INTRODUCTION

Since it was first detected, novel coronavirus disease (COVID-19) rapidly spread, striking over 4 million people worldwide. While adults with COVID-19 demonstrate a range of disease severity with 20% of infected adults being critically ill and an estimated fatality rate as high as 2%, children mostly suffer from a mild disease, only minority presenting with respiratory distress syndrome or multi-organ failure. However, the role of infected children in spreading the virus to their older relatives and caregivers is yet to be determined.

Many countries struggle to stave off the spreading of COVID-19 by using different strategies. In many countries, including Israel, authorities instructed the public to stay at home and to avoid visiting local clinics and hospitals as much as possible while using more telemedicine-based practice. However, emergent medical situations continue to appear alongside the current outbreak and their diagnosis should still be made promptly. Delayed diagnosis and treatment of those common paediatric conditions may lead to significant morbidity that may overweigh the harm caused by COVID-19 infection.

Appendicitis is the most common abdominal surgical emergency in paediatric population. Early diagnosis of appendicitis...
in children and consequent appropriate surgical and/or antibiotic treatment is important as it may prevent complications such as appendix perforation, abscess formation and other postoperative complications.\textsuperscript{7,8} Generally, appendix perforation occurs 36-48 hours after onset of symptoms, and its rate in children aged 10-17 years is approximately 20%.\textsuperscript{7,9} Abscess formation rate in children with perforated appendicitis is roughly 20% and for patients with nonperforated appendix 0.8%.\textsuperscript{10} However, in the era of COVID-19, more patients should be expected to address medical care at a late stage of the disease and with significant complications.

Herein, we present seven cases with a delayed diagnosis of appendicitis in the era of patients and physicians’ fear from in-person encounters and physical examination. The aim of the current report is to highlight the importance of appropriate evaluation in paediatric population in the era of COVID-19 pandemic.

\section{Methods}

Patients were compiled from three medical centres in Israel via an Internet-based hospital paediatricians and surgeons’ forum. Data were collected from patients’ medical files, and interviews were conducted with patients and their families regarding the decision-making process and the course of the disease. In addition, the incidence of appendicitis and its complication rate were obtained from computerised hospital registries in all three surgical wards. Comparison was made between complication rates in the COVID-19 era in Israel (March 1 to April 30, 2020) and same time period in the previous year.

A waiver was given from each institutional Helsinki committees for this case series collection.

\section{Results}

\subsection{Case 1}

A 15-year-old male patient presented to the emergency room (ER) with a history of abdominal pain for a 3-day period. Upon arrival, he was taken to the area assigned for COVID-19 suspected patients’ despite the fact he was not suffering from any typical symptom. The patient was examined hastily by a paediatric emergency care expert, and after a telephone consultation with a surgeon, he was diagnosed with post-surgical transition seasonal pain due to previous inguinal hernia repair carried out 2 years earlier. Pain relievers were prescribed, and he was discharged. Later that day when symptoms persisted, the patient’s family was concerned by the very brief examination in the ER and contacted their primary care physician. Physical examination revealed right lower quadrant abdominal tenderness with signs of peritonitis. The patient was referred again to another ER and was diagnosed with appendicitis per abdominal ultrasound (US). He underwent a laparoscopic approach appendectomy. Macroscopic assessment revealed gangrenous perforated appendicitis with peri-appendicular abscess.

\subsection{Case 2}

The parents of an 11-year-old female patient contacted her primary care physician with abdominal pain of 2-day duration. They were instructed by her physician to stay home due to COVID-19 situation. Diagnosis of “probable viral infection” was given. The symptoms persisted and high-grade fever (>38.5°C) and intermittent diarrhoea appeared. The physician was contacted once again, and once more they were guided not to come to the clinic. On the 9th day...
of symptoms, she arrived to the clinic with a general deterioration. Upon examination, signs of peritoneal irritation were found and she was referred to the ER. Abdominal US and computed tomography (CT) revealed large peri-appendicular intraabdominal collection with multiple loculations (Figure 1). She underwent percutaneous drainage and required prolonged hospitalisation.

### 3.3 | Case 3

A 15-year-old male patient presented with 24 hours of abdominal pain, anorexia and vomiting. The patient's family was concerned with the COVID-19 outbreak and avoided visiting the primary care physician or the ER even when symptoms worsened. On the 3rd day, the patient's parents contacted a healthcare call centre and were referred to the ER. Physical examination revealed right abdominal tenderness with signs of peritoneal irritation. Abdominal US signs were consistent with acute appendicitis and suspected perforation. The patient underwent laparoscopic appendectomy, macroscopic assessment revealed gangrenous appendix covered with omentum and purulent fluid in pelvis and right gutter.

### 3.4 | Case 4

A 14-year-old otherwise healthy female patient contacted her primary care physician with a history of 3 days of high-grade fever (39°C) and weakness. She was guided by her physician not to come to the clinic due to a possible risk of contracting COVID-19 infection. When symptoms persisted the next day, the patient's parents were disturbed by the child's ill appearance and called her doctor raising concern for not being examined by a physician. Once again, they were asked by her paediatrician to stay at home. On the 5th day of fever and fatigue, additional peri-umbilical and right quadrant abdominal pain appeared. The patient was briefly examined by a physician after the parents insisted upon it, and the child was diagnosed with a viral infection and instructed to avoid visiting the clinic until the symptoms disappear. On the 6th day, shivering and vomiting appeared in addition to worsening of her previous symptoms. Upon arrival to the ER, despite earlier given instructions, physical examination revealed signs of peritoneal irritation and laboratory results showed elevated inflammatory markers. Abdominal US and CT demonstrated appendicitis and a peri-appendicular abscess. She underwent trans-cutaneous drainage and required long-term hospitalisation with broad-spectrum antibiotic treatment.

### 3.5 | Case 5

A 13-year-old male patient presented with 24 hours of abdominal pain and vomiting to his primary care clinic. He was briefly examined by a physician and sent home with pain relievers. The next day a general deterioration was noticed, his pain was aggravated and a fever (>38°C) appeared. He contacted his primary care clinic and was urged not to go to the ER due to the COVID-19 pandemic, but rather come into the local clinic for examination. Once examined in the local clinic, he was found to be ill appearing, tachycardic and had signs of peritoneal irritation. He was referred to the ER. Abdominal CT showed an extensive inflammatory process with involvement of the appendix, terminal ileum and cecum with intraperitoneal free gas. He underwent urgent laparoscopy that showed gangrenous appendix with multiple abscesses and purulent fluid in the abdomen. He was admitted to the intensive care unit (ICU) and required sequential abscess drainage. The patient was hospitalised for more than 3 weeks.

### 3.6 | Case 6

A 14-year-old otherwise healthy male patient presented to his primary care physician with high-grade fever (38.6°C), abdominal pain and vomiting. The patient was referred to the ER but due to parental concerns regarding COVID-19 exposure the family decided not to go. On the 2nd day, the paediatrician contacted the parents and urged them to visit the ER if there was no improvement in the patient's symptoms, but they stayed at home. On day 3, due to parental concerns from visiting the ER, the patient underwent an abdominal ultrasound in a local clinic that did not reveal any pathology. The family did not contact any healthcare provider until the 6th day of symptoms when the patient was re-examined by his physician and right abdominal tenderness along with signs of peritonitis were found. He was referred to the ER. Abdominal US revealed a 20 mm inflamed appendix with mild to moderate amount of free abdominal fluid. He underwent abdominal laparoscopy which revealed an auto-amputated gangrenous appendix and a peri-appendicular abscess formation.

### 3.7 | Case 7

A 2.5-year-old male patient suffered from fever (38°C) and vomiting. Due to the COVID-19 outbreak, the parents did not want to visit the clinic but rather called their paediatrician after 3 days of symptoms. The child was diagnosed with acute gastroenteritis, pain relievers were prescribed and adequate fluid intake was recommended. The child's parents feared from possible COVID-19 contraction and avoided visiting the ER until the 6th day of symptoms. Upon arrival to the ER, the child was diagnosed with appendicitis and peri-appendicular abscess.

### 3.8 | Comparison of appendicitis and complication rates during the COVID-19 period and the previous year

From data collected in all three medical centres, during the time period between March 1 and April 30, 2020, a collective of 81 children were diagnosed with appendicitis, 18 of them (22%) suffered from complications such as perforation or abscess formation.
During the same time period in 2019, an overall of 80 children were diagnosed with appendicitis but only nine of them (11%) suffered from complications. Although the complication rate was twice as high in 2020, this difference was not statistically significant ($P$-value = .06).

4 | DISCUSSION

In this case series, we report seven paediatric cases of appendicitis with a delayed diagnosis resulted in considerable intraabdominal complications. These cases were collected from three paediatric surgical wards in Israel. Moreover, we found that appendicitis complication rate in the COVID-19 period in Israel was roughly twice as high as complication rate during the same period in the previous year. We believe these findings represent a far more widespread phenomenon of paediatric emergencies usually diagnosed earlier in the course of the disease that are being addressed at a later stage due to COVID-19 pandemic. (Table 1).

The COVID-19 global pandemic has completely changed the medical evaluation and decision-making process of patients, family members and physicians. We recognise a few major reasons for delay in diagnosis during the COVID-19 pandemic. The first is parental concern; as seen in a few of the above cases, families were extremely concerned with the possibility of contracting COVID-19 in public places such as clinics or the ER. In more than one of the described cases, parents were reluctant to contact their primary care physician and even after a specific referral to the ER, chose to refrain from visiting medical facilities. The second reason is inadequate clinical evaluation and the settings of the consultation; in the COVID-19 era, many of the medical activities were run through a telemedicine platform which allows evaluating patients while limiting exposure. However, one of these methods’ disadvantages is the inability to conduct a full physical examination which may lead to a misdiagnosis. Video input in a telemedicine consult, which was not available in the described cases, may provide additional information which may allow for a more accurate evaluation and assist in recognising toxic or ill-appearing child. Moreover, even in cases when a physical examination was performed, physicians’ fear resulted in limited evaluation. Another aspect is the lack of healthcare workers’ instructions regarding the optimal setting and timing of medical advice; we believe that in the current situation, it is crucial to provide both parents and medical staff with instructions regarding child monitoring, warning signs and timing of urgent medical care in order to prevent unnecessary complications of routinely seen childhood emergencies.

Two major complications of appendicitis include perforation with peritonitis and peri-appendicular abscess formation. Perforation rate in children aged 10-17 years is approximately 20%. Peri-appendicular abscess formation rate in children with perforated appendicitis is roughly 20% and for patients with nonperforated appendix 0.8%. In our series, all patients were diagnosed 48 hours or more after the onset of symptoms. All patients presented with perforated appendix, and 6/7 cases had peri-appendicular abscess. These findings stand in line with previous findings suggesting late diagnosis related to higher incidence of complications. Rothrock et al showed nearly a 100% perforation rate in children diagnosed with appendicitis more than 48 hours after onset of symptoms. Another study found that children with appendicitis presenting after 48 hours of symptoms were roughly five times more likely to suffer from perforation and experienced 56% longer length of hospital stay than those presenting within the first 24 hours. While most adolescents diagnosed with appendicitis do not experience complications such as appendix perforation and abscess formation, the cases described in this report paint a different picture, raising concern regarding the current methods used for evaluation of paediatric population during the COVID-19 outbreak.

Our study is limited in one main aspect; presented cases were collected within a short period of time from only three paediatric

| Case number | Age (years) | Pitfalls             | Time to diagnosis | Complications                                                                 |
|-------------|-------------|----------------------|-------------------|------------------------------------------------------------------------------|
| 1           | 15          | Insufficient evaluation | 72 h              | Appendix perforation, Peri-appendicular abscess                               |
| 2           | 11          | Telemedicine, Insufficient evaluation | 240 h           | Appendix perforation, Peri-appendicular abscess                              |
| 3           | 15          | Parental concern       | 72 h              | Appendix perforation                                                          |
| 4           | 14          | Telemedicine, Insufficient evaluation | 144 h           | Appendix perforation, Peri-appendicular abscess                              |
| 5           | 13          | Telemedicine, Insufficient evaluation | 48 h            | Appendix perforation, Peri-appendicular abscesses, ICU admission, Sequential abscess drainage, Prolonged hospitalisation |
| 6           | 14          | Parental concern       | 144 h             | Appendix perforation, Peri-appendicular abscess                              |
| 7           | 2.5         | Telemedicine, Parental concern | 144 h           | Appendix perforation, Peri-appendicular abscess                              |
surgical wards, and a systematic collection of all cases with complicated appendicitis was not done. However, we did compare complication rates between the two time periods and demonstrate higher rates during the pandemic era, suggesting the phenomenon is greater than the described cases.

In conclusion, we report a series of cases with a delayed diagnosed of appendicitis, all resulted in complications that might have been avoided. We believe these case series represent a more widespread phenomenon of misdiagnoses and potential harmful events related to the fear from the coronavirus. While the era of COVID-19 outbreak poses challenges in both mitigating the virus transmission and treating the infected patients, we attempt to highlight the necessity of preserving sufficient medical evaluation and treatment in children which might be affected by misdiagnoses of other diseases more than from COVID-19. More than ever, we remind clinicians the importance of a comprehensive evaluation and physical examination in children suspected of having any surgical condition. We believe a balance should be achieved between measures designed to mitigate viral transmission and the appropriate care of paediatric population requiring medical assessment.

CONFLICT OF INTEREST
The authors have conflicts of interest to disclose.

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REFERENCES
1. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) Situation report - 75. May 13th, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200513-covid-19-sitrep-114.pdf?sfvrsn=17ebbbe_4
2. Fauci AS, Lane HC, Redfield RR. Covid-19 - navigating the uncharted. N Engl J Med. 2020;382(13):1268-1269.
3. Baker T, Schell CO, Petersen DB, et al. Essential care of critical illness must not be forgotten in the COVID-19 pandemic. Lancet. 2020; 395: 1253-1254.
4. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020; e20200702. Epub ahead of print. http://dx.doi.org/10.1542/peds.2020-0702
5. Centers for Disease Control and Prevention (CDC). What to do if you are sick; 2020. https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/steps-when-sick.html. Accessed March 25, 2020
6. Glass CC, Rangel SJ. Overview and diagnosis of acute appendicitis in children. Semin Pediatr Surg. 2016;25(4):198-203.
7. Rothrock SG, Pagane J. Acute appendicitis in children: emergency department diagnosis and management. Ann Emerg Med. 2000;36(1):39-51.
8. Rothrock SG, Skeoch G, Rush JJ, Johnson NE. Clinical features of misdiagnosed appendicitis in children. Ann Emerg Med. 1991;20(1):45-50.
9. Pepper VK, Stanfill AB, Pearl RH. Diagnosis and management of pediatric appendicitis, intussusception, and Meckel diverticulum. Surg Clin North Am. 2012;92(3):505-526.
10. St Peter SD, Sharp SW, Holcomb GW 3rd, Ostlie DJ. An evidence-based definition for perforated appendicitis derived from a prospective randomized trial. J Pediatr Surg. 2008;43(12):2242-2245.
11. Keesara S, Jonas A, Schulman K. Covid-19 and Health Care's Digital Revolution. New England Journal of Medicine. 2020. Epub ahead of print. http://dx.doi.org/10.1056/nejmp2005835
12. Hjelm NM. Benefits and drawbacks of telemedicine. J Telemed Telecare. 2005;11(2):60-70.
13. Mandeville K, Monuteaux M, Pottker T, Bulloch B. Effects of timing to diagnosis and appendectomy in pediatric appendicitis. Pediatr Emerg Care. 2015;31(11):753-758.

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