Acute Abdomen and Appendicitis in 1010 Pediatric Patients With COVID-19 or MIS-C: A Multinational Experience from Latin America

Adriana Yock-Corrales, MD, Jacopo Lenzi, PhD,† Rolando Ulloa-Gutiérrez, MD‡, Jessica Gómez-Vargas, MD,* Omar Yassef Antúnez-Montes, MD,§ Jorge Alberto Rios Aida, MD,¶ Olguita del Aguila, MD‖, Erick Arteaga-Menchaca, MD,** Francisco Campos, MD,†† Fadia Uribe, MD,†† Roger Hernández Díaz,†† Andrea Parra Buitrago, MD,‡‡,§§ Lina Maria Betancur Londoño, MD,‡‡ Verónica Kozicki, MD,¶¶ Martin Brizuela, MD,¶¶ and Danilo Buonsenso, MD‖‖,***,†††*

Background: To date, there are only sporadic reports of acute abdomen and appendicitis in children with coronavirus disease 2019 (COVID-19) and multisystem inflammatory syndrome in children (MIS-C).

Methods: Children 17 years of age or younger assessed in 5 Latin American countries with a diagnosis of microbiologically confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and children fulfilling MIS-C definition were included. For children with acute abdomen, we investigate main radiologic patterns, surgical treatment and intraoperative findings, outcomes.

Findings: One-thousand ten children were enrolled. Forty-two children (4.2%) had a clinical diagnosis of acute abdomen. Four (9.5%) were diagnosed with MIS-C and did not undergo surgery. The remaining 38 children (3.8%) underwent abdominal surgery due to suspected appendicitis, 34 of them (89.7%) had an intraoperative diagnosis of acute appendicitis (AA), while 4 of them had nonsurgical findings. Eight children died (0.8%), none of them being diagnosed with appendicitis. Children with AA were significantly older than those without ($P < 0.0001$). Children with complicated appendicitis had more frequently fever (85.7% vs. 60%), intestinal distension on the abdominal radiograph (7.1% vs. none), leukocytosis (85.7% vs. 40%) and high levels of C-reactive protein (35.7% vs. 5%), although differences were not statistically significant.

Conclusions: Our study showed that children may present with acute abdomen during COVID-19 or MIS-C, which is not always associated with intraoperative findings of appendicitis, particularly in case of MIS-C. Further studies are needed to better characterize children with acute abdomen during COVID-19 or MIS-C, to avoid delay in diagnosis of surgical conditions and at the same time, minimize unnecessary surgical approaches.

Key Words: COVID-19, SARS-CoV-2, appendicitis, children

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Clinical features of coronavirus disease 2019 (COVID-19) in children have resulted in a mild disease in the majority of patients.[1] Abdominal pain is one of the most common reasons for child's assessment in the pediatric emergency departments with over 1,345,000 annual visits in the US in under 15 years of age.[2] Acute appendicitis (AA) is the most common abdominal surgical emergency in childhood with an incidence of 1–2 cases per 100,000 children per year between birth and 4 years to 25 cases for every 10,000 children between 10 and 17 years.[3] Incidence of AA in children with COVID-19 is unknown, with sporadic publications of small case series.[4] Also, surgical outcomes in this pediatric population with severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) needing an abdominal surgery are not well studied.

Antibiotic therapy for uncomplicated appendicitis is an alternative option that can be safely used in selected patients with an increased risk of recurrent appendicitis in 20% of the cases, without increasing the likelihood of perforation.[5] In the context of COVID-19, nonoperative management of AA is an alternative to surgery with low failure and complication rates.[6]

Delayed presentation in patients with AA during the pandemic has been reported, leading to major risk of perforation in younger patients and more complications during hospitalization.[7,8] Children with COVID-19 may present with clinical features suggestive of appendicitis/AA in relation to terminal ileitis and it has not been clear whether appendicitis might occur as a complication of SARS-CoV-2 infection.[9] Multisystem inflammatory syndrome in children (MIS-C), another entity related to SARS-CoV-2 infection, was also reported as a mimicker of AA.[10,11]

Since cases are constantly raising worldwide, it is expected that SARS-CoV-2 will circulate still for a long time; therefore, the appropriate management of children with COVID-19 is a priority. While the pandemic only determined a limited direct impact on children, delayed diagnosis of patients with AA and COVID-19 could lead to increased morbidity. Due to the gap in the available literature, we performed a multinational study in Latin America aiming to describe the presentation and possible delays of pediatric patients with AA and COVID-19.

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From the *Pediatric Emergency Department, Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera", CCSS, San José, Costa Rica; †Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum – University of Bologna, Bologna, Italy; ‡Infectious Disease Department, Hospital Nacional de Niños "Dr. Carlos Sáenz Herrera", CCSS, San José, Costa Rica; §Departamento de Docencia e Investigación, Instituto Latinoamericano de Ecografía en Medicina (ILEM), Ciudad de Mexico, Mexico; ¶Clínica Jas Médica, Lima, Perù; ‖Department of Pediatrics, Unidad de Infectología Pediátrica del Hospital Nacional Edgardo Rebagliati Martins-Lima-Perú; **Department of Pediatrics, Hospital General Regional 200 IMSS, Mexico; ††Department of Pediatrics, Hospital Madre Niño San Bartolome, Lima, Peru; ‡‡Department of Pediatrics, Hospital Pablo Tobon Uribe Medellin, Colombia; §§Department of Pediatrics, Fundacion Neumologica Colombiana, Bogotà, Colombia; ¶¶Pediatric Infectious Disease, Hospital isidoro Iriarte, Quilmes, Buenos Aires, Argentina; ‖Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; ***Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy; and †††Department of Pediatrics, Global Health Research Institute, Istituto di Igiene, Università Cattolica del Sacro Cuore, Roma, Italia.

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Address for correspondence: Danilo Buonsenso, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168 Roma, Italy. E-mail: danilobuonsenso@gmail.com.

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MATERIALS AND METHODS

Study Design and Participants

This study is part of an ongoing independent, unfunded project that aims to provide urgent information on COVID-19 and MIS-C in Latin American children. The project was presented during the first peak in Latin America[12] and led to the publication of different papers describing an initial group of 409 children with confirmed COVID-19,[1] antibiotic uses in children with COVID-19 or with MIS-C,[13] and the impact of sex on disease severity in children.[14] For the current study, we aimed to assess the diagnoses of AA in children with COVID-19 or with MIS-C. We implemented the previously used dataset[1,12–14] including specific variables for this aim: clinically diagnosed acute abdomen; abdominal ultrasound; abdominal radiograph; complete blood count and C-reactive protein (CRP); surgical findings; culture results from intraoperative specimens. Appendicitis with peritonitis or abdominal abscesses were considered as complicated. These adjunctive data were collected only for children with a clinical diagnosis of appendicitis, since the current emergency situation in Latin America and the burden on health workers, along with the lack of dedicated research resources in our Institutions, did not allow a comprehensive data collection for all children. The remaining variables were collected for all children and are those previously used and included: age, gender, symptoms, imaging, underlying medical conditions, need for hospital and neonatal intensive care unit/pediatric intensive care unit (PICU) admission, respiratory and cardiovascular support, other viral coinfections, drugs used to treat COVID-19, development of MIS-C and type of organ involvement, and outcome. SARS-CoV-2 infection was defined as a positive polymerase chain reaction (PCR) test on nasopharyngeal swab.

MIS-C due to SARS-CoV-2 was defined according to the Centers for Disease Control and Prevention criteria. The study was reviewed and approved by the CoviD in sOuth aMerIcaN children—study GrOup core group and approved by the ethics committee of the coordinating center and by each participating center (Mexico: COMINVETICA-30072020-CEI0100120160207; Colombia: PE-CEI-FT-06; Peru: No. 42-IETSI-ESSALUD-2020 and Costa Rica: CEC-HNN-243-2020). The study was conducted in accordance with the Declaration of Helsinki and its amendments. No personal or identifiable data were collected during the conduct of this study.

Statistical Analysis

Summary statistics were presented as counts and percentages. Crude comparisons between groups were evaluated with the chi-squared test or Fisher's exact test, as appropriate. The association of relevant demographic characteristics and clinical factors with the diagnosis of appendicitis was assessed through logistic regression analysis; the effect size of covariates was expressed by odds ratios with 95% confidence intervals (CIs), and the presence of systematic differences (i.e., statistical significance) was assessed using the 2-sided Wald test. Standard errors were adjusted for clustering of patients within hospitals (m = 8). All data were analyzed using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP). The significance level was set at 5%.

RESULTS

Study Population

A total of 1010 children were enrolled: 941 children (93.2%) with COVID-19 and 69 children (6.8%) with MIS-C: Peru (n = 391, 38.7%), Costa Rica (n = 303, 30%), Argentina (n = 260, 25.7%), Colombia (n = 44, 4.4%) and Mexico (n = 12, 1.2%).

The demographic and clinical characteristics of the 1010 study patients, and according to the final diagnosis of appendicitis or not, are summarized in Table 1. Four hundred ninety-four (48.9%) were female. A total of 323 (32%) children were admitted to the hospital and 47 (4.7%) required admission to a PICU.

Forty-two children (4.2%) had a clinical diagnosis of acute abdomen. Of them, 4 (9.5%) were diagnosed with MIS-C and did not undergo surgery. The remaining 38 children (3.8% of the study population) underwent abdominal surgery due to suspected appendicitis, 34 of them (89.7%) had an intraoperative diagnosis of AA, while 4 of them had nonsurgical findings (mesenteric adenitis in 2 cases, and normal abdominal findings in the remaining 2). The 2 children with mesenteric adenitis but no appendicitis who underwent surgery, were eventually diagnosed with MIS-C with myocarditis. Eight children died (0.8%), none of them being diagnosed with appendicitis. Further details are described in Table 1.

Characteristics of Children With Acute Appendicitis

Children with AA were significantly older than those without ($P < 0.0001$) and did not experience a delay at diagnoses, compared with the other group (Table 1).

Table 2 describes details of the cohort of children with appendicitis and according to the presence of surgical complications or not (peritonitis, abdominal abscesses). Children with complicated appendicitis had more frequently fever (85.7% vs. 60%), intestinal distension on the abdominal radiograph (7.1% vs. none), leukocytosis (85.7% vs. 40%) and high levels of CRP (35.7% vs. 5%), although differences were not statistically significant probably due to the overall low number of children with appendicitis. On multivariate analyses (Table 3), age >5 years was associated with a higher risk of appendicitis ($P < 0.001$, 95% CI: 4.17–32.83), while the presence of upper respiratory tract symptoms with a reduced risk ($P = 0.019$, 95% CI: 0.02–0.71).

DISCUSSION

Abdominal pain is one of the clinical manifestations in children with COVID-19 and the MIS associated with SARS CoV-2 infection. According to available literature, it has been shown that patients with MIS-C could present in up to 30% as an acute abdomen.[15–17] To our knowledge, this is the first multinational study assessing the outcomes of AA in children with COVID-19 and MIS-C. We found that a non-negligible percentage of children with COVID-19 or MIS-C presented with the acute abdomen (42 children, 4.2%) and 34 had AA. Interestingly, 4 children underwent surgery without finding surgical reasons for the abdominal pain, suggesting that COVID-19 and MIS-C can both present with acute abdomen and simulate appendicitis. In fact, a recent case series clearly showed that MIS-C can have a similar presentation with acute enteritis or acute abdomen for surgical reasons and the conditions may be misdiagnosed.[18]

There are reports of case series of pediatric patients with AA during COVID-19 and MIS-C which describe the relationship between this infection and delays in diagnosis and management.[4,19,20] In our study, we found a low prevalence of diagnosis of AA (4.2%) but higher than other reported series.[21] Gastrointestinal symptoms were present in a third of all COVID-19 patients and present in all patients with the diagnosis of AA. Similar findings were reported by Tullie et al and Meyer et al.[19,22]

The delay in the approach and treatment of patients with AA implies a higher risk of perforation and complications leading to an increased length of stay.[8] However, we did not find that a delay in the diagnosis of appendicitis in these patients was associated with

TABLE 1. Characteristics of the Study Sample, Overall and by Diagnosis of Appendicitis

			Appendicitis				
	All (n = 1010)		Yes (n = 34)		No (n = 976)		
Characteristic	n	%	n	%	n	%	*P* value
Female sex	494	48.9	13	38.2	481	49.3	0.205
Age group							<0.001
0 yr	202	20.0	0	0.0	202	20.7	
1–2 yr	229	22.7	0	0.0	229	23.5	
3–5 yr	146	14.5	5	14.7	141	14.4	
6–11 yr	259	25.6	22	64.7	237	24.3	
12–17 yr	174	17.2	7	20.6	167	17.1	
Delay between onset and diagnosis							0.061
0–1 d	448	44.4	20	58.8	428	43.9	
2–7 d	469	46.4	14	41.2	455	46.6	
>7 d	93	9.2	0	0.0	93	9.5	
Likely index case							0.220
Parent	290	28.7	14	41.2	276	28.3	
Sibling	14	1.4	0	0.0	14	1.4	
Other	120	11.9	1	2.9	119	12.2	
Unknown	586	58.0	19	55.9	567	58.1	
Medical history							
Known history of BCG vaccine	760	75.2	34	100.0	726	74.4	0.001
Pre-existing medical conditions	133	13.2	7	20.6	126	12.9	0.196
Immunosuppressants at the time of diagnosis	11	1.1	0	0.0	11	1.1	1.000
Primary or secondary immunodeficiency	8	0.8	0	0.0	8	0.8	1.000
Chemotherapy over the last 6 months	8	0.8	0	0.0	8	0.8	1.000
Admitted to the hospital	323	32.0	34	100.0	289	29.6	<0.001
Intensive care during hospital stay	47	4.7	1	2.9	46	4.7	1.000
Symptoms							
Pyrexia (≥38.0/≥100.4°C/°F)	692	68.5	24	70.6	668	68.4	0.791
Upper respiratory tract infection	468	46.3	3	8.8	465	47.6	<0.001
Diarrhea and/or vomiting	321	31.8	34	100.0	287	29.4	<0.001
Lower respiratory tract infection	217	21.5	5	14.7	212	21.7	0.328
Headache	105	10.4	1	2.9	104	10.7	0.246
Acute abdomen	42	4.2	33	97.1	9	0.9	<0.001
Chest radiograph							0.257
Negative	194	19.2	3	8.8	191	19.6	
Positive (pneumonia* and/or ARDS†)	93	9.2	4	11.8	89	9.1	
Not performed	723	71.6	27	79.4	696	71.3	
Respiratory support							
Oxygen support	118	11.7	5	14.7	113	11.6	0.584
Mechanical ventilation	31	3.1	1	2.9	30	3.1	1.000
Continuous positive airway pressure (CPAP)	11	1.1	0	0.0	11	1.1	1.000
Extracorporeal membrane oxygenation (ECMO)	0	0.0	0	0.0	0	0.0	.
Administration of inotropes	29	2.9	2	5.9	27	2.8	0.255
Coinfections detected in respiratory samples(s)‡	15	1.5	1	2.9	14	1.4	0.404
Abdominal surgery	38	3.8	34	100.0	4	0.4	<0.001
Drug administration							
Systemic corticosteroids	90	8.9	2	5.9	88	9.0	0.761
Intravenous immunoglobulin (IVIG)	60	5.9	3	8.8	57	5.8	0.449
Hydroxychloroquine	9	0.9	0	0.0	9	0.9	1.000
Oseltamivir	8	0.8	0	0.0	8	0.8	1.000
Lopinavir or ritonavir	3	0.3	0	0.0	3	0.3	1.000
Noncorticosteroid immunosuppressants	3	0.3	0	0.0	3	0.3	1.000
Favipiravir	2	0.2	0	0.0	2	0.2	1.000
Remdesivir	2	0.2	0	0.0	2	0.2	1.000
MIS-C diagnosis							0.300
No	941	93.2	31	91.2	910	93.2	
Yes, with no cardiac or joint involvement	33	3.3	3	8.8	30	3.1	
Yes, with cardiac involvement§	23	2.3	0	0.0	23	2.4	
Yes, with joint involvement	11	1.1	0	0.0	11	1.1	
Yes, with cardiac and joint involvement§	2	0.2	0	0.0	2	0.2	
Tocilizumab administration to treat MIS-C	8	0.8	0	0.0	8	0.8	1.000
Current status							0.040
All symptoms resolved	989	97.9	32	94.1	957	98.1	
Dead¶	8	0.8	0	0.0	8	0.8	
Still symptomatic	7	0.7	0	0.0	7	0.7	
Long-term sequelae	6	0.6	2	5.9	4	0.4	
Country							0.737
Peru	391	38.7	11	32.4	380	38.9	
Costa Rica	303	30.0	14	41.2	289	29.6	
Argentina	260	25.7	8	23.5	252	25.8	
Colombia	44	4.4	1	2.9	43	4.4	
Mexico	12	1.2	0	0.0	12	1.2	

*Forty-five cases of interstitial disease, 31 cases of consolidation, 4 cases of pleural effusion and 13 unspecified diagnoses.

†Three cases of interstitial disease, 3 cases of consolidation and 10 unspecified diagnoses.

‡Eight mycoplasmas, 4 rhinoviruses, 1 cytomegalovirus, 1 Epstein–Barr virus and 1 unspecified virus.

§Ten cases of pericardial effusion, 6 cases of coronary dilatation, 5 cases of myocarditis and 4 cases of "other" cardiac involvement.

¶Mean time from symptom onset to death was 14 ± 8 days, ranging from 3 to 27.

ARDS indicates acute respiratory distress syndrome; BCG, bacillus Calmette–Guérin; COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; MIS-C, multisystem inflammatory syndrome; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 2. Characteristics of the Study Patients Diagnosed With Appendicitis, Overall and by Presence of Complications

			Complicated appendicitis				
	All (n = 34)		Yes (n = 14)		No (n = 20)		
Characteristic	n	%	n	%	n	%	*P* value
Female sex	13	38.2	5	35.7	8	40.0	0.800
Age group							0.302
3–5 yr	5	14.7	2	14.3	3	15.0	
6–11 yr	22	64.7	11	78.6	11	55.0	
12–17 yr	7	20.6	1	7.1	6	30.0	
Pre-existing medical conditions	7	20.6	1	7.1	6	30.0	0.198
Intensive care during hospital stay	1	2.9	0	0.0	1	5.0	1.000
Symptoms							
Pyrexia (≥38.0/≥100.4°C/°F)	24	70.6	12	85.7	12	60.0	0.141
Upper respiratory tract infection	3	8.8	1	7.1	2	10.0	1.000
Lower respiratory tract infection	5	14.7	0	0.0	5	25.0	0.063
Headache	1	2.9	0	0.0	1	5.0	1.000
Acute abdomen	33	97.1	14	100.0	19	95.0	1.000
Chest radiograph							0.255
Negative	3	8.8	1	7.1	2	10.0	
Positive (pneumonia and/or ARDS)	4	11.8	0	0.0	4	20.0	
Not performed	27	79.4	13	92.9	14	70.0	
Abdominal ultrasound							0.097
Appendicitis	4	11.8	0	0.0	4	20.0	
Mesenteric adenitis	2	5.9	0	0.0	2	10.0	
Abdominal distension	1	2.9	0	0.0	1	5.0	
Fluid	1	2.9	0	0.0	1	5.0	
Hepatic abscess	1	2.9	1	7.1	0	0.0	
Not performed	25	73.5	13	92.9	12	60.0	
Abdominal radiograph							0.412
Distended bowel loop	1	2.9	1	7.1	0	0.0	
Not performed	33	97.1	13	92.9	20	100.0	
Microbiologic findings							0.328
Negative	10	29.4	2	14.3	8	40.0	
Escherichia coli	4	11.8	2	14.3	2	10.0	
E. coli + *Enterobacter cloacae*	1	2.9	0	0.0	1	5.0	
Not detected	19	55.9	10	71.4	9	45.0	
White blood cells							0.008
≤15.0 × 10^9/L	14	41.2	2	14.3	12	60.0	
>15.0 × 10^9/L	20	58.8	12	85.7	8	40.0	
C-reactive protein							0.111
<100 mg/L	10	29.4	3	21.4	7	35.0	
≥100 mg/L	6	17.6	5	35.7	1	5.0	
Not detected	18	52.9	6	42.9	12	60.0	
Respiratory support							
Oxygen support	5	14.7	1	7.1	4	20.0	0.379
Mechanical ventilation	1	2.9	0	0.0	1	5.0	1.000
Administration of inotropes	2	5.9	0	0.0	2	10.0	0.501
Coinfections detected in respiratory samples(s)	1	2.9	0	0.0	1	5.0	1.000
Drug administration							
Systemic corticosteroids	2	5.9	0	0.0	2	10.0	0.501
Intravenous immunoglobulin (IVIG)	3	8.8	0	0.0	3	15.0	0.251
MIS-C diagnosis (no cardiac/joint involvement)	3	8.8	0	0.0	3	15.0	0.251
Current status							0.501
All symptoms resolved	32	94.1	14	100.0	18	90.0	
Long-term sequelae	2	5.9	0	0.0	2	10.0	
Country							0.061
Peru	11	32.4	5	35.7	6	30.0	
Costa Rica	14	41.2	3	21.4	11	55.0	
Argentina	8	23.5	6	42.9	2	10.0	
Colombia	1	2.9	0	0.0	1	5.0	

ARDS indicates acute respiratory distress syndrome; MIS-C, multisystem inflammatory syndrome.

a higher incidence of complications (41.1%). Complications rate in Israel were reported in 22% associated with parental concern in contracting COVID-19 in the hospital, inadequate clinical evaluation and settings for clinical evaluation (telemedicine), and the lack of healthcare worker's instructions in regard to the time to seek medical advice[8]

About the management of AA, 81% of our patients underwent surgery as the preferred modality of treatment; this differs from the practice reported in some hospitals that suggest conservative management of patients with the diagnosis of SARS-CoV-2 and acute abdomen.[6,7] Some centers have used more conservative approaches for uncomplicated cases of AA in patients with

TABLE 3. Multivariable Logistic Regression Analysis of Appendicitis Diagnosis (n = 1010)

Characteristic	Odds ratio	*P* value	95% Confidence interval	
			Lower bound	Upper bound
Sex				
Male	Ref.			
Female	0.60	0.067	0.35	1.04
Age group				
≤5 yr	Ref.			
>5 yr	11.71	<0.001	4.17	32.83
Hospitalization				
No	Ref.			
Yes, without intensive care	5.07	0.024	1.24	20.71
Yes, with intensive care	1.29	0.749	0.27	6.15
Pyrexia (≥38.0/≥100.4°C/°F)				
No	Ref.			
Yes	2.55	0.289	0.45	14.41
Upper respiratory tract infection				
No	Ref.			
Yes	0.13	0.019	0.02	0.71
Lower respiratory tract infection				
No	Ref.			
Yes	0.29	0.299	0.03	3.00
Headache				
No	Ref.			
Yes	0.15	0.177	0.01	2.36
Chest radiograph abnormalities (pneumonia and/or ARDS)				
No	Ref.			
Yes	2.13	0.323	0.48	9.53
Oxygen support, mechanical ventilation and/or CPAP				
No	Ref.			
Yes	0.98	0.974	0.27	3.59
Administration of systemic corticosteroids				
No	Ref.			
Yes	0.57	0.343	0.18	1.81
MIS-C diagnosis				
No	Ref.			
Yes	0.57	0.252	0.22	1.49

Covariates that predict the outcome perfectly (immunosuppressants/immunodeficiency/chemo and diarrhea/vomiting) were excluded from the model.

ARDS indicates acute respiratory distress syndrome; CPAP, continuous positive airway pressure.

COVID-19, including home care and nonoperative management with antibiotics.[23]

Reports of patients with AA and MIS-C has been described as part of the clinical features of the inflammatory syndrome.[4,22,24] In our study, we found 4 patients with MIS-C and a clinical diagnosis of the acute abdomen who were treated with nonoperative management with no overall complications, suggesting that appendicitis was not the cause of abdominal pain. Interestingly, we also found 4 children who underwent but had not intra-operative findings of appendicitis, suggesting that the inflammatory response was the cause of pain rather than appendicitis. Two of these patients had mesenteric adenitis and were eventually diagnosed with MIS-C, supporting the evidence that AA may be one of the presenting symptoms of MIS-C and the difficulty in distinguishing the 2 conditions.

Our study has some limitations to address. We could not determine the time from diagnosis and the surgical management, limiting the result of the association between delayed treatment and complications. The small number of patients with AA and COVID-19 could be less than the real number of patients with these 2 conditions because a large proportion of children have not been tested with PCR test on nasopharyngeal test due to unavailability of them during certain periods of the pandemic, as may have happened in low-to-middle income countries settings worldwide. Despite these limitations, this study provides the largest overview of AA in children with COVID-19 and MIS-C to date.

In conclusion, our study found that both MIS-C and COVID-19 can present acute abdomen, with or without appendicitis. Further studies are needed to better recognize these cohorts of children and optimize diagnosis and both conservative or surgical treatment.

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