied according to the patient population. Twelve studies that included adult population reported NOM failure in 60 (10.4%) out of 578 patients whereas two studies comprising pediatric population reported failure of NOM in 111 (29.1%) out of 381 patients (OR = 3.5, 95%CI: 2.5–5, $p < 0.0001$).

The rate of NOM failure also differed according to the rate of application of NOM in each study. Seven studies (553 patients) that had a NOM rate > 50% reported NOM failure in 83 (15%) patients as compared to seven studies (406 patients) with lower NOM rates that reported failure in 88 (21.7%) patients ($p = 0.009$).

In seven studies including 575 patients who had NOM, there were 94 (16.3%) patients with complicated appendicitis (Table 3). The weighted mean NOM failure rate across the studies that included complicated appendicitis was 21.8% (95%CI: 10.7–32.9, $I^2 = 90.3\%$).

Complications and Readmission

Six studies including 746 patients reported complications of NOM in 30 (4%) patients. The weighted mean complication rate after NOM was 4.5% (95%CI: 1.4–7.7, $I^2 = 70.5\%$) (Fig. 4). Complications included intra-abdominal collection (abscess) and appendicular mass. The weighted mean 30-day readmission rate after NOM was 10% (95%CI: 3.8–16.1, $I^2 = 66\%$). The application of NOM was not associated with any mortality in the studies.

Table 2 Comparison of the rate of application of NOM before and after COVID-19

Study	During COVID-19		Before COVID-19	
	Total appendicitis	Appendicitis that had NOM	Total appendicitis	Appendicitis that had NOM
English et al.[11]	79	51 (64.5%)	63	11 (17.4%)
Finkelstein et al.[12]	48	5 (10.4%)	59	4 (6.8%)
Ganesh et al.[13]	32	14 (43.7%)	64	0
Javanmard-Emamghissi et al.[14]	500	271 (54.2%)	NA	NA
Kvasnovsky et al.[15]	55	55 (100%)	41	0
Patel et al.[16]	75	24 (32%)	111	6 (5.4%)
Verma et al.[17]	91	63 (69.2%)	126	28 (22.2%)
Zhou et al.[18]	90	9 (10%)	NA	NA
Kelly et al.[20]	18	11 (61.1%)	NA	NA
Khanal et al.[20]	73	60 (82.2%)	NA	NA
Bethel et al.[21]	838	326 (38.9%)	NA	NA
Basamh et al.[22]	42	42 (100%)	NA	NA
Gao et al.[23]	58	17 (29.3%)	105	12 (11.4%)
Tankel et al.[24]	141	11 (7.8%)	237	35 (14.7%)

NOM, non-operative management; *COVID-19*, coronavirus disease 2019

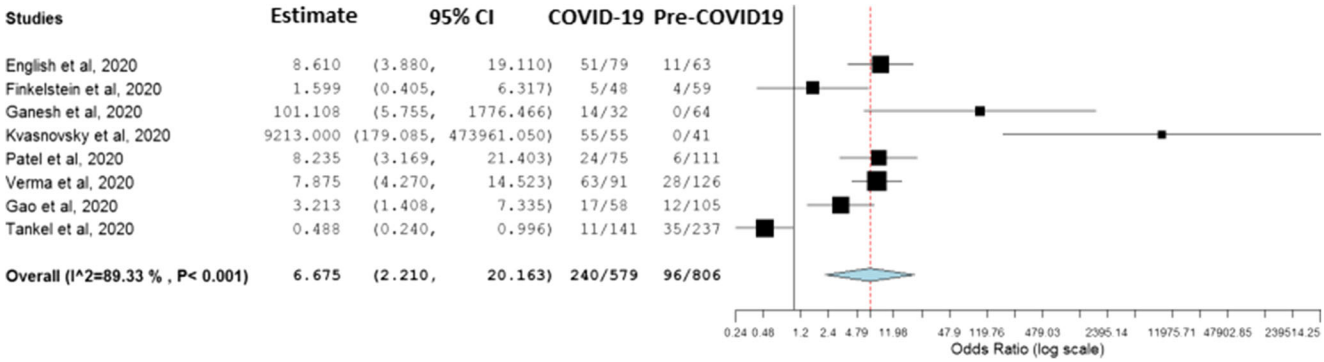

Fig. 2 Forest plot for the odds ratio of the NOM application rate before and after COVID-19

Outcome of Appendectomy

A total of 1181 patients underwent upfront appendectomy without a trial of NOM. According to eight studies that reported the approach of appendectomy, 631 (57.8%) of 1092 patients underwent laparoscopic appendectomy whereas the remaining 42.2% had open appendectomy (Table 4).

Ninety-four (7.9%) patients developed postoperative complications that included intra-abdominal collection (abscess) (n = 39; 3.3%), wound dehiscence (n = 12; 1%), SSI (n = 2; 0.17%), ileus (n = 3; 0.25%), pneumonia (n = 2; 0.17%), small bowel obstruction (n = 2; 0.17%), acute kidney injury (n = 1; 0.08%), and deep vein thrombosis of lower limbs (n = 1; 0.08%). The weighted mean complication rate of appendectomy was 9.8% (95%CI: 4.8–14.9, I^2 = 83.2%).

Twelve (1.9%) patients required conversion to open surgery and eight (0.6%) needed reoperation. Three studies including 769 patients reported negative appendectomy in 50 (6.5%) patients.

Comparing Outcomes of NOM and Appendectomy

NOM had significantly lower odds for complications than appendectomy, (OR = 0.36, 95%CI: 0.14–0.93, p = 0.03, I^2 = 57.9%) (Fig. 5). The median hospital stay of NOM was 2 days (range: 22.5 h–5.2 days), shorter than after appendectomy (3 days, range: 17 h–3 days).

Comparing Outcomes of NOM of Acute Appendicitis Before and After COVID-19

The study by Verma et al.[17] compared failure of NOM in the COVID-19 era (11/63) and before COVID-19 (2/28) and there was no significant difference in failure rates between

Table 3 Outcome of NOM of acute appendicitis during COVID-19

Study	Number	Complicated appendicitis	Patients needed surgery (failure)	Complications (N)	Stay in days
English et al.[11]	51/79 (64.5%)	NA	2 (3.9%)	10 (19.6%)	1
Finkelstein et al.[12]	5/48 (10.5%)	0	0	NA	NA
Ganesh et al.[13]	14/32 (43.7%)	NA	0	0	2
Javanmard-Emamghissi et al.[14]	271/500 (54.2%)	NA	26 (9.5)	11 (4%)	2
Kvasnovsky et al.[15]	55/55 (100%)	5 (9.1%)	30 (54.5%)	NA	1
Patel et al.[16]	24/75 (32%)	3 (12.5%)	7 (29.1%)	1 (4.1%)	NA
Verma et al.[17]	63/91 (69.2%)	7 (11.1%)	11 (17.4%)	NA	5.2
Zhou et al.[18]	9/90 (10%)	NA	0	NA	NA
Kelly et al.[20]	11/18 (61.1%)	NA	5 (45.4)	NA	3.5
Khanal et al.[20]	60/73 (74%)	4 (6.7%)	3 (5%)	4 (6.7%)	3
Bethel et al.[21]	326/838 (38.9%)	65 (19.9%)	81 (24.8%)	4 (1.2%)	2
Basamh et al.[22]	42/42 (100%)	10 (23.8%)	6 (14.2%)	NA	2.57
Gao et al.[23]	17/58 (29.3%)	NA	NA	NA	NA
Tankel et al.[24]	11/142 (7.8%)	NA	NA	NA	NA

NOM, non-operative management; *COVID-19*, coronavirus disease 2019

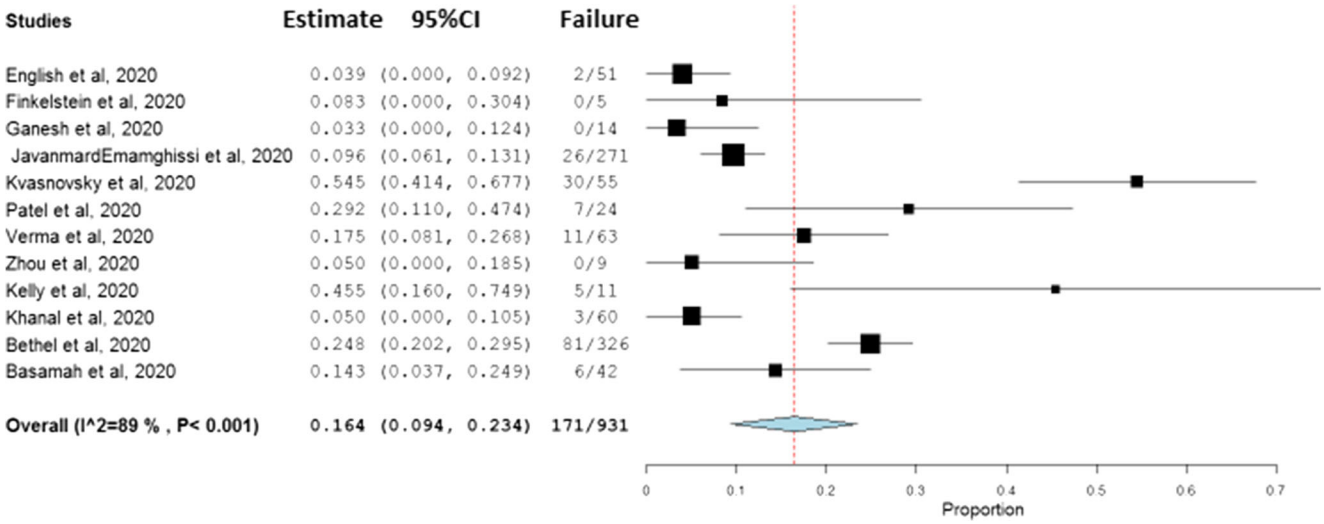

Fig. 3 Forest plot for the weighted mean failure rate of NOM

the two groups (p = 0.33). Another study by Patel et al.[16] found no significant difference in complication rates of NOM in the setting of COVID-19 (1/24) and before COVID-19 (1/6) (p = 0.36). The adoption of NOM as a main treatment strategy during the pandemic did not increase readmission rates significantly as reported by Ganesh et al.[13] (9.4% vs 12.5%, p = 0.75) nor increased the length of hospital stay.[13, 16]

Outcome of NOM in COVID-19 Positive Patients

Two studies[15, 22] reported on the outcomes of NOM in patients with COVID-19. Overall, seven patients with COVID-19 were treated initially with NOM, with a failure rate of 43% at discharge. None of these patients died or developed recurrent appendicitis at 30 days.

Meta-regression of the Risk Factors of Failure of NOM

Risk factors that were significantly associated with failure of NOM were male sex (SE = 0.0001, p < 0.001), younger age (SE = −0.009, p = 0.001), and complicated appendicitis (SE = 0.003, p < 0.001). The region of the study (SE = −0.1, p = 0.27) and number of participating center (SE = 0.19, p = 0.05) were not significantly associated with failure of NOM.

Outcome of Publication Bias Assessment

The funnel plots of the rates of application and failure of NOM in the studies were symmetrical with more than 95% of studies present near the vertical midline, denoting absence of publication bias (Fig. 6). p values of Egger's regression were > 0.05 for both analyses (p = 0.88 for NOM application and p = 0.37 for NOM failure) confirming the absence of significant publication bias.

Discussion

Over the past decade several controlled studies and meta-analyses[2, 5] have assessed the outcome of NOM of acute appendicitis. As the current crisis of COVID-19 has unfolded, NOM of appendicitis has been increasingly used and advocated. The present systematic review aimed to assess the rate of

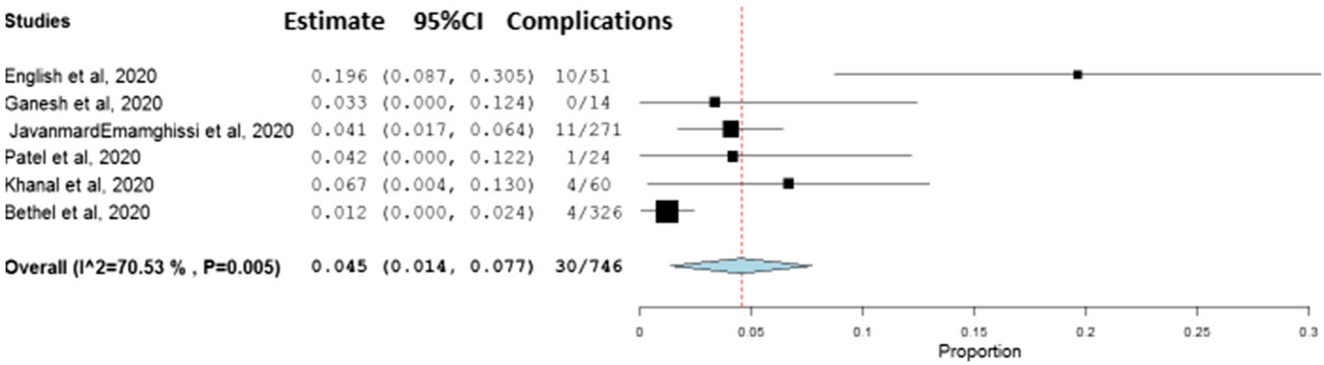

Fig. 4 Forest plot for the weighted mean complication rate of NOM

Table 4 Outcome of upfront appendectomy during COVID-19

Study	Number	Complications (*N*)	Laparoscopy (*N*)	Stay in days
English et al.[11]	28/79 (35.5%)	4 (14.3%)	2 (7.1%)	12
Finkelstein et al.[12]	43/48 (89.5%)	3 (7%)	43 (100%)	NA
Ganesh et al.[13]	18/32 (56.2%)	0	11 (61.1%)	30
Javanmard-Emamghissi et al.[14]	229/500 (45.8%)	47 (20.5%)	93 (40.6%)	30
Kvasnovsky et al.[15]	0/55	NA	NA	30
Patel et al.[16]	51/75 (68%)	7 (13.7%)	46 (90.1%)	30
Verma et al.[17]	28/91 (30.7%)	6 (21.4%)	NA	NA
Zhou et al.[18]	81/90 (90%)	3 (3.7%)	69 (85.1%)	14
Kelly et al.[20]	7/18 (38/9%)	NA	NA	7
Khanal et al.[20]	13/78 (16.7%)	NA	NA	NA
Bethel et al.[21]	512/838 (61.1%)	24 (4.7%)	243 (47.5%)	3
Basamh et al.[22]	0/42	NA	NA	NA
Gao et al.[23]	41/58 (70.7%)	NA	NA	NA
Tankel et al.[24]	130/142 (91.5%)	NA	124	NA

COVID-19, coronavirus disease 2019

adoption and outcomes of NOM of acute appendicitis in unique circumstances, amid the COVID-19 pandemic.

Considering the increased risks associated with surgical intervention during the pandemic, surgical societies have advocated an initial trial of NOM for acute appendicitis based on the surgeons' judgment and patient condition.[25, 26] Ever since, NOM has been adopted by many hospitals around the world as the primary treatment approach for acute appendicitis. This was reflected by the findings of this meta-analysis as the application of NOM during COVID-19 was seven times more likely to be implemented in comparison to similar time periods before the onset of the pandemic.

The rate of adoption of NOM varied in relation to geographic factors. It was notable that the median application rate of NOM in the studies conducted in Western countries exceeded 50% whereas it was less than 30% in Eastern countries, namely China. While the reasons of this difference are unclear, it may be attributed to cultural and demographic differences between the two groups.

The weighted mean rate of NOM failure was 16%, much lower than the failure rates reported in previous meta-analyses published before COVID-19 which ranged from 28–37%.[2, 5, 27] This is quite reasonable since the studies included in the present meta-analysis assessed only the 30-day outcome of NOM as compared to 12 months of follow-up in previous meta-analyses.

The application of NOM during the pandemic can be challenging since recent reports highlighted a more complicated course and higher risk of perforation of acute appendicitis during the pandemic.[28] This observation is probably attributed to an increased time interval between the onset of symptoms and admission and decreased patients' willingness to receive in-hospital treatment.[23] As a consequence, a significant proportion of patients with acute appendicitis may not meet the criteria for NOM and the question remains whether NOM can offer an effective alternative to surgery in patients with acute appendicitis during the pandemic.

On exploring the possible risk factors of NOM failure, we noted that children and patients with complicated appendicitis were more amenable to experience failure of NOM. NOM failure rate in the studies that included pediatric population was almost three times that of the studies involving mainly

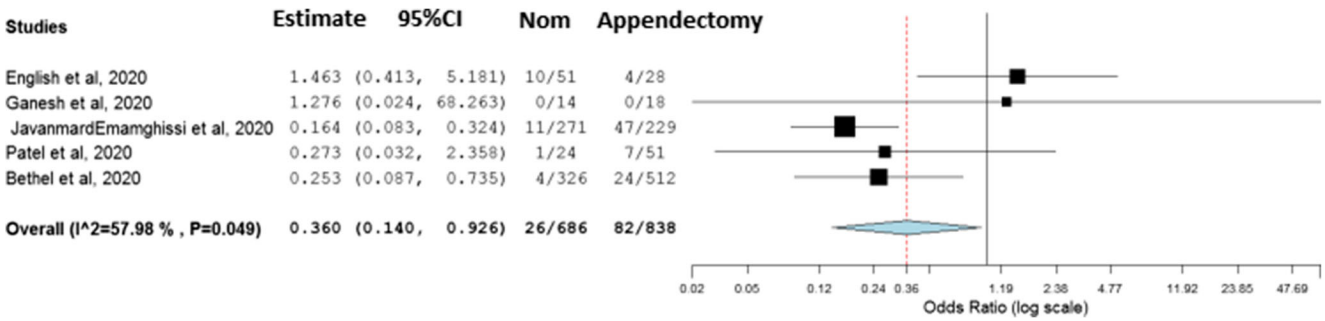

Fig. 5 Forest plot for the odds ratio of complications after NOM versus after appendectomy

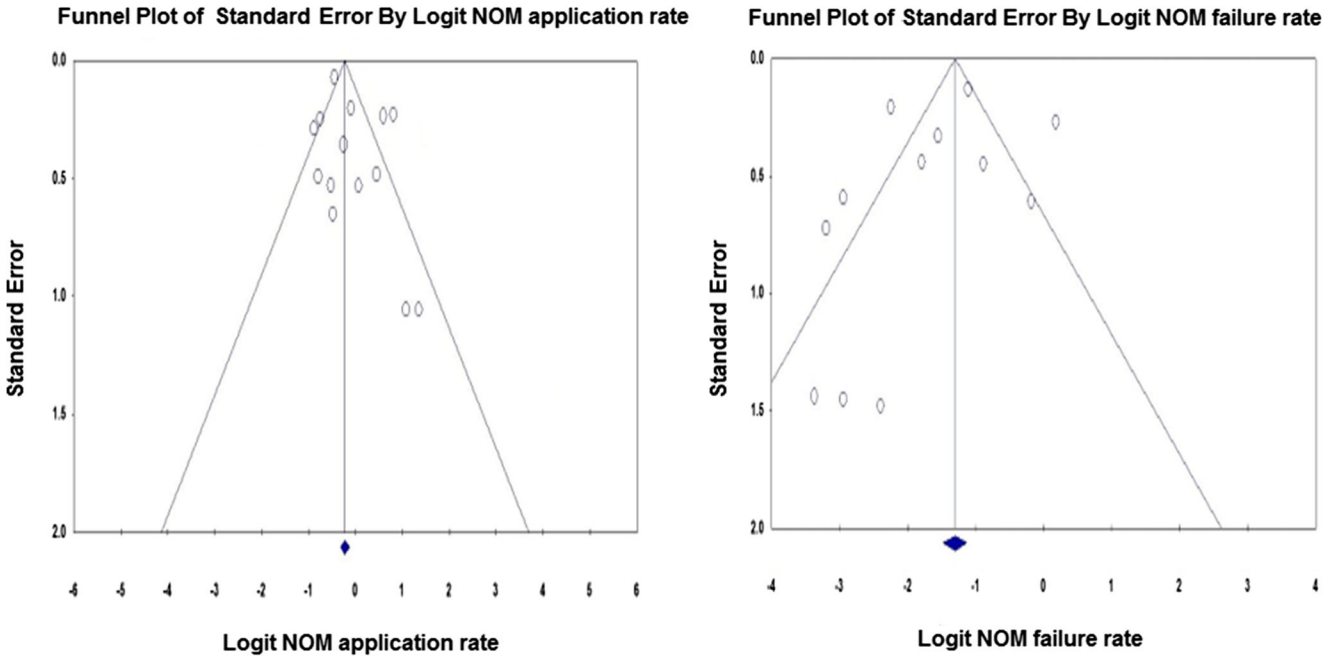

Fig. 6 Funnel plot for publication bias assessment

adults. This may highlight the different criteria for NOM application between children and adults as has been reported previously.[29] In contradiction to our findings, a previous meta-analysis of NOM of acute uncomplicated appendicitis in children before CVOID-19 revealed a success rate of 90%.[30] This discrepancy may be attributed to the delayed presentation of patients and inclusion of complicated appendicitis in the studies that reported on NOM efficacy in children during the pandemic.[15, 21]

Individual studies[13, 16, 17] compared the outcome of NOM during and before COVID-19 and no significant difference in the failure, complication, and 30-day readmission rates was found. Although these were single-center experiences, they may have an implication that the adoption of NOM as a main treatment strategy of acute appendicitis during the pandemic was not associated with a compromise of the short-term efficacy of NOM.

To further assess the overall safety of NOM during the pandemic, we compared its outcome with that of upfront appendectomy in the same time period. NOM was found to be associated with significantly lower odds of developing complications of treatment as compared to appendectomy (4.5% vs 9.8%). Furthermore, the median hospital stay of NOM was 1 day shorter than surgery which would be associated with less nosocomial exposure to the virus and less costs. The costs of treatment of acute appendicitis during COVID-19 was assessed by Khanal et al.[20] who found the successful application of NOM to be associated with a cost benefit of 100 US dollars.

NOM might be the optimal strategy in patients with acute appendicitis who are SARS-CoV-2 positive to avoid progression of the disease and development of pulmonary complications which can occur in up to 51% of patients after surgery.[8] This review entailed seven COVID-19 positive patients who received NOM of acute appendicitis, yet 43% of whom experienced failure of treatment. This higher failure rate, as compared to the average weighted failure of the meta-analysis, may imply a possible impact of COVID-19 on the body response to NOM.

Although not directly relevant to the main purpose of this review, we noticed that the outcomes of upfront appendectomy during COVID-19 were not particularly different to those reported in the pre-COVID19 literature. The conversion and complication rates of appendectomy were similar to those reported in previous studies.[31] The percentage of laparoscopic appendectomy (58%) was slightly lower than that reported in high-income countries (67.7%).[32] However, this indicated that laparoscopic appendectomy remained a viable option despite the concerns of possible spread of the virus in the aerosol generated during laparoscopy which led many surgeons to abandon laparoscopy at the take-off of the pandemic.[33, 34]

This meta-analysis has a number of limitations. Firstly, all data were derived from cohort and case-series studies, most of which were retrospective with no available randomized trials. Secondly, the comparison between NOM and upfront appendectomy should be interpreted with caution because the surgery group entailed more patients with complicated and perforated appendicitis. Finally, the results of this meta-analysis represent the short-term outcome of NOM with no assessment of recurrent appendicitis in patients with initially successful NOM.

Conclusions

NOM of acute appendicitis in the setting of COVID-19 may be a safe, short-term alternative to surgery with acceptably low failure and complication rates. Failure of NOM was more likely in children and patients with complicated appendicitis, thus further assessment and careful decision-making is crucial in these patients.

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Author Contribution Sameh Emile designed the study, collected and analyzed data, and wrote the manuscript. Hytham Hamid participated in the study conception, collection and interpretation of data, and drafting and revision of the manuscript. Sualeh Khan participated in the study design, data collection, and critical revision of the manuscript. George Davis contributed to data collection, quality assessment, and critical revision of the manuscript. All authors approved the final version of the manuscript.

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Humes DJ, Simpson J. Acute appendicitis. *BMJ*. 2006;333(7567): 530-534. Doi:https://doi.org/10.1136/bmj.38940.664363.AE
2. Podda M, Gerardi C, Cillara N, Fearnhead N, Gomes CA, Birindelli A, Mulliri A, Davies RJ, Di Saverio S. Antibiotic Treatment and Appendectomy for Uncomplicated Acute Appendicitis in Adults and Children: A Systematic Review and Meta-analysis. Ann Surg. 2019 Dec;270(6):1028-1040.
3. Kooij IA, Sahami S, Meijer SL, Buskens CJ, Te Velde AA. The immunology of the vermiform appendix: a review of the literature. *Clin Exp Immunol*. 2016;186(1):1-9. Doi:https://doi.org/10.1111/cei.12821
4. Moreira LF, Garbin HI, Da-Natividade GR, Silveira BV, Xavier TV. Predicting factors of postoperative complications in appendectomies. Rev Col Bras Cir. 2018 Nov 14;45(5):e19. Portuguese, English. https://doi.org/10.1590/0100-6991e-20181920.
5. Poprom N, Numthavaj P, Wilasrusmee C, Rattanasiri S, Attia J, McEvoy M, Thakkinstian A. The efficacy of antibiotic treatment versus surgical treatment of uncomplicated acute appendicitis: Systematic review and network meta-analysis of randomized controlled trial. Am J Surg. 2019 Jul;218(1):192-200. https://doi.org/10.1016/j.amjsurg.2018.10.009.
6. COVIDSurg Collaborative. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. Br J Surg. 2020 May 12:10.1002/bjs.11746. doi: https://doi.org/10.1002/bjs.11746. Epub ahead of print.
7. Patriti A, Baiocchi GL, Catena F, Marini P, Catarci M; FACS on behalf of the Associazione Chirurghi Ospedalieri Italiani (ACOI). Emergency general surgery in Italy during the COVID-19 outbreak: first survey from the real life. World J Emerg Surg. 2020 May 24;15(1):36. https://doi.org/10.1186/s13017-020-00314-3.
8. COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet. 2020 Jul 4;396(10243):27-38.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PloS Med 6(6): e1000097. https://doi.org/10.1371/journal.pmed1000097.
10. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003 Sep;73(9):712-6.
11. English W, Habib Bedwani N, Smith C, Doganay E, Marsden M, Muse S, Mak WK, Chana M, Eves J, Shatkar V. Suspected appendicitis and COVID-19, a change in investigation and management-a multicentre cohort study. Langenbecks Arch Surg. 2020 Nov 9:1–9. https://doi.org/10.1007/s00423-020-02023-6.
12. Finkelstein P, Picado O, Muddasani K, Wodnicki H, Mesko T, Unger S, Bao P, Jorge I, Narayanan S, Ben-David K. R J Laparoendosc Adv Surg Tech A. 2020 Nov 11. https://doi.org/10.1089/lap.2020.0749.
13. Ganesh R, Lucocq J, Ekpete NO, Ain NU, Lim SK, Alwash A, Bibi S, Alijani A. Management of appendicitis during COVID-19 pandemic; short-term outcomes. Scott Med J. 2020 Nov;65(4):144-148. https://doi.org/10.1177/0036933020956316.
14. Javanmard-Emamghissi H, Boyd-Carson H, Hollyman M, Doleman B, Adiamah A, Lund JN, Clifford R, Dickerson L, Richards S, Pearce L, Cornish J, Hare S, Lockwood S, Moug SJ, Tierney GM; COVID: HAREM (Had Appendicitis, Resolved/Recurred Emergency Morbidity/Mortality) Collaborators Group. The management of adult appendicitis during the COVID-19 pandemic: an interim analysis of a UK cohort study. Tech Coloproctol. 2020 Jul 15:1â€“11. https://doi.org/10.1007/s10151-020-02297-4.
15. Kvasnovsky CL, Shi Y, Rich BS, Glick RD, Soffer SZ, Lipskar AM, Dolgin S, Bagrodia N, Hong A, Prince JM, James DE, Sathya C. Limiting hospital resources for acute appendicitis in children: Lessons learned from the U.S. epicenter of the COVID-19 pandemic. J Pediatr Surg. 2020 Jun 23:S0022-3468(20)30444-9. https://doi.org/10.1016/j.jpedsurg.2020.06.024.
16. Patel VK, Ye K, In H, Scheinfeld MH. Non-operative Management for Acute Appendicitis During the COVID-19 Pandemic Does Not Increase the Rate of Complications [published online ahead of print, 2020 Nov 2]. *J Gastrointest Surg*. 2020;1-3. https://doi.org/10.1007/s11605-020-04844-8
17. Verma S, Garg P, Verma A, Sirohi V. Careful Non-operative Management with Surveillance of Acute Appendicitis During COVID-19 Pandemic [published online ahead of print, 2020 Oct 5]. *Indian J Surg*. 2020;1-2. https://doi.org/10.1007/s12262-020-02620-1.
18. Zhou Y, Cen LS. Managing acute appendicitis during the COVID-19 pandemic in Jiaxing, China. World J Clin Cases. 2020 Oct 6;8(19):4349-4359. https://doi.org/10.12998/wjcc.v8.i19.4349.
19. Kelly ME, Murphy E, Bolger JC, Cahill RA. COVID-19 and the treatment of acute appendicitis in Ireland: a new era or short-term pivot?. *Colorectal Dis*. 2020;22(6):648-649. https://doi.org/10.1111/codi.15141.
20. Khanal B, Agrawal S, Suresh S, Sangroula RK, Gupta RK. Non-Operative Management of Uncomplicated Acute Appendicitis during COVID-19 Pandemic: A Single Institution Based Prospective Study. J Surg Surgic Case Rep. 2020;1(2):1007.
21. Bethell GS, Rees CM, Sutcliffe JR CASCADE study Collaborators, et al. Management and early outcomes of children with appendicitis in the UK and Ireland during the COVID-19 pandemic: a survey of surgeons and observational study BMJ Paediatrics Open 2020;4:e000831. https://doi.org/10.1136/bmjpo-2020-0008

22. Basamh M, Rajendiran A, Chung WY, Runau F, Sangal S. Management of appendicitis during the COVID pandemic: Lessons from the first month of the outbreak. Br J Surg. 2020 Aug 10. https://doi.org/10.1002/bjs.11910.
23. Gao Z, Li M, Zhou H, Liang Y, Zheng C, Li S, Zhang T, Deng W. Complicated appendicitis are common during the epidemic period of 2019 novel coronavirus (2019-nCoV). Asian J Surg. 2020 Oct;43(10):1002-1005. https://doi.org/10.1016/j.asjsur.2020.07.019.
24. Tankel J, Keinan A, Blich O, Koussa M, Helou B, Shay S, Zugayar D, Pikarsky A, Mazeh H, Spira R, Reissman P. The Decreasing Incidence of Acute Appendicitis During COVID-19: A Retrospective Multi-centre Study. World J Surg. 2020 Aug;44(8):2458-2463. https://doi.org/10.1007/s00268-020-05599-8.
25. COVID-19 Guidelines for Triage of Emergency General Surgery Patients. ACS. Available online at https://www.facs.org/covid-19/clinical-guidance/elective-case/emergency-surgery. Accessed on November 27, 2020.
26. Griffin SM, Alderson D, Taylor J, Mealy K. Intercollegiate General Surgery Guidance on COVID-19; 2020. Available online at: https://www.rcsed.ac.uk/news-public-affairs/news/2020/march/intercollegiate-general-surgery-guidance-on-covid-19-update. Accessed on November 27, 2020.
27. Prechal D, Damirov F, Grilli M, Ronellenfitsch U. Antibiotic therapy for acute uncomplicated appendicitis: a systematic review and meta-analysis. Int J Colorectal Dis. 2019 Jun;34(6):963-971. https://doi.org/10.1007/s00384-019-03296-0.
28. Orthopoulos G, Santone E, Izzo F, Tirabassi M, Pérez-Caraballo AM, Corriveau N, Jabbour N. Increasing incidence of complicated appendicitis during COVID-19 pandemic. Am J Surg. 2020 Sep 28: S0002-9610(20)30595-X. https://doi.org/10.1016/j.amjsurg.2020.09.026.
29. Georgiou R, Eaton S, Stanton MP, Pierro A, Hall NJ. Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis. Pediatrics. 2017 Mar;139(3):e20163003. https://doi.org/10.1542/peds.2016-3003.
30. Huang L, Yin Y, Yang L, Wang C, Li Y, Zhou Z. Comparison of Antibiotic Therapy and Appendectomy for Acute Uncomplicated Appendicitis in Children: A Meta-analysis. JAMA Pediatr. 2017 May 1;171(5):426-434. https://doi.org/10.1001/jamapediatrics.2017.0057.
31. Biondi, A., Di Stefano, C., Ferrara, F. et al. Laparoscopic versus open appendectomy: a retrospective cohort study assessing outcomes and cost-effectiveness. World J Emerg Surg 11, 44 (2016). https://doi.org/10.1186/s13017-016-0102-5
32. GlobalSurg Collaborative. Laparoscopy in management of appendicitis in high-, middle-, and low-income countries: a multicenter, prospective, cohort study. Surg Endosc. 2018 Aug;32(8):3450-3466. https://doi.org/10.1007/s00464-018-6064-9.
33. Emile SH, Hamid HKS. A critical review of the safety of minimally invasive surgery in the era of COVID-19. Minim Invasive Ther Allied Technol. 2020 Oct 27:1-7. https://doi.org/10.1080/13645706.2020.1838549.
34. Dreifuss NH, Schlottmann F, Sadava EE, Rotholtz NA. Acute appendicitis does not quarantine: surgical outcomes of laparoscopic appendectomy in COVID-19 times. Br J Surg. 2020 Jul 25. https://doi.org/10.1002/bjs.11806. Epub ahead of print.