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***Observational Study***

**Effect of the COVID-19 pandemic on patients with presumed diagnosis of acute appendicitis**

Akbulut S *et al.* Management of AAP during COVID-19 pandemic

## **Abstract**

### **BACKGROUND**

Acute appendicitis (AAp) is the most frequent cause of acute abdominal pain, and appendectomy is the most frequent emergency procedure that is performed worldwide. The coronavirus disease 2019 (COVID-19) pandemic has caused delays in managing diseases requiring emergency approaches such as AAp and trauma.

### **AIM**

To compare the demographic, clinical and histopathological outcomes of patients with AAp who underwent appendectomy during pre-COVID and COVID-19 periods.

### **METHODS**

The demographic, clinical, biochemical, and histopathological parameters were evaluated and compared in patients who underwent appendectomy with the presumed diagnosis of AAp in the pre-COVID (October 2018-March 2020) and COVID (March 2020-July 2021) periods.

### **RESULTS**

Admissions to our tertiary care hospital for AAp have increased 44.8% in the COVID period. Pre-COVID ( $n = 154$ ) and COVID ( $n = 223$ ) periods were compared for various parameters and we have found that there was statistically significant difference in terms of variables such as procedures performed on the weekdays or weekends [odds ratio (OR): 1.76;  $P = 0.018$ ], presence of AAp findings in ultrasonography (OR: 15.4;  $P < 0.001$ ), confirmation of AAp in the histopathologic analysis (OR: 2.6;  $P = 0.003$ ), determination of perforation in the appendectomy specimen (OR: 2.2;  $P = 0.004$ ), the diameter of the appendix ( $P < 0.001$ ) and hospital stay ( $P = 0.003$ ). There was no statistically significant difference in terms of interval between the initiation of symptoms and admission to the hospital between the pre-COVID [median: 24 h; interquartile range (IQR): 34] and COVID (median: 36 h; IQR: 60) periods ( $P = 0.348$ ).

The interval between the initiation of symptoms until the hospital admission was significantly longer in patients with perforated AAp regardless of the COVID or pre-COVID status ( $P < 0.001$ ).

## CONCLUSION

The present study showed that in the COVID period, the ultrasonographic determination rate of AAp, perforation rate of AAp and duration of hospital stay increased; the other hand, negative appendectomy rate decreased. There was no statistically significant delay in hospital admissions that would delay the diagnosis of AAp in the COVID period.

**Key Words:** SARS-CoV-2; COVID-19 pandemic; Acute appendicitis; Perforated appendicitis; Negative appendectomy

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**Core Tip:** World Health Organization declared the coronavirus disease 2019 (COVID-19) pandemic as a public health emergency of international concern. Previous studies have shown that the anxiety related with the fear of the COVID-19 pandemic has reframed individuals from admission to hospitals even in very emergent conditions. The present study showed that the complicated acute appendicitis rate increased which has led to prolonged durations of hospital stay during the COVID-19 pandemic. The present study also showed that the negative appendectomy rate decreased during the pandemic.

## INTRODUCTION

5 Coronavirus disease 2019 (COVID-19) emerged as a severe acute viral pneumonia in the Wuhan city of Hubei province in China. Soon, investigations showed that a new type of coronavirus caused this condition and it was genotyped and renamed as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease was renamed as the COVID-19<sup>[1-5]</sup>. Soon the disease spread to the globe and caused a world-wide catastrophe<sup>[2]</sup>. In January 30, 2020, World Health Organization (WHO) declared the disease as a public health emergency of international concern (PHEIC) or in other words a pandemic. In the beginning of the pandemic, there were no effective anti-viral treatment or a preventive vaccination which led to promotion of isolation methods such as social distancing, mask and staying at home to prevent transmission of the disease between the individuals<sup>[1]</sup>. The first confirmed case of COVID-19 in Turkey was declared on March 11, 2020. Rapidly, Turkish Ministry of Health established a scientific advisory board and various guidelines were determined in accord with the recommendations of WHO for the prevention and management of COVID-19 pandemic. Cancer surgeries, emergent cases such as appendectomy, viscus perforations and trauma were allowed provided that necessary precautions were taken in the operating theatre and in-patients wards. It was recommended that any elective procedure shall be postponed<sup>[6,7]</sup>.

In general, acute appendicitis (AAp) is the most frequent cause of acute abdominal pain that requires hospital admissions and appendectomy is the most frequent emergency procedure that is performed<sup>[2,4,8,9]</sup>. Appendectomy is the gold standard treatment for AAp; however, non-operative treatment can be performed in selected cases (non-complicated AAp) and in global crisis such as COVID-19 pandemic<sup>[9-11]</sup>. The delay in the diagnosis and management of AAp leads to life threatening conditions such as uncontained perforation, peritonitis and abscess formation<sup>[2,11]</sup>. Studies have shown that SARS-CoV-2 infection had a significant impact on the physical and psychological health of the individuals. The anxiety related with the fear of the disease has reframed individuals from admission to hospitals even in very emergent conditions<sup>[2]</sup>. This condition had an impact on the patients with AAp for these patients

had delayed hospital admissions and preferred non-operative treatments such as antibiotic therapy during the pandemic<sup>[2,9,12-16]</sup>. Studies have reported that delay in hospital admissions of the patients with AAP have led to increased complication rates<sup>[2,17]</sup>. There are also contradictory studies that show that the hospital admissions did not show significant difference during the COVID-19 pandemic<sup>[18-22]</sup>. The aim of the present study is to comparatively evaluate the impact COVID-19 pandemic with pre-pandemic period regarding the patients who were operated for AAP in terms of negative appendectomy rates and perforation rates. Our secondary aim was to evaluate the impact of pandemic on the hospital admission rates of the patients with AAP.

## **MATERIALS AND METHODS**

In Turkey, the first confirmed case of COVID-19 was declared in March 11<sup>th</sup> 2020. Between March 2020 and July 2021, 223 patients were operated on with the presumed diagnosis AAP at the Department of Surgery, Inonu University Faculty of Medicine, Malatya, Turkey. These patients were included in the COVID group (case group). To evaluate the impact of the COVID-19 pandemic on patients' behavioral patterns, 154 patients who underwent appendectomy between October 2018 and March 2020 were included in the pre-COVID group (control group).

The study parameters include age (years), gender (female, male), timing of surgery (daytime *vs* night-time), timing of surgery by working days (weekdays *vs* weekends), ultrasonographic (US) findings (AAP present or absent), histopathologic findings (AAP present or absent), status of appendiceal perforation (present or absent), type of surgery (open *vs* laparoscopic), postoperative antibiotics use (yes or no), other histopathological features detected in surgical specimens (neuroendocrine tumor, granulomatous appendicitis, serrated adenoma, cystadenocarcinoma, mucinous adenocarcinoma, fibrous obliteration, hyperplastic polyps, lymphoid hyperplasia *etc.*), white blood cell (WBC), neutrophil, lymphocyte, platelets (PLTs), platecrit (PCT), red cell distribution width (RDW), platelet distribution width (PDW), mean corpuscular hemoglobin (MCH), mean platelet volume (MPV), mean corpuscular volume (MCV), C-reactive

protein (CRP), total bilirubin (TBil), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), white cell neutrophil ratio (WNR), white cell lymphocyte ratio (WLR), length of appendix (mm), width (diameter) of appendix (mm), duration of hospital stay (days), and pre-admission interval (hour). The city that our institution is situated in Malatya city with a total population of 806156 people. Our institution has 301 intensive care unit bed and 1368 beds in in-patient wards.

### ***Diagnostic work-up of the patients in our institution***

The diagnosis of AAp was established using the results of combination of patient symptoms, anamnesis, findings of physical examination, plain abdominal graphy, complete blood cell count, CRP, and urinalysis. In patients with a suspicion of AAp, follow-up visits in the emergency department was performed to re-evaluate the complaints and findings of the physical examination. In our institution, we use the Alvarado scoring system for evaluation of the patients with right lower quadrant pain. In summary, in patients with a low Alvarado score ranging between 1-4 were discharged because they had a low risk of AAp. Patients with a Alvarado score ranging between 5 to 6 were followed closely. We chose to perform imaging techniques such as US, abdominal computerized tomography (CT), and magnetic resonance imaging (MRI) in this group of patients. The patients with Alvarado scores ranging between 7 to 10 were considered as AAp and emergency operation was planned. Majority of the patients who admitted to the emergency department with the complaints of abdominal pain that were considered as AAp were operated. The non-operative management (NOM) that consists of antibiotic therapy was performed to a limited number of patients and these patients were excluded from our study<sup>[23,24]</sup>.

During the COVID-19 pandemic, every patient that was admitted to the emergency department with abdominal pain were tested for SARS-CoV-2 with polymerase chain reaction (PCR) test and also chest X-ray was performed for surveillance of the patients. The patients with suspected lung lesions were further evaluated with thorax CT. Some patients were refereed from other centers with all the diagnostic work-up performed

including the PCR and thorax CT. These patients had already confirmed diagnosis of AAP and no further tests were performed in our institution and emergency operation was planned. The patients with high suspicion of COVID-19 infection such as symptoms of pneumonia, fever, or respiratory tract, traveled abroad in the past two weeks, or had a history of contact with patients with COVID-19 infection were quarantined after the PCR tests and the thorax CT ruled out COVID-19 infection<sup>[3,25]</sup>. No emergency operation was postponed related with the COVID-19 status of the patients, only the precautions were taken in the operating room and the patient wards to protect the staff and other patients. Retrospectively, thirty-five patients in our COVID-19 cohort had positive COVID-19 PCR tests and 22 of these patients were infected in a median of 146 d [interquartile range (IQR): 219] following the operation. The remaining 13 patients were infected in median of 162 d (IQR: 146) prior to appendectomy. None of the patients had contracted COVID-19 during the early perioperative period.

#### *Study protocol and ethics committee approval*

This retrospective case-controlled study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. First, the required official administrative permissions from the Directorate of the Surgery were granted (2021/61490). Then, Ethical approval was obtained from the Inonu University Institutional Review Board for non-interventional studies (2021/2293). This study was registered in Research Registry, where the protocol and data collections proforma can be accessed (Research Registry UIN: researchregistry7378). Strengthening the reporting of observational studies in epidemiology guideline was utilized to assess the likelihood of bias and overall quality for this study<sup>[26]</sup>.

#### *Statistical analysis*



The statistical analyses were performed using IBM SPSS Statistics v25.0 (Statistical Package for the Social Sciences, Inc, Chicago, IL, United States). The continuous variables were expressed as median, IQR and 95% confidence interval (CI) for median value. The categorical variables were reported as number and percent (%). Kolmogorov-Smirnov were used to assess normality of continuous variables' distribution. Non-parametric Mann Whitney-U test was used to compare continuous variables. Pearson's chi-square test was used to compare categorical variables.  $P \leq 0.05$  was considered statistically significant value.

## **RESULTS**

### ***General characteristics of the study population***

Three hundred and seventy-seven patients with ages ranging between 17-92 years (median: 36, IQR: 27) were included for analysis in the study. Two hundred and twenty-five (59.7%) of the patients were male and 152 (40.3%) were female. Hundred and fifty-four patients (40.8%) were operated in the pre-COVID-19 pandemic and 223 patients (59.2%) were operated during the COVID-19 pandemic. There was 44.8% increase in the number of patients admitted to our hospital with presumed diagnosis of AAp. Two hundred patients (53.1%) were operated during the daytime and 177 (46.9%) patients were operated during the night-time. Two hundred and seventy-four patients (72.7%) were operated at weekdays and 103 patients (27.3%) were operated during the weekends. Two hundred and forty five patients received laparoscopic appendectomy (65.0%) and 132 patients (35.0%) underwent conventional open appendectomy. In four patients of the 132 who underwent open appendectomy, the procedure started with laparoscopy and was converted due to technical difficulties. Histopathological analysis showed that 79 patients (21.0%) had appendiceal perforation and 42 patients (11.1%) underwent negative appendectomy. Therefore, 335 of the 377 patients (88.9%) included in the study had confirmed AAp with histopathologic analysis.

### ***Comparison of pre-COVID vs COVID groups***

The patients in the study were divided into two groups; pre-COVID ( $n = 154$ ) and COVID ( $n = 223$ ). The two groups did not show statistical significant difference in terms of age, timing of the operation (daytime *vs* night-time) WBC, neutrophil, lymphocyte, or PLT counts, PCT, RDW, PDW, MCH, MPV, MCV, TBil concentration, CRP, NLR, PLR, platelet-to-neutrophil ratio, WLR, WNR and the length of the appendectomy specimen. On the other hand, the groups were statistically different in terms of surgery being performed at the weekends *vs* weekdays ( $P = 0.018$ ), detection of AAp on US ( $P < 0.001$ ), histopathologic confirmation of AAp ( $P = 0.003$ ), presence of perforation in the surgical specimen ( $P = 0.004$ ), diameter of the appendiceal surgical specimen ( $P < 0.001$ ), and duration of hospital stay ( $P = 0.003$ ). Evaluation of our results show that, during the COVID-19 pandemic, appendectomy was 1.76 times more frequent during the weekends, the diagnostic rate (AAp) of US was 15.4 times higher, negative appendectomy rate was reduced by 2.6 folds, and the perforation rate was increased by 2.2 folds. The duration of hospital stay following appendectomy in the pre-COVID and COVID groups were 1 to 11 d (mean  $\pm$  SD:  $2.2 \pm 1.5$ ) and 1 to 17 d (mean  $\pm$  SD:  $3.3 \pm 3.2$ ), respectively. The sensitivity, pulse pressure variation (PPV) and accuracy of US during the COVID-19 pandemic period are 97%, 93% and 90%; respectively. The sensitivity, PPV and accuracy in the pre-COVID period are 77%, 83% and 68%, respectively. The results of the univariate analysis of the patients are presented in Tables 1 and 2.

We aimed to evaluate the correlation between the pre-admission interval and the COVID-19 pandemic. We used telephone interview of the patients included in the study tried to obtain the interval between initiation of the pain and admission to the hospital, in both groups. In total 60 patients gave accurate answers to the questions that we have asked. The preadmission interval in the pre-COVID and the COVID groups were 4 to 96 h (median: 24, IQR: 33, 95%CI: 17-48) and 4 to 192 h (median: 36, IQR: 60, 95%CI: 18-48), respectively. This difference in the pre-admission intervals between the groups was not statistically significant ( $P = 0.348$ ).

We evaluated the preadmission intervals of the patients regardless of the COVID *vs* pre-COVID periods. The preadmission intervals of the patients with and without

perforation were 9 to 192 h (median: 72, IQR: 48) and 4 to 120 h (median: 18, IQR: 24), respectively ( $P < 0.001$ ). In the pre-COVID period, the median pre-admission time interval of the perforated and non-perforated AAp cases were 48 h (IQR: 36) *vs* 20 h (IQR), respectively ( $P = 0.048$ ). During the COVID-19 pandemic, the median pre-admission intervals of the patients with perforated and non-perforated AAp were 72 h (IQR: 48) *vs* 12 h (IQR: 16), respectively ( $P < 0.001$ ).

## **DISCUSSION**

Since WHO declared COVID-19 as PHEIC (*i.e.*, a pandemic), 236132082 people have been infected with COVID-19 and 4822472 (2.04%) people have died due to severe COVID-19 infection or complications related to it. The recommendations of who including wearing a mask, social distancing and social isolation were effective in controlling the spread of the disease. Despite all the preventive measures, COVID-19 had devastating effects on the global health and socio-economic status<sup>[4]</sup>. In other words, COVID-19 became a serious public health problem that threatens the physical, psychological and social well-being of the individuals around the world. The fear of COVID-19 infection have prevented people who are seriously ill to admit to the emergency department<sup>[2]</sup>. This has led to a delay in the diagnosis and the management of life-threatening conditions such as myocardial infarction, embolism, AAp, acute cholecystitis, perforation, trauma and cancers<sup>[27-30]</sup>. Nourazari *et al*<sup>[31]</sup> have shown that there was a 32% drop in the rate of emergency department admissions during the COVID-19 pandemic when compared to previous periods. The results of the study by Göksoy *et al*<sup>[32]</sup> have shown that there was a 25% drop in admissions to the emergency surgery, and 20% of the patients that admitted refused the surgical treatment recommended by the attending physicians. Furthermore, they stated that majority of the surgeons preferred open surgical procedures during the COVID-19 pandemic<sup>[32]</sup>.

AAp is one of the most common causes of emergency department admissions and a rapid diagnosis and management is a crucial factor regardless of the conditions. The current literature regarding "COVID-19 and AAp" emphasize on three main

arguments: (1) Delay in hospital admissions (prolongation of the preadmission period) and in-hospital delay of the patients (prolongation of the preoperative period due to overwhelming work load of the hospital staff and facilities) until the definitive treatment is performed; (2) Increase in complication rates related with AAp (such as perforation, abscess formation and plastron); and (3) Change in the treatment modality (open *vs* laparoscopic or surgical *vs* medical therapies) increasing the complication rate in the postoperative and post-treatment course. We would like to evaluate these main arguments in accord with our results.

The hospital admissions in the COVID-19 era are a matter of debate. The hospital admission rates have dropped during the quarantine. We have evaluated 25 studies related with COVID-19 and AAp and 23 of these articles report that there was a 24% (IQR: 15%-39%; min-max: 5.4%-81%) drop in the hospital admissions due to AAp during the quarantine regulations<sup>[1-4,10,12,14-22,33-39]</sup>. In only one of the 25 studies, there was a 7% increase in the hospital admissions<sup>[40]</sup>. The results of our study have shown that there was a 44.8% increase in the hospital admissions due to AAp and subsequent appendectomies that were performed. The studies emphasized that the reasons for drop in the hospital admissions were due to fear of disease transmissions and the perception that the hospitals were source of the disease. This has caused a increase in the rate of pre-admission self-medication with antibiotics and non-steroidal anti-inflammatory drug (NSAID) use. Gao *et al*<sup>[2]</sup> have shown that pre-admission self-medication with antibiotics have increased by 8.7 folds in the COVID-19 period when compared to the pre-pandemic period [odds ratio (OR): 8.7; 55.2% *vs* 12.4;  $P < 0.001$ ]. The results of the study by Yang *et al*<sup>[4]</sup> have shown that pre-admission antibiotic use increased by 2.76 folds during the pandemic when compared to pre-pandemic period (OR: 2.76; 18.9% *vs* 7.8%;  $P = 0.011$ ). In our study we have found an increase in the hospital admissions due to AAp because the municipal hospital in our city was re-organized as the pandemic hospital while our institution treated all the non-COVID-19 emergencies in our city. In larger metropolitans even the private hospitals were organized as the pandemic hospitals because of the overwhelming cases.

The second argument is the hypothesis that COVID-19 pandemic caused a prolongation of the re-admission period of the patients. This may be due to hesitation of the patients to seek medical help or may be related with overwhelmed hospitals that could not provide the necessary medical care of these patients. Twenty-five studies have been evaluated regarding COVID-19 and AAP and 6 of these studies have stated that the interval between the initiation of the symptoms and hospital admission had been prolonged<sup>[1,2,4,15,17,36]</sup>. Particularly, in two of these 6 studies, this difference in pre-admission intervals during the COVID-19 pandemic have been evaluated and confirmed with different regression models. Gao *et al*<sup>[2]</sup> have stated that prolonged pre-hospital intervals (OR: 1.075;  $P = 0.005$ ) and reluctance of the patients towards the recommended surgical/medical therapy (OR: 1.848;  $P = 0.007$ ) were independent risk factors for increased rates of complicated AAP. Similarly, Rudnick *et al*<sup>[17]</sup> have found that prolongation of the interval between initiation of the symptoms and hospital admission was an independent risk factor for development of complicated AAP (OR: 1.139;  $P = 0.032$ ). In various other studies it was reported that there was no statistical significant difference in the pre-admission intervals between the pandemic and pre-pandemic periods<sup>[18,19,22,37]</sup>. However, detailed analysis of the results of these studies have shown that pre-admission intervals were longer during the pandemic period<sup>[18,19,22,37]</sup>. In our study the pre-admission intervals in the pre-pandemic and pandemic periods were 24 h and 36 h, respectively. Our literature analysis showed that there is only one study that reported a prolonged pre-admission interval in the pre-pandemic period<sup>[40]</sup>. On the other hand, the fact that overwhelming circumstances during the pandemic may delay the intended surgical treatment planned for the patients. Of the 25 studies regarding AAP during COVID-19, we have found 5 studies reporting the intervals before the operation. Three of these studies reported a prolonged interval before the planned operation<sup>[4,35,37]</sup>. On the other hand, prolonged preoperative intervals were reported during the pre-pandemic period in two studies<sup>[15,18]</sup>. There were two studies that concluded that the diagnostic process was prolonged during the COVID-19 period<sup>[10,13]</sup>. One important point that should be emphasized regarding the

reported intervals in studies that all of them are self-reported intervals. This means that the patients are retrospectively interviewed, and they state the intervals if they remember them accurately. Similarly, in the present study we interviewed our patients by telephone and tried to obtain similar information. Only 60 patients could accurately remember the pre-admission and preoperative intervals. Therefore, these (including our own) should be evaluated with a certain level of skepticism.

The impact of COVID-19 pandemic on the use of radiologic imaging modalities for the diagnosis of AAP is another argument that should be emphasized. Analysis of the results of the study reported by Ganesh *et al*<sup>[12]</sup> have shown that use of radiologic imaging modalities such as CT or MRI have increased by 42 folds during the pandemic period (OR: 42; 60.9% *vs* 100%;). Somers *et al*<sup>[16]</sup> have reported that radiologic imaging modalities have been used 1.26 times more frequently during the COVID-19 period (OR: 1.26;  $P = 0.007$ ). The authors stated that all three radiological instruments (US, CT, MRI) are used more during the COVID period. Antakia *et al*<sup>[18]</sup> have reported that during the COVID-19 pandemic, they have used CT 2.6 times more frequently (OR: 2.6;  $P = 0.008$ ); but the use of US was reduced by 1.6 folds (OR: 1.6;  $P = 0.227$ ). Khan *et al*<sup>[13]</sup> have shown that US was performed less frequently and use of CT for the diagnosis of AAP increased during the pandemic period (OR: 3.7;  $P < 0.001$ ). The COVID-19 pandemic changed the way we evaluate the patients. Patients who are admitted to the emergency departments with various major complaints who have concomitant respiratory symptoms and/or a fever are initially evaluated by thorax CT. Therefore, any patient with an abdominal complain receive both thorax and abdominal CT during the evaluation process. This may be the reason behind the increased CT use during the pandemic period. On the contrary to the majority of the studies, Romero *et al*<sup>[41]</sup> have reported that use of CT dropped by 61% during the COVID-19 pandemic. In our study we have found that radiologic evaluation for the diagnosis of AAP in the pre-pandemic and pandemic periods were 96.7% and 86.8%, respectively ( $P = 0.001$ ). This drop in the use of radiologic evaluation in our study can be due to two factors. First, the delay in the hospital admissions of the patients have led to prominent symptoms that did not

need any radiologic evaluation. The second reason can be due to the fact that these patients were evaluated in other centers or private hospitals where all the radiologic modalities have been performed and the patient was sent to our institution once the diagnosis was established.

We would like to emphasize the impact of the pandemic on occurrence of complications (perforated AAp, gangrenous AAp, peri-appendicular abscess) seen during the course of AAp. In literature, there is no consensus on the definition of complications (plastron, abscess, phlegmon, gangrene, perforation, periappendicular abscess, pelvic abscess, severe peritonitis) that are related to AAp. Ten of the 25 studies that are related to the COVID-19 pandemic and AAp reported that perforation rates significantly increased during the pandemic period (5%-45.6%)<sup>[1-4,9,13,15,16,40]</sup>. In addition, another two of the 25 studies reported an increase in the perforation rates (17.5%-31%) that did not reach statistical significance<sup>[37,38]</sup>. Interestingly, perforation rates have been reported to be reduced (5%-10.7%) during the COVID-19 pandemic in two studies<sup>[14,17]</sup>. Five studies in our literature review have reported that peri-appendicular and pelvic abscess rates (5.6%-33.9%) have increases during the pandemic period<sup>[2,13,17,18,35]</sup>. Some of the studies have reported complications altogether as “complicated AAp”. In twelve studies, the frequency of complicated AAp (15.9%-64.4%) was reported to be increased during the pandemic period. Nine of the 12 studies reported that pre-admission interval was longer during the pandemic period. Only two studies used a logistic regression model and showed that longer pre-admission intervals were a risk factor for the development of complicated AAp<sup>[2,17]</sup>. Analysis of the results of all these studies shows that the delay in hospital admissions during the COVID-19 pandemic is correlated with the incidence of complicated AAp.

Negative appendectomy is an important concept in the treatment of AAp. This has been a matter of debate and the consensus states that there should be a balance between negative appendectomy and perforated AAp rates to ensure patient safety. Ten of the 25 studies that were reviewed gave their results regarding negative appendectomy rates. The results of these studies showed that negative appendectomy rates have

dropped during the COVID-19 pandemic<sup>[1,6,13-16,18,33,34,39]</sup>. Five of the ten studies stated that this drop showed statistical significance. In our study, we have observed that negative appendectomy dropped by 2.6 times during the pandemic period (OR: 2.6; 16.9% *vs* 7.2%;  $P = 0.003$ ). These results suggests that during the pandemic period the patients were more meticulously evaluated before establishing the diagnosis and performing surgery for AAp. Another reason can be attributed to the fact that patients did not come to the hospital until the definitive symptoms of AAp developed because of the reluctance due to the COVID-19 pandemic.

Another point that needs to be emphasize is the impact of COVID-19 pandemic on the demographic, clinical and laboratory parameters of the patients with AAp. All 25 studies that have been analyzed in our literature search have shown that pandemic and pre-pandemic periods did not differ significantly in terms of age, and body mass index. However, one study reported that significantly older patients were admitted to the hospital for AAp during the COVID-19 period<sup>[13]</sup>. Differences in gender was analyzed in 4 studies in literature. Three of these studies stated that female gender was predominant<sup>[13,17,20]</sup> and in the remaining one study male gender was stated to be the predominant gender during hospital admissions related with AAp<sup>[38]</sup>. One study reported that American Society of Anesthesiologists scores were higher in the pre-pandemic period<sup>[18]</sup>. In another studies, comorbidity rate was reported to be higher in patients treated for AAp during the COVID-19 pandemic<sup>[3]</sup>. The frequency of smokers were not different in patients in COVID-19 and pre-COVID-19 periods<sup>[15,18,38]</sup>. The data regarding the leukocyte counts were presented in 18 studies and 14 of them showed no difference before and after the COVID-19 pandemic. Three studies showed a lower WBC counts in patients with AAp during the pandemic period<sup>[13,14,41]</sup>. One study reported a higher WBC count in patients with AAp during the COVID-19 pandemic<sup>[22]</sup>. CRP levels were reported in 12 studies and in 3 of these studies, it was reported that the CRP levels were significantly different between the COVID-19 and pre-COVID-19 periods<sup>[1,13,40]</sup>. In one of these studies CRP was significantly higher in patients with AAp in the COVID-19 period and in the remaining 2 studies it was higher in AAp cases in



the pandemic period. Gao *et al*<sup>[2]</sup> have suggested that the CRP levels and WBC count did not show significant change because of the high rate (reaching 55% of the patients) of pre-admission self-medication with antibiotics during the COVID-19 pandemic. In literature, studies are usually retrospective in nature and there is no data regarding the NSAID and antibiotic use of the patients. For this reason, we believe that there is no data to support the hypothesis of Gao *et al*<sup>[2]</sup>. We have analyzed all markers of inflammation that has been mentioned above and we could not find a significant difference between the two different time intervals. When the pandemic and pre-pandemic periods are internally grouped according to the perforation status of the patients, inflammatory markers are found to be significantly elevated in patients with perforated AAp. For this reason, prospective studies are needed to further evaluate this specific topic.

Furthermore, COVID-19 causes multisystem inflammatory syndrome that can occasionally manifest itself as acute abdomen; especially invulnerable population such as children. It is the result of immune dysregulation and causes gastrointestinal symptoms that mimic AAp. Multiple systemic inflammatory reaction during or after COVID-19 generally implies active infection or complication of COVID-19 that is misdiagnosed as AAp<sup>[42]</sup>. In the present study the preadmission duration in both AAp and perforated AAp increased during the pandemic period when compared to the pre-pandemic period. Furthermore, the US and histopathologic confirmation rate of the AAp increased while the negative appendectomy rate decreased. Our results suggest that during the pandemic period, surgical team took more time in diagnosing AAp which increased preoperative waiting period. This is also reflected as the increase in the perforation rates in our patients. Therefore, our diagnostic accuracy increased during the pandemic which rules out our COVID-19 related multiple systemic inflammatory reaction. Although the studies related with association of AAp and COVID-19 infection is lacking, it is quite possible that dysregulated inflammatory reaction in infected patients may cause expansion of the Peyer patches in the causing, lymphoid hyperplasia related obstruction of the appendiceal lumen leading to increased incidence

of AAp. In accordance with our study the case series presented by Anderson *et al*<sup>[42]</sup> have shown that there was an increased lympho-histiocytic infiltration in submucosa and mesoappendix.

The treatment modality of choice for patients with AAp during the COVID-19 pandemic is also a matter of debate and needs to be clarified. The two alternatives are appendectomy *vs* NOM. The studies performed in the last two decades show that the two treatment alternatives have no superiority over one and another. This discussion is crucial during the COVID-19 pandemic. The metanalysis published by Emile *et al*<sup>[43]</sup> suggests that during the COVID-19 pandemic, patients treated with NOM had significantly lower complication rates and shorter duration of hospitalization. However, it has been shown that in young, male and complicated AAp patients, the success of NOM is lower than appendectomy. The authors have shown that the success rate of NOM did not change significantly between the pre-pandemic and pandemic periods. Yang *et al*<sup>[44]</sup> have recently published the results of their meta-analysis regarding AAp in the pre-COVID period and have shown that NOM has reduced complication rate and duration of hospitalization in both complicated and non-complicated AAp. Furthermore, they have shown that appendectomy was a highly effective treatment with reduced relapse rates. The Javanmard-Emamghissi *et al*<sup>[45]</sup> have performed a multicentric study regarding AAp during the COVID-19 pandemic and found that complication rates and duration of hospitalization was significantly lower in the patients with AAp who received NOM. A multicentric study organized by Italian Association of Surgery in 66 countries with contributions of 706 surgeons showed that during the pandemic surgeons preference of treatment modality for non-complicated AAp shifted from laparoscopic approach (57.2% *vs* 22.5%) to open appendectomy (7.2% *vs* 15.0%) or NOM (6.6% *vs* 23.7%)<sup>[46]</sup>. Furthermore, surgeons participating in the study stated that their preferred treatment for complicated AAp shifted from laparoscopic appendectomy (62.5% *vs* 33.7%) to open appendectomy (14.0% *vs* 28.1%), NOM (2.4% *vs* 5.3%) or NOM and percutaneous drainage (21.1% *vs* 32.9%). The guidelines of American College of Surgeons recommend the use of oral/parenteral antibiotics as the

first line treatment of patients with complicated or non-complicated AAp during the COVID-19 pandemic. These guidelines recommend appendectomy should be performed in patients with a relapse of the disease<sup>[34]</sup>. Also, it is suggested that in patients with abscess, perforation, or failure of NOM, minimal invasive or conventional surgical treatment should be performed<sup>[34]</sup>. Moletta *et al*<sup>[47]</sup> have analyzed various treatment guidelines and recommendations for AAp published during the COVID-19 pandemic and have stated that in non-complicated AAp, NOM should be performed. On the other hand, in complicated cases and in patients whom NOM failed, surgical therapy should be treatment of choice<sup>[44]</sup>. Our literature review including 25 studies showed that in 6 studies the rate of NOM increased during the COVID-19 pandemic. Our experience regarding the NOM is very limited and therefore, we cannot share any data regarding NOM in AAp in our study. However, in our opinion and clinical practice, we do not use NOM for elderly patients (because of high rates of complicated AAp), patients with complicated AAp and patients who refuse to choose NOM. In our opinion, during the COVID-19 pandemic, instead of a considerable duration of hospitalization and parenteral antibiotic use, we recommend appendectomy especially in patients with complicated AAp.

The efficacy of laparoscopy in the treatment of AAp have been extensively studied in patients and in specialized groups such as the gravid patients, pediatric patients, elderly and non-complicated AAp. Jaschinski *et al*<sup>[48]</sup> have performed a systematic review for the Cochrane database and have shown that laparoscopic appendectomy is associated with reduced surgical site infections, shorter duration of hospitalization, early return to work and better quality of life when compared to conventional appendectomy. However, the intraabdominal abscess rate was higher in laparoscopic appendectomy. The main concern of the physicians regarding laparoscopy during the pandemic is aerosolization of the virus and risk of transmission due to insufflation and exsufflation of the abdomen. Moletta *et al*<sup>[47]</sup> have analyzed different guidelines and four original studies. They have concluded that laparoscopic surgery can be performed provided that the medical staff takes the necessary precautions, and the fume

extraction-ventilation of the operating room is provided. Authors state that laparoscopy is based upon the creation and maintenance of a pneumoperitoneum and the use of energy devices result in formation of smoke bioproducts. Aerosolization of blood born viruses has been previously detected in surgical smoke during laparoscopy. Therefore, a potential risk of aerosol exposure must also be considered for COVID-19 even though it is not currently demonstrated. In conclusion, there is no clear cut evidence showing increased risk of disease transmission during laparoscopy and therefore there is no reason to stop laparoscopic procedures<sup>[49]</sup>.

The postoperative complications, prolonged postoperative antibiotic therapy and hospital stay is another argument regarding COVID-19 pandemic and AAP. Fourteen articles in our literature presented data regarding the duration of hospital stay in AAP during the pandemic. Ten of these studies showed no difference in durations between the different time intervals<sup>[4,13,19-22,35,36,39,40]</sup>; while one study reported a prolonged hospital stay<sup>[1]</sup> whole another study reported that this duration was shorter during the pandemic<sup>[14]</sup>. Besides, three studies reported that although there was no statistical difference, the duration of hospitalization during the pandemic tended to be longer<sup>[3,10,18]</sup>. Seven studies have reported data regarding the postoperative complications and five of these studies reported that the rate of complications did not change. In one study, surgical site infection rate (1.9% *vs* 6.9%) was found to be increased during COVID-19 pandemic. In another study, the postoperative complication rates (25 % *vs* 16.7%) were found to be reduced during the pandemic. In the present study we have found that the duration of hospital stay was longer in patients treated during the COVID-19 pandemic ( $P = 0.003$ ). This was related with the high rates of complicated AAP observed during this period. In the present study, we could not find a significant difference in terms of duration of postoperative antibiotic use and complication rates.

There are various limitations of the present study. The main limitation is the significant recall bias regarding the hospital admissions and interval to operation. The main reason for this is the telephone interview of the patients to receive these data. This

is especially important for patients operated in the pre-pandemic era. The retrospective study design for obtaining the data analyzed in the present study is another limitation of our study. However, our results are striking because we have higher incidence of AAP as well as perforation rate during the COVID-19 era. In addition, our data regarding the COVID-19 infection rates in the pre- and postoperative period in our patients are missing which should also be noted as a limitation of our study.

## **CONCLUSION**

The results of our study suggests that the complicated AAP rates increased which has led to prolonged durations of hospital stay during the COVID-19 pandemic. The number of patients treated with AAP increased during the pandemic which is attributed to the shift of role of the two state hospitals in our city. Fortunately, although the rate of complicated AAP increased, this did not increase our postoperative complication rates. Therefore, we can conclude that during global catastrophes such as the COVID-19 pandemic more complicated forms of the diseases such as AAP can be seen. Although the system is overwhelmed by the workload of the patients with COVID-19 infection, this should not change our attitude towards performing surgical therapy in these patients because any delay will lead to dismal consequences, prolonged hospital stay.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Although, during the coronavirus disease 2019 (COVID-19) pandemic, emergency procedures were allowed provided that necessary precautions were taken in the operating theatre and in-patient wards, it was believed that there were serious disruptions in the management of patients with acute appendicitis (AAP). AAP management is critical because AAP is the most common cause of acute abdominal pain, and appendectomy is the most frequent emergency procedure.

### ***Research motivation***

AAp management is critical because AAp is the most common <sup>2</sup> cause of acute abdominal pain, and appendectomy is the most frequent emergency procedure.

### ***Research objectives***

The present study aims to comparatively evaluate the impact COVID-19 pandemic in the pre-pandemic period regarding the patients who were operated on for AAp in terms of negative appendectomy and perforation rates. Our secondary aim was <sup>1</sup> to evaluate the impact of the COVID-19 pandemic on the hospital admission rates of patients with AAp.

### ***Research methods***

Demographic, clinical, and histopathological characteristics of 223 patients (COVID group) who underwent appendectomy with a preliminary diagnosis of AAp between March 2020 and July 2021 were compared with 154 patients (pre-COVID group) who operated with the same indication between October 2018 and March 2020.

### ***Research results***

There was a 44.8% increase in the number of patients admitted to our hospital with a presumed diagnosis of AAp during the pandemic. Significant differences were found between pre-COVID and COVID groups in terms of procedures performed on the weekdays or weekends [odds ratio (OR): 1.76;  $P = 0.018$ ], presence of AAp findings in ultrasonography (OR: 15.4;  $P < 0.001$ ), confirmation of AAp in the histopathologic analysis (OR: 2.6;  $P = 0.003$ ), determination of perforation in the appendectomy specimen (OR: 2.2;  $P = 0.004$ ), the diameter of the appendix ( $P < 0.001$ ) and hospital stay ( $P = 0.003$ ).

### ***Research conclusions***

The results of our study suggests that the perforated AAP rates increased which has led to prolonged durations of hospital stay during the COVID-19 pandemic. The number of patients treated with AAP increased during the pandemic which is attributed to the shift of role of the two state hospitals in our city. Fortunately, although the rate of complicated AAP increased, this did not increase our postoperative complication rates. Therefore, we can conclude that during global catastrophes such as the COVID-19 pandemic more complicated forms of the diseases such as AAP can be seen.

### *Research perspectives*

This study has shown that even diseases that require emergency management, such as AAP, can be ignored during the COVID-19 pandemic. It is known that this situation is directly related to both patient behavior and healthcare professionals' increased workload. The most important way to overcome this problem is to learn from the pandemic process, preventive measures properly, and create social awareness.

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