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Changes in appendicitis treatment during the COVID-19 pandemic – A systematic review and meta-analysis

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ABSTRACT

Background: During the COVID-19 pandemic in 2020 a decrease of emergency consultations and modification in treatment of numerous medical conditions were observed. Aim of this paper was to evaluate the effect of the COVID-19 pandemic on incidence, treatment strategies, severity, length of hospital stay and time of presentation in adults and children with acute appendicitis.

Methods: A systematic literature search of Pubmed, Embase and Cochrane databases was performed, and eligible studies used to perform a meta-analysis.

Results: 46 suitable studies were identified with an overall reduction of appendicitis cases by 20.9% in adults and an increase of 13.4% in children. The rate of open appendectomies increased without statistical significance in both groups (adults: 8.5% vs. 7.1%, $P = 0.32$; children: 7.1% vs. 5.3%, $P = 0.13$), whereas the rate of antibiotic treatment increased significantly ($P = 0.007$; $P = 0.03$). Higher rates of complicated appendicitis were observed in adults (adults: OR 2.00, $P < 0.0001$; children: OR 1.64, $P = 0.12$). Time to first consultation did not change significantly (adults: 52.3 vs. 38.5 h – $P = 0.057$; children: 51.5 vs. 32.0 h – $P = 0.062$) and length of stay was also not lengthened during the pandemic (adults: 2.9 vs. 2.7 days, $P = 0.057$; children: 4.2 vs. 3.7 days, $P = 0.062$).

Conclusion: The COVID-19 pandemic of 2020 had major impact on incidence and treatment strategies of acute appendicitis. Results of this meta-analysis might be another hint to support the theory that appendicitis is not a progressive disease and surgeons can safely consider antibiotic therapy for acute uncomplicated appendicitis.

1. Introduction

Acute appendicitis (AA) is a common cause for acute abdominal pain and the most frequent indication for abdominal emergency surgery worldwide. Lifetime risk for developing AA is approximated at 6.7% for women and 8.6% for men [1,2]. AA can be divided into uncomplicated appendicitis i.e. phlegmonous and complicated appendicitis including perforation, abscess and peritonitis [2].

Current gold standard treatment is the appendectomy, in the majority of cases performed laparoscopically. However, a number of studies, including a Cochrane systematic review and meta-analysis, evaluated the option of antibiotic treatment (AT) for acute, uncomplicated appendicitis [3–6]. Successful treatment was reported in 73.4% of patients treated with antibiotics and 97.4% of patients who received appendectomy, respectively [6].

COVID-19 began to spread in December 2019 in Wuhan, China and over the course of weeks worldwide [7,8]. Until March 2021 more than 500,000 people in the Unites States and over 2.5 million people worldwide lost their lives due to the disease [9]. To preserve hospital capacity for COVID-19 patients and urgent Non-COVID patients, strategies were proposed to postpone elective surgery and non-surgical therapy was counselled where possible [10,11]. During the pandemic,

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a significant change in overall emergency room visits was noticeable leading to reduced incidence of myocardial infarction, traumatology patients and likewise patients with AA [12,13].

Aim of this systematic literature review and meta-analysis was to evaluate the overall effect of COVID-19 on acute appendicitis and its treatment.

2. Methods

2.1. Study selection and search strategy

PubMed database, Embase database and Cochrane database were searched on February 1st' 2021. Search terms were *COVID* and *append** with MESH terms *sars cov 2, sars-cov-2, covid 19* and *covid-19*. No time filter was applied. Studies with available full text in English or German language were included in the analysis. No study type was excluded. Studies that addressed at least one of the outcomes of interest regarding patients with AA and compared a time period before the onset of the COVID-19 pandemic to a time period during the pandemic were included. Case numbers of COVID-19 started rising progressively throughout the world, therefore no specific date was set to divide the two groups. If more than two time periods were analysed in one study, the same period in the prior year was chosen. Frequently, the compared periods were not equally long, making studies ineligible for inclusion in selected outcomes of interest. Manuscripts that focused solemnly on paediatric patients were analysed separately.

Duplicates were removed and articles were firstly screened by title and abstract and secondly reviewed in full text for eligibility criteria by two independent reviewers (FK and SM). Disagreement on eligibility of articles was discussed and solved by consensus.

The systematic review and meta-analysis has been performed in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines [14].

The study selection process is pictured in the PRISMA flowchart (Fig. 1) [14]. Outcomes of interest were defined and are listed in Table 1. The systematic review and meta-analysis was registered to PROSPERO on 5th of March 2021 and was updated regularly (registration number: CRD42021240722).

Table 1
Defined outcomes of interest.

Outcomes of interest
Overall change in the number of patients with AA
Rate of performed open appendectomies
Rate of AA patients treated with antibiotics
Rate of complicated appendicitis including abscess, peritonitis and perforation
Time from beginning of symptoms to presentation in the emergency unit – Delay in presentation
Length of hospital stay

Literature organization was performed with EndNoteX9 while charts, tables and the statistical analysis were performed using Rev-Man5, Graphpad Prism 9, Microsoft Excel, Word and PowerPoint. Measure of effects was assessed with odds ratio (OR) and random effects model as well as corresponding 95% confidence interval (CI 95%). Statistical significance was assessed by performing descriptive statistics. Statistical heterogeneity was assessed by calculating the Chi^2 and I^2 tests.

2.2. Risk of bias assessment

Risk of bias was assessed using the ROBINS-I tool for uncontrolled before-after studies [15]. Evaluated risks of bias were: bias due to confounding, in selection of participants into the study, in classification of intervention, due to deviations from intended interventions, due to missing data, in measurement of outcome and in selection of the reported result.

The risk of bias was divided into low, medium and high risk of bias as well as unclear risk of bias if no information regarding the evaluated risk of bias was available in the study.

Most commonly, a risk of bias was noticeable in the selection of participants in the study. A great majority included only patients who received surgical therapy or were treated on surgical wards. Therefore, no information about conservatively treated patients during the time period was available in these studies. Furthermore, a number of studies did not mention the intended therapy and reported predominantly the outcome. Therefore, these studies were marked with an unclear risk in risk of bias due to deviations from intended interventions. Detailed risk

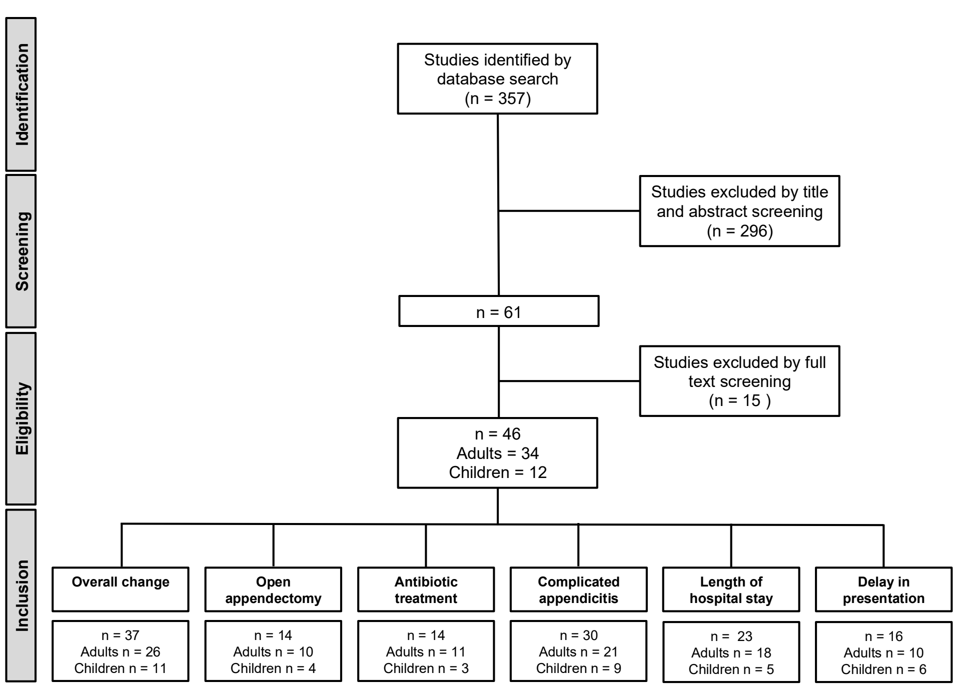

Fig. 1. PRISMA flow diagram of the study identification and selection process.

of bias is listed in Table 2 in the appendix.

3. Results

After removing duplicates, 357 articles were identified. Screening by title and abstract left 61 manuscripts for full text analysis. Of these, 46 manuscripts were eligible with 34 articles on adults and 12 on paediatric patients (below the age of 18). Articles were matched according to the defined outcomes of interest (Fig. 1 and Table 3 - appendix). Most studies were case series, single-centre or multi-centre retrospective analysis. Two studies were population bases analysis on insurance claims data.

3.1. Incidence of acute appendicitis

3.1.1. Adults

26 studies described a change in case number of appendicitis and/or appendectomies between comparable time periods before and during the COVID-19 pandemic in adults [16–41]. Studies were conducted in 15 countries (as shown in Figs. 2 and 3). Several studies did not report the number of included patients but the change of appendicitis cases in percent. Therefore, no absolute data are available on the change in appendicitis. Overall, 23 studies reported a reduction of appendicitis/appendectomy cases during the pandemic, compared to a similarly long time period in previous years. 3 studies described an increase of cases (mean increase: 80,0%) [16,25,36]. These three studies were performed in Austria, Nepal and Turkey. Two unrelated studies from turkey [30,34] depicted a decrease in appendectomy numbers.

Overall, the number of appendicitis/appendectomies was reduced by 20.9% (95% CI -2.41 to −39.44). Two studies were population-based analysis that evaluated data from more than 23,000 patients (Köhler et al.: 16,498, Maneck et al.: 6505) in Germany and reported a reduction of cases of 12.9% and 18.9%, respectively [23,26].

3.1.2. Children

11 studies from 7 different countries (Australia, France, Israel, Italy, Spain, UK and US) described the influence of the pandemic on appendicitis cases in children. Overall, there was great heterogeneity with 7 studies describing an increase of appendicitis cases and 4 studies reporting a reduction in case numbers. The mean change of appendicitis cases revealed an increase by 13.4% compared to the period before the onset of COVID-19 (Table 4) [42–52]. Similar to the results in adults, some studies did not report absolute data and a change of cases in percent was available.

3.2. Surgical therapy

3.2.1. Adults

10 studies compared the rate of open and laparoscopic appendectomies (OA and LA) before and during the COVID-19 pandemic in adults [11,16,23,30,35,40,53–56]. Overall, 15,589 appendectomies were performed. Due to the unequally long time periods in these studies 11,942 appendectomies were performed before the pandemic and 3647 during the pandemic. Overall, the majority of appendectomies (n = 14,436) were performed laparoscopically while only 1153 procedures were performed open. Absolute numbers of open surgeries before and during the pandemic are not comparable due to the above-mentioned difference of the observation periods. During the pandemic the percentage of open procedures was higher than before the pandemic (8,5% vs. 7.1%). Results are shown in Fig. 4A, the P-value was 0.32. The evaluated OR when comparing the number of open procedures before and during COVID-19 was 1.77 (95% CI 0.58–5.38).

3.2.2. Children

4 studies, including 208 children aged 0–18 years, described the influence of the pandemic on the rate of open appendectomies in children [43,46–48]. Of these 208 children, 13 received an open

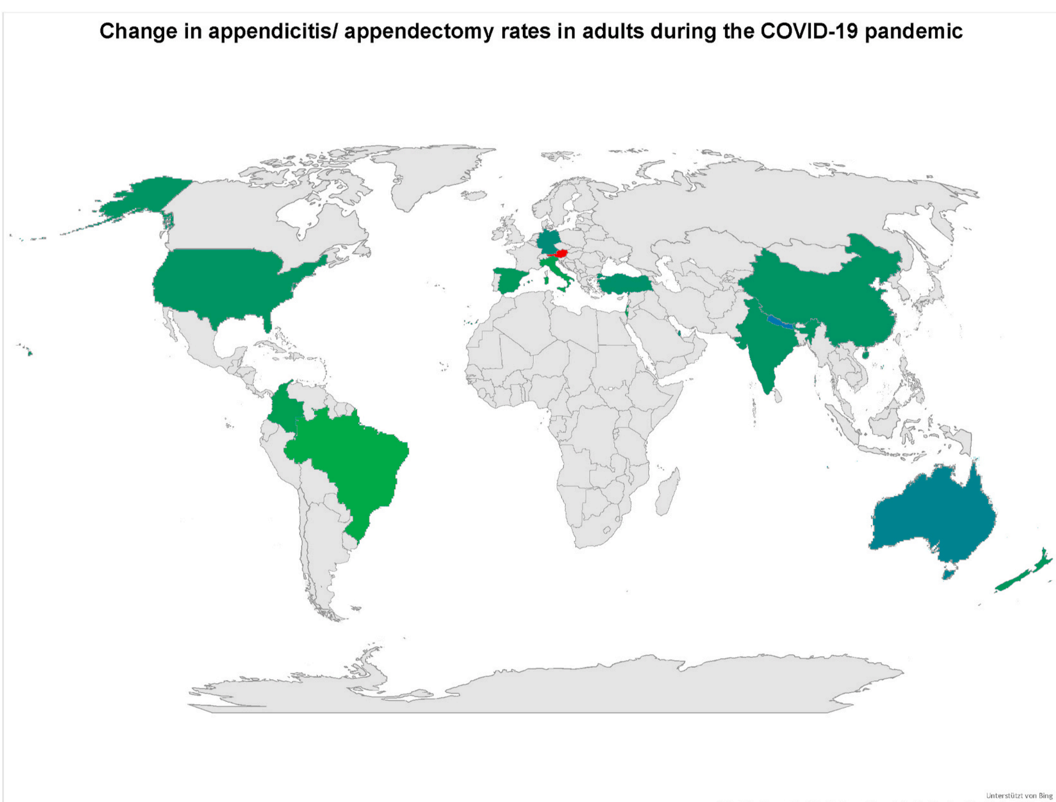

Fig. 2. Map of changes in appendicitis/appendectomy rates in adults. Green – reduction; blue – no change; red – increase; grey – no information available. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

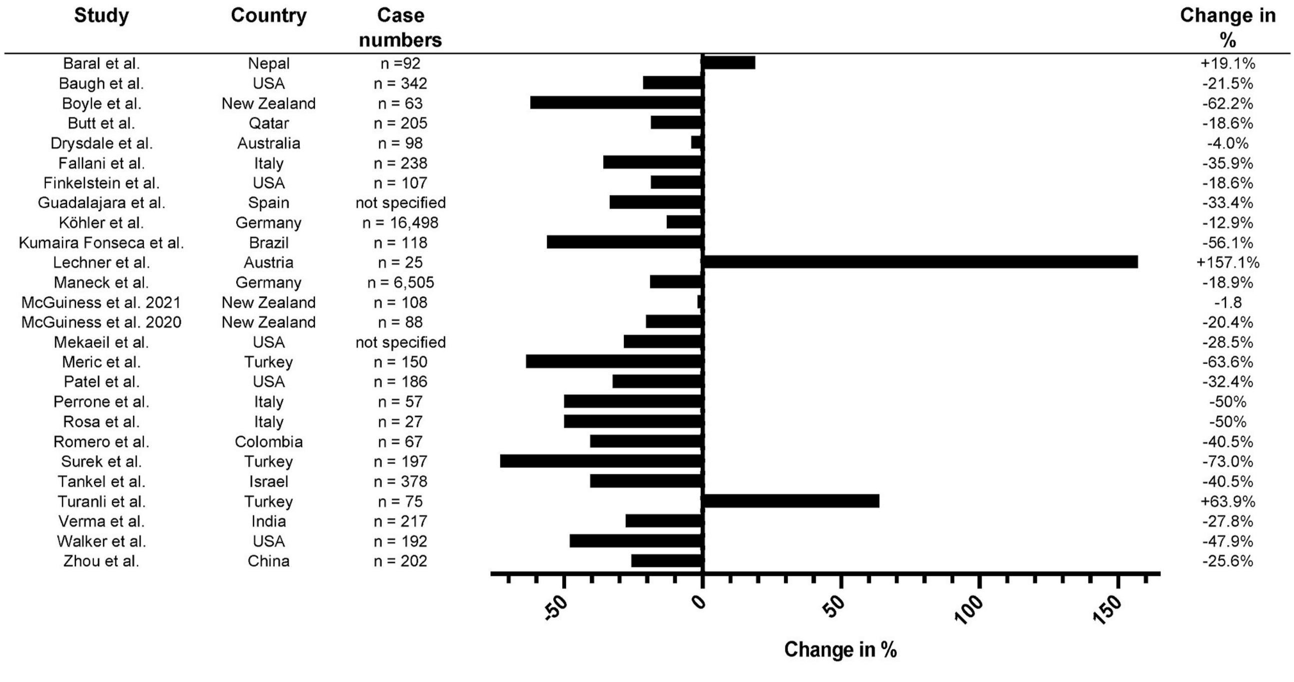

Fig. 3. Change of appendicitis/appendectomy rates in during the COVID-19 pandemic compared to a similar time period before the onset of the pandemic.

Table 4
Changes in appendicitis/appendectomy cases in children.

Study-ID	Country	Case numbers	Change in %
Bada-Bosch et al.	Spain	n = 46	−60.6%
Fisher et al.	US	n = 1346	+19.6%
Gerall et al.	US	n = 89	+17.1%
Lee-Archer et al.	Australia	n = 115	−15.8%
La-Pergola et al.	Italy	n = 178	−6.5%
Montalva et al.	France	n = 108	+76.9%
Pines et al.	US	n = 388	−19%
Place et al.	US	n = 160	+28.6%
Raffaele et al.	Italy	n = 27	+7.7%
Sheath et al.	UK	n = 172	+80%
Snapiri et al.	Israel	n = 161	+1.3%

appendectomy (6.3%). In the study performed by Montalva et al., no child received OA, therefore data of this manuscript was not calculable. The difference in surgical approach was not significant with an OR of 2.35 (CI 95% 0.78–7.05) and P-value of 0.13. The included studies displayed a rather high heterogeneity (P = 0.04). Results are shown in Fig. 4B.

3.3. *Antibiotic therapy*

3.3.1. *Adults*

11 studies examined the amount of conservatively treated patients with suspected AA before and during the COVID-19 pandemic [11,16,18,23,31,35,37,41,53–55]. Overall data of 18,084 patients were analysed, 4242 during and 13,842 before the onset of COVID-19. The great difference in overall numbers is again due to the unequal time periods compared in a number of studies. During the pandemic 16.1% of patients with AA were treated with AT instead of appendectomy, while before the pandemic 13.1% received AT. As shown in Fig. 5A, the rate of appendicitis treated with AT in adults increased significantly during the pandemic (P = 0.007) with an OR of 2.89 (CI 95% 1.34–6.20).

3.3.2. *Children*

3 studies including 144 patients investigated the rate of children treated with antibiotics instead of appendectomy [46,48,49]. As shown in Fig. 5B, children were more likely to receive antibiotic treatment instead of appendectomy for AA during the pandemic. OR for receiving an antibiotic agent was 3.65 (CI 95% 1.14–11.67) with a P-value of 0.03. Before the pandemic 4.7% of children with AA received antibiotic treatment, during the pandemic the percentage arose to 17.5%.

3.4. *Complicated appendicitis*

3.4.1. *Adults*

21 studies evaluated the rate of complicated appendicitis (defined as abscess, perforation and peritonitis) before and during the onset of the COVID-19 pandemic.

Overall 25.581 patients were analysed: 18,107 before the onset of the pandemic and 7474 during the pandemic [16,18,20,23–27,30,31,34–36,41,54–59]. During the pandemic 26.6% of patients had complicated appendicitis, compared to 22.2% before the onset of the pandemic. As shown in Fig. 6A the relative rate of complicated appendicitis was higher during the pandemic with an OR of 2.00 (CI 95% 1.60–2.50). This effect has statistical significance with P-value < 0.00001.

3.4.2. *Children*

9 studies examined the effect of COVID-19 on the rate of complicated appendicitis in children, covering 2065 children (1650 before and 415 during the pandemic) [42–44,46–49,52,60]. There was a trend seen towards more CA during the pandemic, but this effect is without statistical significance (P = 0.12). Odds ratio was described at 1.64 (95% CI 0.88–3.04) as shown in Fig. 6B.

3.5. *Length of stay*

3.5.1. *Adults*

18 studies [11,16,18,24,26,27,30,31,35,39–41,53–58] described the length of hospital stay (in days) in adults before and during the COVID-19 pandemic.

Mean length of stay for adults in the Non-COVID group was 2.7 days (95% CI 2.05–3.27) and 2.9 days (95% CI 2.23–3.57) during the pandemic. The *t*-test did reveal no statistical significance (P = 0.69).

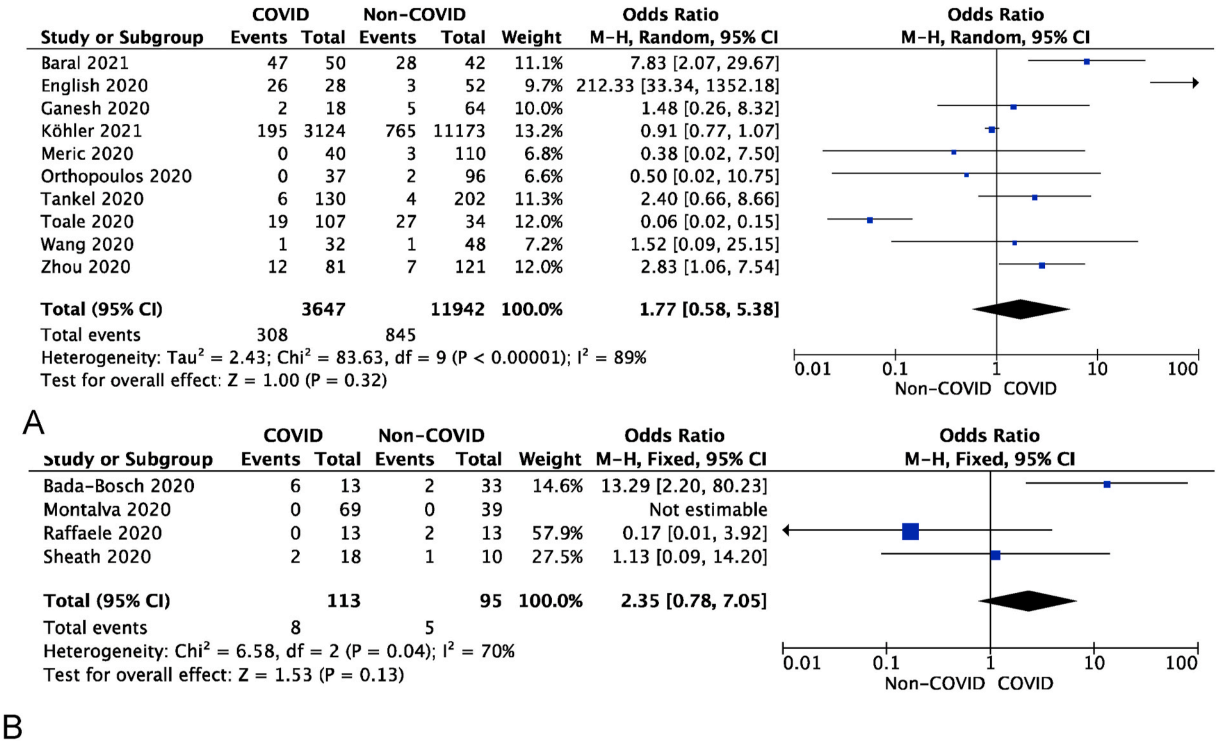

Fig. 4. A/B Forest plot of open appendectomies in adults (A) and children (B) before and during the onset of the pandemic.

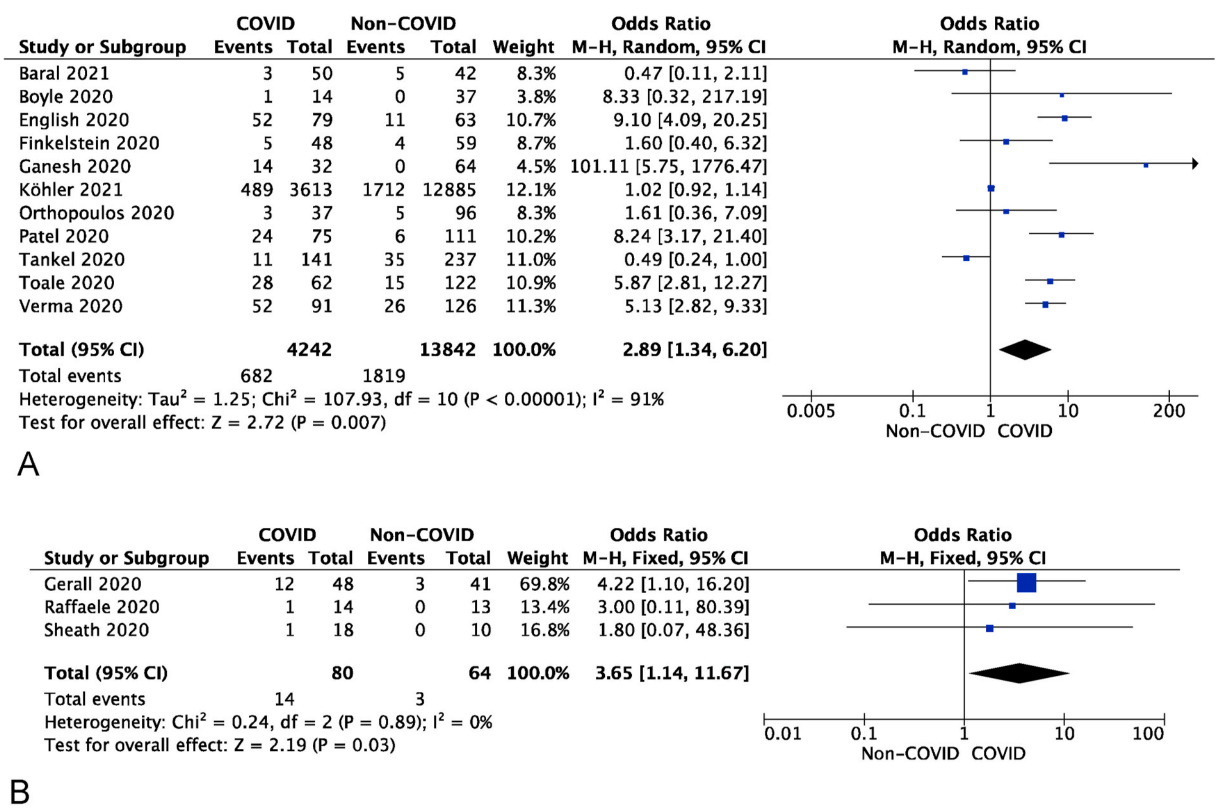

Fig. 5. A/B Forest plot of antibiotic treatment for AA before and during the pandemic in adults (A) and children (B).

3.5.2. Children

5 studies evaluated the length of hospital stay in children before and during the COVID-19 pandemic [43,46–49].

Mean length of stay before the pandemic was 3.7 days (95% CI 2.53–4.79). During the pandemic length of stay was 4.2 days (95% CI 3.77–4.64), which is without statistical significance (P = 0.25). The results are graphically shown in Fig. 7 A and B.

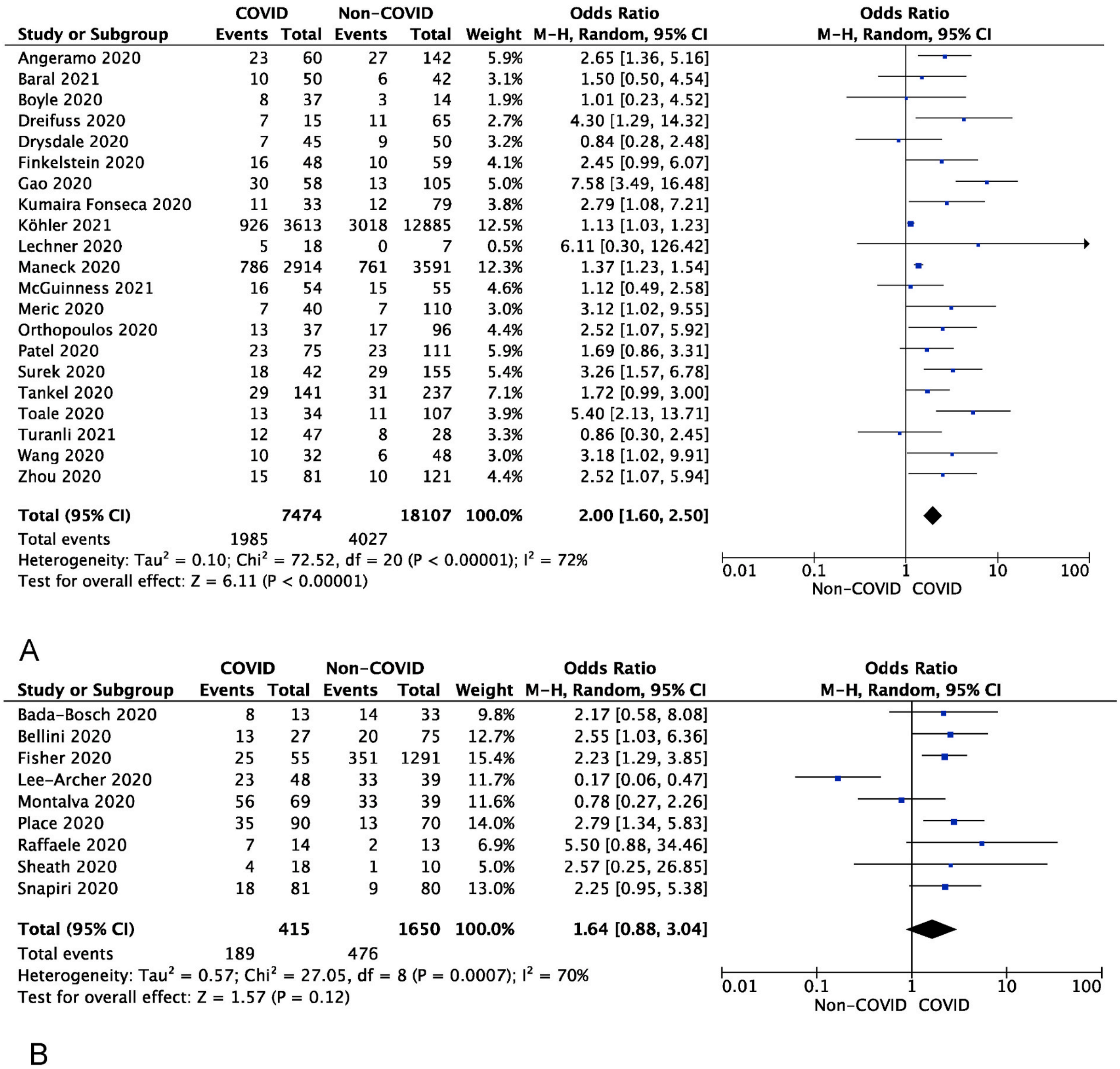

Fig. 6. A/B Forest plot of complicated appendicitis in adults (A) and children (B) before and after the onset of COVID-19.

3.6. *Time from onset of symptoms until presentation in the emergency unit*

3.6.1. *Adults*

10 studies examined the time from beginning of symptoms until presentation in hospital for adults [16,18,24,31,35,41,56–59]. Studies described the duration in hours or full days. Before the onset of COVID-19, mean time until presentation in hospital was 38.5 h (95% CI 27.6–49.40) and after the onset of COVID 52.3 h (95% CI 41.47–63.13). The difference between the means of both groups was 13.8 h and the P-value was 0.057.

3.6.2. *Children*

6 studies examined the effect of COVID-19 on symptom duration until presentation in hospital in children [43,45,46,48–50].

Symptom duration was 32 h (95% CI 19.39–44.61) before seeking medical help before the pandemic and 51.5 h during the pandemic (95% CI 31.17–74.53). P-value was 0.062. Changes in time until presentation in hospital are shown in Fig. 7C and D.

4. Discussion

The performed literature search and meta-analysis revealed a mean reduction of appendicitis/appendectomy cases of 20.9% in adults and an increase of 13.4% in children. Due to scarce data in some studies, no further statistical investigations were applicable. Significantly more patients received antibiotic treatment for AA during the pandemic (adults P = 0.0007; children P = 0.03) and the relative rate of adult patients suffering from complicated appendicitis increased (P < 0.00001). The rate of open appendectomies did not change significantly, as well as length of hospital stay and time from symptom onset to presentation in hospital.

The COVID-19 pandemic had a major impact on the number of emergency consultations in all specialties and likewise emergency surgeries. Numerous articles were published describing these changes and one possible explanation, the fear of getting infected with COVID-19 during a hospital visit was stated [12,13]. Even before the beginning of the pandemic, it was an ongoing debate whether acute appendicitis is an evolving disease, that progresses from uncomplicated to complicated and perforation. Furthermore, insecurity remains whether antibiotic treatment presents an equally safe treatment option to surgery for

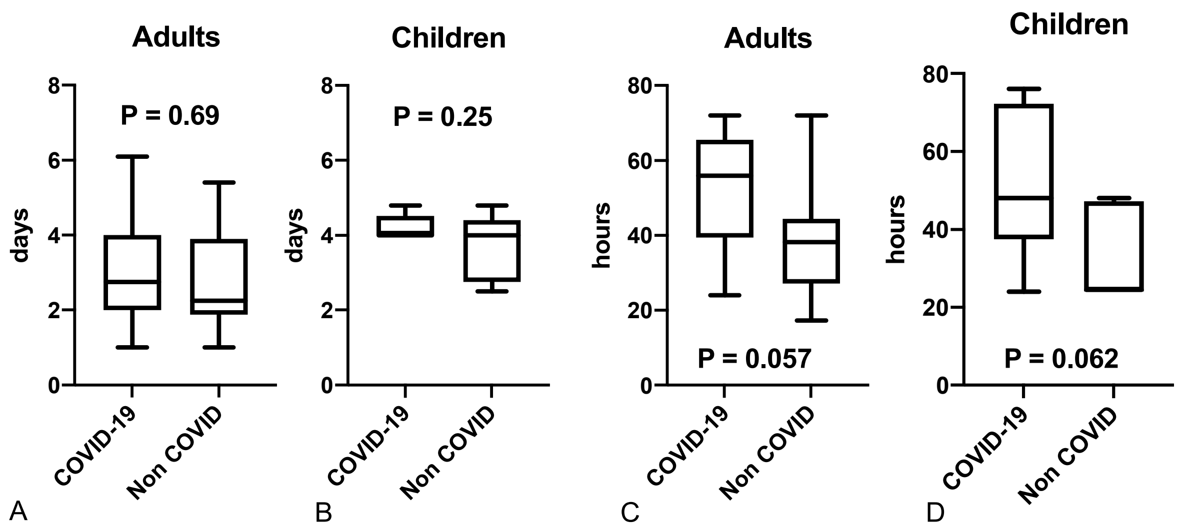

Fig. 7. A–D Length of hospital stay in days during and before the pandemic in adults (A) and children (B). Time from the beginning of symptoms until presentation in the emergency department in hours during and before the pandemic in adults (C) and children (D).

uncomplicated cases [2,6].

During the pandemic significantly more patients (adults as well as children) received antibiotic therapy instead of surgical resection of the appendix. Nevertheless, provided data does not report the outcome of AT, especially the rate of salvage surgery or relapse of appendicitis. Recently, the CODA collaborative reported that 29% of conservatively treated patients needed appendectomy within the following 90 days [3], therefore a similar recurrence rate can be suspected during the pandemic.

It is widely discussed, that AT was increasingly administered due to fear of staff infection with COVID-19 during intubation but in contrast to this assumption, Cook and Lennane described an even lower infection rate for anaesthesia and intensive-care staff, compared to other hospital workers due to the conscientious use of personal protective equipment [61]. Treating patients with AT as inpatients does spare surgical capacity but the overall hospital stay is significantly longer [6]. Oral antibiotics provided by general practitioners would lead to burden relief of hospitals but the data in this study does not include information about outpatient treatment, therefore we are not able to address this point.

Especially in times of limited surgical capacity but vacant overall capacity, antibiotic treatment for uncomplicated appendicitis can be sensible.

In contrast to the results described in adults there was an increase of appendicitis cases in children. Besides respiratory symptoms, abdominal pain is one of the most frequently described symptoms in children with COVID-19 [62]. Most of the included studies describing appendicitis in infants did not report if the participants were tested for COVID-19. Looking on the worldwide incidence of COVID-19 in 2020, it might be possible that part of the increase was due to COVID-related abdominal pain in children.

It is stated, that appendicitis is not a progressive disease which develops from catarrhal to gangrenous and perforation but rather due to two different entities for uncomplicated and complicated appendicitis with uncomplicated appendicitis representing a reversible form that settles with antibiotics or spontaneously [2]. During the pandemic significantly higher rates of complicated appendicitis were visible, while the time period from symptom onset to presentation in the emergency unit was longer but did not reach statistical significance for adults as well as children. This can be another clue to confirm the theory of two different entities of appendicitis. The increase of complicated appendicitis might be explained with the decrease of overall cases that was triggered by the lower numbers of uncomplicated appendicitis while numbers of complicated appendicitis stayed level.

Another interesting aspect is the higher rate of open appendectomies during the pandemic, even if it did not reach statistical significance. On the one hand an explanation might be the higher percentage of complicated appendicitis cases leading to more complex surgeries and the need for open procedures. On the other hand, especially in the beginning of the pandemic in early 2020 only scarce information about SARS-CoV-2 and its transmission risk was available. Therefore, for example the *Royal College of Surgeons*, released a statement intended to minimize the infection risk for medical staff: laparoscopy should be performed with high caution and only in selected cases when benefits of the laparoscopic approach are exceeding the potential risk of SARS-CoV-2 transmission due to aerosol disposal. Due to this statement, a rise in open appendectomies seems allegeable [63]. Looking at the manuscript by English et al., 26 of 28 appendectomies were performed with an open approach during the pandemic compared to 3 out of 52 before the pandemic [11]. Later on, discussion arose if laparoscopy might even be the more secure option as it provides a barrier between surgeons and abdominal fluids while on the other hand laparoscopic surgeries are associated with longer operation time and therefore a possible higher risk of transmission. Filtering surgical smoke seemed to reduce the risk of transmission and was therefore recommended [64]. Recent data showed that abdominal fluid samples of patients with severe COVID-19 pneumonia were tested negative for the virus [65], therefore laparoscopic or open surgery do not seem to influence the risk for infection for surgical staff.

Currently the COVID-19 pandemic is enduring for more than one year and a number of countries are facing a third or fourth wave of infections, partly due to virus mutations and halting progression of vaccinations [66].

The majority of included studies were performed during the first months of the pandemic, in early and mid 2020. During these months, the knowledge about SARS-CoV-2 was only just gathering and furthermore most countries were facing shortages of medical and personal protective equipment as well as testing capacity [67]. Currently, most hospitals and health care providers developed strategies to minimize the risk of infection for patients and medical staff while still providing high quality medical care for COVID-19 patients as well as others i.e. appendicitis patients. Therefore, it is a thought-provoking question if the changes in appendicitis treatment described in this manuscript are still visible or if case numbers and treatment modalities returned to the pre-COVID baseline.

The performed meta-analysis has some limitations: giving the circumstances of the COVID-19 pandemic obviously there are no randomized controlled trials available. This leads to a limitation in explanatory power of this meta-analysis. The included studies differ in quality and completeness of data and in a great number of manuscripts the observation periods were not equally long mostly comparing the added numbers of 2017, 2018 and 2019 with 2020. Therefore, the absolute values regarding the outcomes of interest cannot be compared with each other. In the majority of studies, case numbers were rather small with the most of them having less than 250 participants and being single centre retrospective studies.

5. Conclusion

During the pandemic the overall incidence of acute appendicitis dropped significantly while more patients presented with complicated appendicitis. On the other hand, in these times of special exertion for health care systems, antibiotic treatment for acute, uncomplicated appendicitis was more frequently used and seemed to be an option to spare valuable and concise surgical capacities.

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Authors contribution

FK,AH,CK and AW designed the study, FK, SM, LR and KB performed the literature search, FK and AW performed the data-analysis, FK, AW, JL, SF and CTG wrote the manuscript, FK, AH and AW proofread the manuscript.

Please state whether ethical approval was given, by whom and the relevant Judgement's reference number

No ethical approval needed.

Research registration Unique Identifying number (UIN)

1. Name of the registry: Prospero.
2. Unique Identifying number or registration ID: CRD42021240722.
3. Hyperlink to your specific registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=240722.

Guarantor

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Armin Wiegering.

Data statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials. Furthermore data is openly available on the used databases (Pubmed, Embase and Cochrane).

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors have no conflict of interest to declare.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2021.106148.

Appendix

Table 2
Risk of bias assessment using the ROBINS-I tool.

Table 3
List of in the meta-analysis included studies and attributed outcome of interest, divided into adults and children

Study ID	change in case numbers	surgical therapy	antibiotic treatment	complicated appendicitis	length of stay	time to presentation
Adults:						
Angeramo et al.				X	X	X
Baral et al.	X	X	X	X	X	X
Baugh et al.	X					

(continued on next page)

Table 3 (*continued*)

Study ID	change in case numbers	surgical therapy	antibiotic treatment	complicated appendicitis	length of stay	time to presentation
Boyle et al.	X		X	X	X	X
Butt et al.	X					
Dreifuss et al.				X	X	X
Drysdale et al.	X			X		
English et al.		X	X		X	
Fallani et al.	X					
Finkelstein et al.	X		X	X	X	X
Ganesh et al.		X	X		X	
Gao et al.				X		X
Guadalajara et al.	X					
Köhler et al.	X	X	X	X		
Kumaira Fonseca et al.	X			X	X	X
Lechner et al.	X			X		
Maneck et al.	X			X	X	
McGuiness et al., 2020	X					
McGuiness et al., 2021	X			X	X	
Mekaeil et al.	X					
Meric et al.	X	X		X	X	
Orthopoulos et al.		X	X	X	X	
Patel et al.	X		X	X	X	X
Perrone et al.	X				X	
Romero et al.	X					
Rosa et al.	X					
Surek et al.	X			X		
Tankel et al.	X	X	X	X	X	X
Toale et al.		X	X	X	X	
Turanli et al.	X			X		
Verma et al.	X		X			
Walker et al.	X					
Wang et al.		X		X	X	X
Zhou et al.	X	X		X	X	
Children:						
Bada-Bosch et al.	X	X		X	X	
Bellini et al.				X		
Fisher et al.	X			X	X	X
Gerall et al.	X		X			X
La Pergola et al.	X					X
Lee-Archer et al.	X			X		
Montalva et al.	X	X		X	X	X
Pines et al.	X					
Place et al.	X			X		
Raffaele et al.	X	X	X	X	X	X
Sheath et al.	X	X	X	X	X	X
Snapiri et al.	X			X		

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