Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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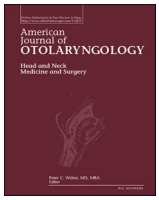

Pediatric COVID-19 infection in Sulaimaniyah Governorate, Iraq

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ABSTRACT

Background: COVID-19 is a severe acute respiratory syndrome caused by SARS-CoV-2.
Objective: To study the demographic and clinical presentations of COVID-19 with their types including MIS-C and Kawasaki among children who were admitted to Doctor Jamal Ahmad Rashid Pediatric Teaching Hospital (DJARPTH) at Sulaimaniyah city, Iraq.
Patients and methods: A prospective cohort study was conducted from June to December 2020 in which 50 cases suspected of COVID-19 were enrolled in the study that was admitted at the first visit to the emergency department of DJARPTH and their age ranged between 3 months to 14 years. Then, the collected data were divided into 3 groups: COVID-19, Kawasaki disease (KD), and MIS-C.
Results: The fever was the most common presented symptom in all cases with COVID-19 regardless of the severity. COVID-19 may be presented as KD as well as MIS-C. There is an increase in the number of Kawasaki cases since 2019 by 6.7 fold due to the increased number of COVID-19 cases in children. Death was more related to MIS-C and primary COVID-19 diseases. Most COVID-19 cases presented with pericardial effusion; although coronary involvement and LV dysfunction mostly seen with MIS-C cases.
Conclusion: COVID-19 is not uncommon in pediatric patients and it presents as either primary, MIS-C, and KD. Most of the deaths and ICU outcomes were related to MIS-C presentations.

1. Introduction

Coronaviruses are a large family of viruses that cause a variety of diseases such as SARS, MERS, and COVID-19. COVID-19 is a viral disease caused by SARS-CoV-2 [1] that was reported for the first time in Wuhan, China in December 2019 [2].

The Common symptoms of COVID-19 are fever, fatigue, dry cough, upper respiratory symptoms such as nasal congestion and running nose, but occasionally gastrointestinal symptoms such as nausea, vomiting, and diarrhea are the main clinical symptoms of COVID-19 [2].

The severe multi-system inflammatory syndrome has been reported in individuals less than 21 years of age. As many of these children may deteriorate quickly and initially present to non-tertiary care facilities, a general guide for an approach to such children is warranted [3].

Recent reports suggest a new COVID-19 related clinical syndrome, with significant inflammation and similarities to Kawasaki disease (KD) that can present in children. Some children have had features of toxic shock syndrome and myocarditis with cardiogenic shock [3–5].

Acute cardiac dysfunction was defined as the appearance of any of the following echocardiographic alterations: global or segmental contractility alterations, ventricular dilatation, reduced ejection fraction, and/or presence of pericardial effusion [6].

Although the presence of KD symptoms has been previously described in patients with infections by other coronaviruses [7]; however, the evidence provided on KD in pediatric patients with SARS-CoV-2 in the scientific literature is very limited [6]. So this research aims to study the demographic and clinical presentations of COVID-19 with their types including MIS-C and Kawasaki among children who were admitted to Doctor Jamal Ahmad Rashid Pediatric Teaching Hospital (DJARPTH) (Fig. 1).

2. Patients and methods

A prospective cohort study was conducted at DJARPTH in

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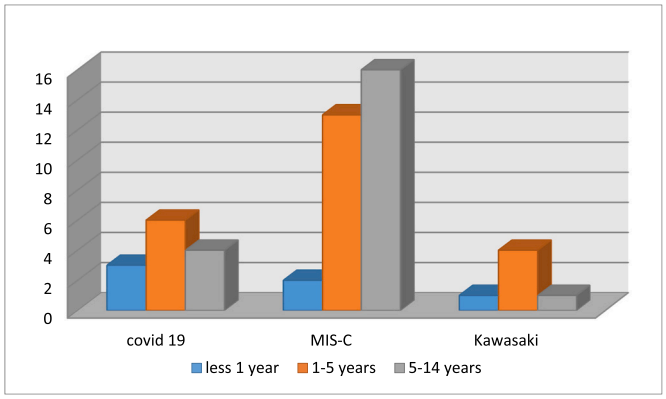

Fig. 1. Age distribution among pediatric patients.

Sulaimaniyah governorate from June to December 2020. The collected data was obtained directly from parents and/or relatives of the enrolled children by a well-designed questionnaire and oral consent was taken from the parents.

In this study, 50 cases of suspected COVID-19 were enrolled who were admitted at the first visit to the emergency department at DJARPTH. The age of the subjects was ranged from 3 months to 14 years old. Patients included in this study based on the criteria of MIS-C diagnosis that defined by WHO and CDC case definitions of the multi-system inflammatory syndrome in children [8,9].

The COVID-19 cases were diagnosed either by positive RT-PCR test result or presence of antibodies (IgG and IgM) to SARS-CoV-2. Regarding the KD, cases were diagnosed based on the criteria of complete Kawasaki disease according to the American Heart Association guideline [10]. Whereas, incomplete Kawasaki cases had overlapping clinical symptoms with MIS-C and they were incorporated into the data of MIS-C cases.

The data of cases were obtained by a specifically designed questionnaire, which includes a full history and physical examination, demographic data, and coexisting conditions such as chronic lung disease and congenital heart disease. Signs and symptoms include fever (38 °C), respiratory symptoms (such as shortness of breath, cough, and sore throat), cardiovascular symptoms (such as shortness of breath, chest pain, and sweating), gastrointestinal symptoms (such as diarrhea, nausea, vomiting, and abdominal pain), neurological symptoms (such as headache and irritability), musculoskeletal symptoms (such as myalgia), dermatological symptoms (such as rash and swelling of hands and feet), mucocutaneous symptoms (such as conjunctivitis and mucosal changes).

Additionally, the history of contact with COVID-19 patients (relative or family member) was considered accordingly, and data were sub-divided into 3 groups of COVID-19, KD, and MIS-C (Fig. 2).

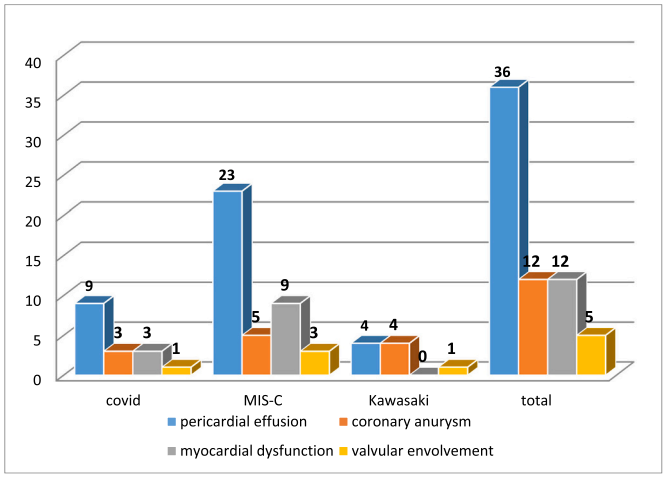

Fig. 2. Cardiac involvement among pediatric patients.

2.1. Statistical analysis

The obtained data were analyzed using Statistical Package for the Social Sciences (IBM SPSS, version 24). Chi-square tests were used; box plot and tabular forms showing the frequency and relative frequency distribution of COVID-19 patients. p-Value considered a significant when $p < 0.05$ and highly significant when $p < 0.01$.

3. Results

Table 1 shows the mean age distribution in COVID-19 patients (4.1 ± 4.1), MIS-C (6.39 ± 4.0), and the KD (3.24 ± 2.0). However, the age, sex, and residency were not statistically significant ($p < 0.05$). The rate of infection in males to females was 1.1 with a median age of 4 years. Age was non-normally distributed ($p < 0.08$) and ranges of ages were more distributed among 1–5 years by 46%, among 6–14 years by 42% and in children under 1 year by 12%.

Table 2 shows a comparison between COVID-19, MIS-C, and Kawasaki according to clinical presentation in which all cases were included in our study suffered from fever, sore throat, irritability, rash, swollen hands and feet, lymphadenopathy, conjunctivitis and mucosal changes all were statistically significant ($p < 0.05$).

Table 3 shows investigations related to COVID-19 and COVID-19 like disease and their relations.

4. Discussion

Global knowledge of COVID-19 epidemiology, clinical characteristics, and management has continued to evolve since the onset of the pandemic. Children have been noted to have relatively lower rates of severe illness and low mortality; however, they have been impacted by MIS-C [11].

In this study, we found the median age of infection was 4 years and the rate of male to female infection was 1.1 with age non-normally distributed ($p < 0.08$). These outcomes are close to the study conducted in Europe where the median age was 5.0 years and the rate of male infection to females was 1.15 with non-normally distributed age ($p < 0.0001$) [12].

On the other hand, our current study is contrary to a study conducted in the US which revealed that the infected male with COVID-19 was 51% with a median age of 10.3 years (IQR: 1.4 months to 16.3 years). Also, the study showed that patient age was not evenly distributed in which

Table 1
Distribution of age, sex, and residency in COVID-19, MIS-C, and Kawasaki diseases.

Variables	COVID19 (n = 13)	MIS-C (n = 31)	Kawasaki (n = 6)	Total	p value
Age (mean ± SD)	4.1 ± 4.1	3.24 ± 2.0	6.39 ± 4.0	5.4 ± 4.04	0.08
<1 years	3 (23.1%)	2 (6.5%)	1 (16.7%)	6 (12%)	
<5 years	6 (46.2%)	13 (41.9%)	4 (66.7%)	23 (64%)	0.30
6–14 years	4 (30.8%)	16 (51.6%)	1 (16.7%)	21 (42)	
Sex					0.18
Male	7 (53.8%)	18 (58.1%)	1 (16.7%)	26 (52%)	
Female	6 (46.2%)	13 (41.9%)	5 (83.3%)	24 (48%)	
Residency					0.08
Urban	4 (30.8%)	20 (64.5%)	2 (33.3%)	26 (52%)	
Rural	9 (69.2%)	11 (35.5%)	4 (66.7%)	24 (48%)	

Table 2
Comparison between COVID-19, MIS-C, and Kawasaki diseases according to clinical features.

Clinical features	COVID 19	(n = 13)	Kawasaki	(n = 6)	MIS-C	(n = 31)	Total	p value
Fever	13	100%	6	100%	31	100%	50	1.0
Rash	2	15.4%	6	100%	24	77.4%	32	<0.001
Conjunctivitis	1	7.7%	6	100%	22	70.9%	29	<0.001
LAP	1	7.7%	5	83.3%	5	16.1%	11	<0.001
Swollen hand and feet	3	23%	5	83.3%	4	12.9%	12	0.0011
Irritability	11	84.6%	6	100%	15	48.4%	32	0.01
Cough	5	38.5%	0	0.0%	8	25.8%	13	0.21
SOB	5	38.5%	0	0.0%	1	3.2%	6	0.66
Sore throat	1	7.7%	1	16.7%	6	19.4%	8	0.63
Chest pain	3	23%	0	0.0%	7	22.6%	10	0.43
Sweating	5	38.5%	2	33.3%	17	54.8%	24	0.46
Diarrhea	10	77%	4	66.7%	17	54.8%	31	0.38
Vomiting	5	38.5%	3	50%	13	42%	31	0.89
Nausea	3	23%	1	16.7%	2	6.5%	6	0.28
Abdominal pain	6	46%	2	33.3%	14	45.2%	22	0.85
Headache	6	46%	2	33.3%	16	51.6%	24	0.71
Myalgia	8	61.5%	4	66.7%	26	83.9%	38	0.24
Mucosal change	2	15.5%	4	66.7%	15	48.4%	21	0.06

Table 3
Showing laboratory investigations of COVID-19 and COVID-19 like disease and their relations.

Investigations	(Mean ± SD)				p value*
	COVID-19	MIS-C	Kawasaki	Total	
WBC count	14.74 ± 9.5	10.97 ± 6.88	13.61 ± 5.13	12.27 ± 7.53	0.29
Lymphocyte %	19.67 ± 16.66	9.36 ± 12.24	22.13 ± 31.12	13.58 ± 16.99	0.08
Granulocyte %	41.03 ± 32.50	35.88 ± 31.02	46.60 ± 43.25	36.11 ± 35.09	0.55
Hemoglobin %	10.14 ± 2.25	10.64 ± 2.00	11.20 ± 1.17	10.57 ± 1.98	0.54
Platelet	407.62 ± 209.47	258.42 ± 149.56	162.00 ± 97.71	285.64 ± 178.05	0.01
ESR	59.15 ± 27.30	55.94 ± 31.08	67.50 ± 32.33	58.16 ± 29.91	0.69
CRP	84.54 ± 53.77	128.79 ± 96.09	188.50 ± 31.08	124.45 ± 91.49	0.06
S. ferritin	925.75 ± 742.68	703.13 ± 599.69	567.50 ± 361.31	729.27 ± 598.77	0.52
D. dimer	2357.80 ± 1498.49	1700.86 ± 1627.65	2486.40 ± 2621.85	1944.98 ± 1718.76	0.45

Performed by ANOVA test.

the largest number of cases was among children aged ≥12 years (48%) followed by infants under 60 days old (29%) [13].

In our study, male case distribution among COVID-19 patients was 53.8% and for MIS-C cases was 58.1% which is relative to a study done in Italy in which male cases in COVID-19 patients were 78.2%, and in MISC cases was 37.5% which might be due to sample size differences compared to our study [14].

In our study, the preexisting disease accounts for 12% while in another recent study the comorbidity was 27.1% [15]. Additionally, another study conducted in Europe shows that 25% of cases had pre-existing medical conditions [12]. Generally, according to US-CDC, the most common comorbidities were chronic lung diseases (11.6%), cardiovascular diseases (7.2%), and immunosuppression (2.9%) [16]; however, a study in the US showed that 55% of children hospital presented with the underline medical condition [13].

There was no significant difference in the incidence of the disease occurrence between inside Sulaimaniyah city and outside the city. The obvious history of contact in our cases was 43/50 cases (86%), whereas a study in the US showed a 57% history of contact [13].

In our study, the most common symptoms were fever (100%), myalgia (76%), headache (48%), gastrointestinal tract (GIT) symptoms (mostly diarrhea) (62%), cough (26%), and rhinorrhea/sore throat (16%). In this regard, a recent study showed that the most common symptoms were fever (63.3%), cough (33.7%) followed by nausea/vomiting (20.0%), diarrhea (19.6%), dyspnea (17.5%), nasal-symptoms (16.6%), skin rashes (15.5%), Kawasaki-like symptoms (13.3%), fatigue (15.5%), abdominal pain (15.3%), conjunctivitis (10.5%), and neurological symptoms (12.1%) [15]. Also, our patients showed 58% conjunctivitis and 42% mucosal and lip changes as presenting symptoms which is higher than a previous study [15].

In another study in the USA, hospitalized children showed fever (69%), cough (49%), poor feeding/anorexia (40%), shortness of breath (35%), and nausea/vomiting (28%). Fever was recorded in 74% of patients based on history or upon presentation [13]. Whereas in another study in the USA, the most common clinical manifestations were fever (59.1%), cough (55.9%), rhinorrhea (20%), and myalgia/fatigue (18.7%) [11]. Pyrexia was the most common sign at presentation (65%), followed by upper respiratory tract infection (54%) and lower respiratory tract infection; then GIT symptoms (22%); however; 16% of patients were asymptomatic [12]. These results have similar rate observation to a study conducted in Italy on 100 patients aged <18 years in the emergency department [17]. Consequently, in another study that based on symptomatology, it was found that patients had a cough (48.5%), rhinorrhea (7.6%), tachypnea (28.7%), fever (41.5%), fatigue (7.6%), diarrhea (8.8%), nausea/vomiting (6.4%), and tachycardia (42.1%) [18].

However, in our study, we could not report asymptomatic cases as our study was on the admitted patients at the hospital with advanced infection. Notably, a recent letter summarizing 171 PCR-confirmed cases in Wuhan of which 20% of children and adolescents with SARS-CoV-2 infection were asymptomatic [19].

In our study, complete KD were 6/50 cases (12%), incomplete Kawasaki were 18/50 cases (36%) (totally, 24 cases over 6 months; mean 4 cases/month). Comparing to a study done in a pre-COVID-19 era in the same hospital (the rate was 0.6/month) [20], the rate is increasing by 6.7 folds. Based on the literature review, incomplete KD phenotype was increased to 45.9%, thus, the rate of incomplete KD during the pandemic is higher compared to the pre-COVID-19 period [21]. In this regard, Aydin et al. reported the prevalence of incomplete KD as 48.0% in their center which was an approximately 3.7 fold increase compared to previous data reported on their center [22]. This finding suggests that we should maintain a high index of suspicion for incomplete KD in COVID-19 patients. For instance, in Italy, a 30-fold increased incidence of KD was reported, and it is expected to reach similar figures in North America [5]. In Turkey, 4 cases with incomplete Kawasaki-like presentation of COVID-19 with high CRP, ESR, and D-dimer were reported [23] similar to our incomplete cases.

Additionally, we found a relatively low lymphocyte/neutrophil ratio

in the MIS-C group as well as high ESR, CRP, serum ferritin, and high D-dimer. In a study done in Italy, patients with MIS-C exhibited lower levels of lymphocytes and LDH, higher levels of CRP and PCT, neutrophils, and a higher lymphocyte/neutrophil ratio [6]. On contrary, a study in the USA showed that neutropenia/lymphopenia was not related to the severity of the disease [13]. We also found that D-dimer was double to triple than that of primary COVID-19 relative to MIS-C and Kawasaki cases.

In our study, we found that at early time presentation, platelet was higher in COVID-19 cases relative to MIS-C cases which is similar to that found in Italy [14], but ferritin value was extremely higher in COVID-19 cases which is contrary to that of Italian study [14]. Also, the neutrophil/lymphocyte ratio was higher in MIS-C relative to COVID-19 cases (milder), which is also noted in an Italian study [14].

Moreover, we demonstrated that most of the MIS-C cases (80.6%) were positive for IgG while 13.3% of them were positive for IgM, however; 83.3% of COVID-19 cases were positive for IgM and 50% were positive for IgG.

Up to date, more than 200 suspected PIMS-TS cases are under investigation in Europe and North America. However, ECDC recently assessed the overall risk of PIMS-TS among children infected with SARS-CoV-2 and considered to be low [24].

In our study, we found that 31 out of 50 (62%) of cases showed signs of severe disease in the form of MIS-C and they received intravenous immunoglobulin (IVIG) and steroids. As well, 10 of MIS-C cases and 3 of primary COVID-19 cases received supportive care for the heart in the form of diuretics and inotropes. Similarly, some studies also displayed that a higher proportion of children with severe disease demonstrated symptoms consistent with MIS-C including fever, abdominal symptoms, rash, neurological symptoms, and conjunctivitis; and received IVIG, steroids, and inotropes [15].

In this current study; some of the MIS-C cases got some symptoms of KD, so still it's confusing, as its clearly this fact is defined as these case definitions are problematic since some cases that are not MIS-C (including Kawasaki-like syndrome) fulfill the definitions of MIS-C [26].

In our study, 17 out of 50 (34%) cases were admitted to intensive care unit (ICU) in which 60% of them were MIS-C cases, whereas, in a meta-analytic study on COVID-19 cases; the rate of admission was 22.9% and nearly half of children (638/1208) who met criteria for MIS-C were admitted to ICU [15].

In addition, we found that the mortality rate was 6/44 (13.6%) among primary COVID-19 and MIS-C cases admitted into hospital as single-center experience with early COVID-19 registry and management, while in a meta-analytic study among the hospitalized cases, 40 deaths were reported in high-income countries with 56 deaths in low income and middle incomes countries (pooled proportion 2.9% vs 5.2%) [15].

Generally, cardiac involvement accounts for most MIS-C cases, and in our study; the total cases of COVID-19 (36/50; 72%) account for a mild form of pericardial effusion and coronary involvement, hence, only a few cases of pericardial effusion reported in the literature [27]. As well, myocardial involvement and left ventricular dysfunction were seen in 29% (9/31) of MIS-C cases and 30% (3/9) of primary COVID-19 cases, while in a study in India; 42.8% (9/21) were presented with left ventricular dysfunction and 25.8% (8/31) with coronary involvement [28]. We also found that coronary involvement in full-blown Kawasaki cases were 4/6 (66.6%) and pericardial effusion were 4/6 (66.6%), but in another study done by Salih et al. before the COVID-19 era; it shows that coronary involvement was 18/36 (50%) and there was no pericardial effusion [20].

5. Conclusion

In conclusion, we realized that **COVID-19 infection is not uncommon in pediatric patients and it presents as either primary, MIS-C, and KD cases. Also, we found that most of the deaths and ICU outcomes were related to MIS-C presentations**.

5.1. Limitation of the study

The main limitation of this study relates to the number of variables for which data were collected. In the context of the ongoing COVID-19 pandemic, to ensure high levels of participation and avoid diverting substantial time away from clinical front-line duties, a decision was made not to collect detailed data on laboratory parameters or ICU interventions and also different medical interventions. A further limitation was that a variety of commercial PCR assays were used, precluding an assessment of diagnostic test performance.

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Declaration of competing interest

The authors declare no conflict of interest to this study.

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