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Coronavirus disease in children: A multicentre study from the Kingdom of Saudi Arabia

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ABSTRACT

Background: The COVID-19 global pandemic caused by severe acute respiratory syndrome coronavirus 2 infection, warranted attention for whether it has unique manifestations in children. Children tend to develop less severe disease with a small percentage present with clinical manifestations of paediatric multisystem inflammatory syndrome and have poor prognosis. We studied the characteristics of COVID-19 in children requiring hospitalisation in the Kingdom of Saudi Arabia and assessed the clinical presentation and the risk factors for mortality, morbidity, and paediatric intensive care (PICU) admission. **Methods:** We conducted a retrospective analysis of COVID-19 patients under 15 years hospitalised at three tertiary academic hospitals between 1 March and 30 June 2020.

Results: Eighty-eight children were enrolled (>20% were infants). Seven (8%) were in critical condition and required PICU admission, and 4 (4.5%) died of which 3 met the full diagnostic criteria of multi-system inflammatory syndrome and had a high Paediatric Risk of Mortality (PRISM) score at the time of admission. The initial polymerase chain reaction (PCR) test result was positive for COVID-19 in most patients (97.7%), and the remaining two patients had positive result in the repeated confirmatory test. In a subset of patients (20 subjects), repeated PCR testing was performed until conversion to negative result, and the average duration for conversion was 8 (95% CI: 5.2–10.5) days. Children requiring PICU admission presented with signs of respiratory distress, dehydration, and heart failure. Most had fever (71.4%) and tonsillitis; 61.4% were discharged within 7 days of hospitalisation. Risk factors for mortality included skin rash, hypotension, hypoxia, signs of heart failure, chest radiograph suggestive of acute respiratory distress syndrome, anaemia, leucocytosis, hypernatraemia, abnormal liver enzymes, and high troponin I, and risk factors for prolonged hospitalisation (>7 days) included the presence of comorbidities, leucopaenia, hyponatraemia, and elevated C-reactive protein.

Conclusions: The majority of hospitalised children had a brief febrile illness and made a full recovery, but a minority had severe disease.

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Introduction

In December 2019, a pneumonia case of unidentified aetiology was reported in the city of Wuhan in China. It was the first reported case of coronavirus disease (COVID-19) due to a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. The first case diagnosed in the Kingdom of Saudi Arabia (KSA)

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was on 2 March 2020 [2,3]. The novel coronavirus outbreak was eventually declared as a pandemic by the World Health Organization on 11 March 2020. As of the fifth of January 2021, more than 86,165,000 cases have been confirmed globally with more than 1,863,000 deaths [4]. The reported cases in KSA is lower than most countries as by fifth of January 2021, 363,259 cases were confirmed and 6265 deaths were reported [5]. Children aged <18 y constitute 1–2% of the total cases, with similar but less severe symptoms [6,7]. In more than 72,000 total cases from China, only 1.2% were children aged 10–19 years, and 0.9% were in patients younger than 10 years [4]. Similarly, data from the Netherlands, Italy, Spain, and the United States of America (USA) show that paediatric patients account for 0.8%–2% of confirmed cases. [8–11]. Children at any age can get infected with COVID-19. A cohort of 582 children from multi-European centres showed the age distribution as follows: 7% in less than one month of age, 22% for 1–12 months of age, 10% for 1–2 years old, 11% for 2–5 years old, 16% for 5–10 years old and 34% for more than 10 years of age [12]. In contrast to the adults, rarely do children have comorbidities apart from a few reported cases that required admission to paediatric intensive care units (PICU) [13]. The reported mortality in children was associated with underlying diseases or medical conditions such as leukaemia [14]. In children, racial and ethnic minorities appear to be disproportionately affected. [15,16]

The need for hospitalisation varied from 5.7 to 20% in the USA [17] to 60% in Spain [10]. Similarly, the need for PICU admission was 0.6–9.7% [10,11], consisting of patients with an underlying medical condition primarily. Since April 2020, findings of multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 have been reported from different countries [17–20]. MIS-C has been observed in critically ill children with COVID-19 and has a wide spectrum of severity that includes heart lesions [17–20], shock, gastrointestinal symptoms [18,20], rash, and conjunctivitis [20]. Rapid and complete clinical and myocardial recovery was observed in most of these children [20]. Overlapping features were noted between Kawasaki disease and MIS-C [19,18–20]. However, Kawasaki disease generally occurs in children at an earlier age than COVID-19 [20]. Further interesting presentations were recently observed, such as incomplete Fanconi syndrome, which preceded acute kidney injury in children with COVID-19 [21]. Similar to other countries, children were a minority of reported cases (4%) in KSA [22,23]. The majority presented with mild symptoms [24]. However, there was a report of ten children that presented with MIS-C, a Kawasaki disease like syndrome [25].

The aim of this study was to assess the epidemiology and clinical features of COVID-19 in children who required hospitalisation in KSA, including their clinical presentation and risk factors for mortality, morbidity, and the need for PICU admission.

Material and methods

Study design

This was a multicentre retrospective cohort study comprising three tertiary centres in KSA: King Abdul-Aziz University Hospital, King Khalid University Hospital, and East Jeddah General Hospital, which represent important academic centres in Saudi Arabia serving two important regions in the kingdom.

Patients and methods

Permission to conduct the study was approved by the research ethics committees of the three institutions involved in the research with approval number Ref. No. 232-20 and, Ref. No. 20/0337/IRB. The requirement for informed patient consent was waived, as it

was a retrospective study using data collected for routine clinical practice.

We performed a retrospective cohort study of children aged 14 years or younger, with confirmed SARS-CoV-2 infection, admitted to any of the three participating centres between 1 March and 30 June 2020. All participating centres used the same visual triage checklist for diagnosing an acute respiratory infection for suggested cases and assessing who required screening using the nasopharyngeal swab testing. All patients labelled positive for COVID-19 were confirmed positive for the disease with the nucleic acid detection using a real-time reverse transcription polymerase chain reaction (rRT-PCR) test for the qualitative detection of nucleic acid from SARS-CoV-2 from upper and lower respiratory specimens (such as nasopharyngeal or oropharyngeal swabs, or bronchoalveolar lavage). Nasopharyngeal/oropharyngeal swabs were obtained in a child-friendly environment from all conscious children after explaining the technique of the test to older children.

Patients were considered to have the infection if the initial swab result was positive or if it was negative initially but positive on the subsequent test. The swab test was repeated shortly after the initial swab results were negative if there was a prominent clinical suspicion of COVID-19 or a risk of false-negative owing to a technical error during sample collection. Some patients had many positive swab samples during admission as requested by the responsible team in line with the local protocol of each centre and according to the changes in the recommendation by the Ministry of Health, which changed over time based on the latest published evidence. We excluded patients with insufficient data, those admitted to the emergency room only for a nasal swab test that should not have been admitted, and those previously admitted for the same reason.

Data were collected from the electronic health records of all the participating centres and were merged. Data collected included patient demographics (age, gender, and nationality), current weight, and height, and body mass index centile, need for PICU admission, presenting symptoms and signs, and associated comorbidities. We reported any history of contact with an individual with COVID-19 or recent travel to any country positively predicted infection during the pandemic. We also considered the severity of respiratory distress, blood pressure interpretation, chest radiograph findings, oxygen saturation, and the need for oxygen therapy and/or mechanical ventilation.

For any patient who required intensive care admission, we calculated the Paediatric Risk of Mortality (PRISM version IV) [26] during the first and after 24 h of PICU admission. Detailed clinical data such as urine output, fluid balance, the need, and duration of mechanical ventilation and/or inotropes, and electrocardiogram (ECG) abnormalities were collected. The laboratory results were recorded and followed by the assessment of the associated haematological abnormalities such as significant anaemia, leukopenia, leucocytosis, neutropenia or neutrophilia, thrombocytopenia, and disturbed coagulation profiles. Other associated laboratory abnormalities such as hypernatraemia, hyperkalaemia, and high troponin level were also reported. Evidence of any associated infection (blood and urine culture) and high acute phase reactants (C-reactive protein [CRP] and ferritin) was highlighted.

We referred to the most common medications used by the participating centres as active COVID-19 therapy used in the paediatric age group. All clinical outcomes were reported for the patients who had completed their hospitalisation by the end of the study period, including patients who were either discharged or died. Clinical outcome indicators included the mortality rate, length of stay (LOS), PICU admission, and the need for invasive therapy such as mechanical ventilation.

COVID-19 PCR methodology

Viral RNA extraction

Processing of nasopharyngeal samples was performed in a Class II biosafety cabinet in a negatively pressured lab. The extraction was performed using the ExiPrep™ 96 Viral DNA/RNA kit (BiONEER, Korea) on the automatic extractor BiONEER according to the manufacturer's instructions.

Reverse transcription real-time PCR

The PowerChek 2019-nCov Real-Time PCR Kit (Seoul, Korea) was used for the detection of SARS-CoV-2, briefly, by adding 5 µL of the extracted RNA to the reaction master mix consisted of 11 µL RT-PCR Premix and 4 µL of Primer/Probe Mix for a total reaction volume of 20 µL. As per WHO recommendations, two targets were separately amplified: the E gene of beta coronaviruses and the RdRp gene of the SARS-CoV-2 viral genome [27]. Both probes were labelled with FAM. The reaction mixture included an internal control for PCR inhibition with a Victoria (VIC)-labelled probe. The reaction's thermal profile was 50 °C for 30 min, then 95 °C for 10 min, followed by 40 cycles of 95 °C for 15 s and 60 °C for 1 min on the LightCycler® 480 Instrument II (Roche) [28].

Definitions

PRISM IV is the updated version of the scoring system of risk of mortality in children admitted to the intensive care unit. It depends on many important variables recorded during the first 24 h of admission. WHO defines paediatric multi-system inflammatory syndrome in children and adolescents aged 0–19 years as fever for 3 days or more and two of the following: skin rash or signs of mucocutaneous inflammation hypotension or shock, features of myocardial dysfunction, evidence of coagulopathy, acute gastrointestinal problems, in addition to elevated markers of inflammation such as erythrocyte sedimentation rate, C-reactive protein or procalcitonin, with evidence of COVID-19 and no other obvious microbial cause of inflammation [29].

Hypertension and hypotension were defined as two or more readings of systolic and/or diastolic blood pressure at 2 different time points, which were higher than the 95th centile and lower than the 50th centile, respectively, for gender, age, and height. Hyperkalaemia was defined as the serum potassium level <5.5 mmol/L. Hyponatremia was defined as the serum sodium level <146 mmol/L. Anaemia was defined as reduced haemoglobin concentration two standard deviations below the mean, based on age-specific normal. Leucocytosis and leukopenia were defined as total leucocytic count higher/lower than the mean based on age-specific normal level and neutropenia was defined as a neutrophilic count less than 500/mm³.

Statistical analysis

All analyses were performed using Stata Version 12 (StataCorp. LP, College Station, TX, USA). Results of categorical variables were reported as frequencies and percentages, and means for continuous variables. The in-hospital survival among children admitted with confirmed COVID-19 was estimated using the Kaplan–Meier curve. Factors associated with in-hospital mortality and prolonged LOS (>7 d) were determined using the chi-square test. Statistical significance was set at a p-value of 0.05.

Results

Eighty-eight children admitted with a confirmed diagnosis of COVID-19 were included, of whom >20% were infants (Fig. 1), 42%

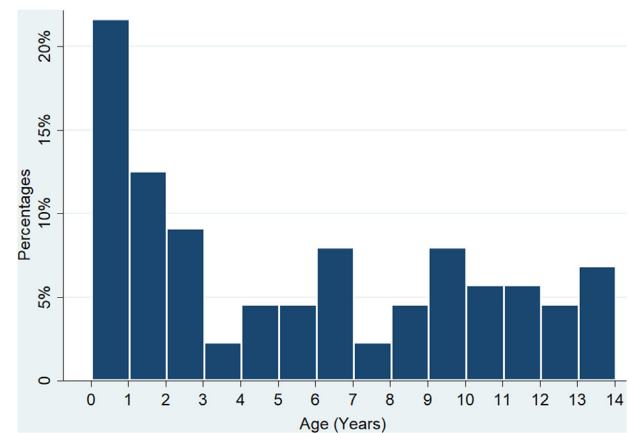


Fig. 1. Age distribution of children admitted with a confirmed diagnosis of COVID-19.

Table 1 Patients' demographic and clinical characteristics.

Characteristics	
Sex, No. (%)	
Male	37 (42.0)
Female	51 (58.0)
Nationality, No. (%)	
Saudi	47 (53.4)
Non-Saudi	41 (46.6)
Weight (kg), median (IQR)	19.8 (10–31.8)
Weight (centile), median (IQR)	75 (9–91)
Height (cm), median (IQR)	100 (73.5–129.8)
Height (centile), median (IQR)	9.0 (0.3–75)
BMI (kg/m ²), median (IQR)	18.8 (14.6–24.5)
BMI (centile), median (IQR)	91 (25–99.7)
Contact with COVID-19, No. (%)	73 (83.0)
Recent travel, No. (%)	5 (5.7)
Comorbidities, No. (%)	
Diabetes ^a	1 (1.1)
Renal disease	2 (2.3)
Cardiac disease	6 (6.8)
Respiratory disease	11 (12.5)
Haematological disorder	3 (3.4)
Malignancy	1 (1.1)

Abbreviations: BMI, body mass index; CI, confidence interval.

^a Type I diabetes.

were male, 83% had a definite history of exposure to SARS-CoV-2, 27.2% had a chronic illness, and 12.5% had a chronic respiratory illness. Table 1 shows patient demographics and disease characteristics.

The most common presenting symptom was fever, followed by respiratory and gastrointestinal symptoms. Headache, muscle ache, and skin rash were uncommon (Fig. 2).

Of the 88 children admitted, 7 (8%) were in critical condition and required PICU admission. Abnormal physical examination included fever and tonsillitis, whereas signs of respiratory distress, dehydration, and heart failure were more frequently encountered in children who required PICU admission. Among PICU patients: 4 died (4.5%) of which 3 met the full diagnostic criteria of multi-system inflammatory syndrome and had a high Paediatric Risk of Mortality (PRISM score IV from 29 to 87%) at time of admission. Most patients (61.4%) were discharged within 7 days of hospitalisation (Fig. 3). (Table 2).

The initial PCR test result was positive for COVID-19 in most patients (97.7%), and the remaining two patients had positive results in the repeated confirmatory test. In a subset of patients (20 subjects), repeated PCR testing was performed until conversion to a negative result, and the average duration for conversion was 8 (95% CI: 5.2–10.5) days (Table 3).

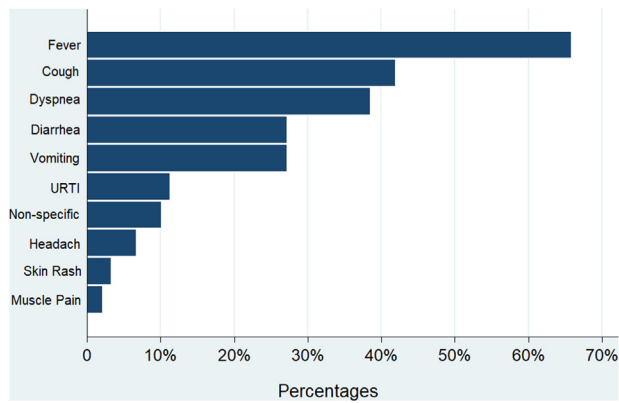


Fig. 2. Presenting symptoms of children admitted with a confirmed diagnosis of COVID-19.

Abbreviation: URTI, upper respiratory tract infection.

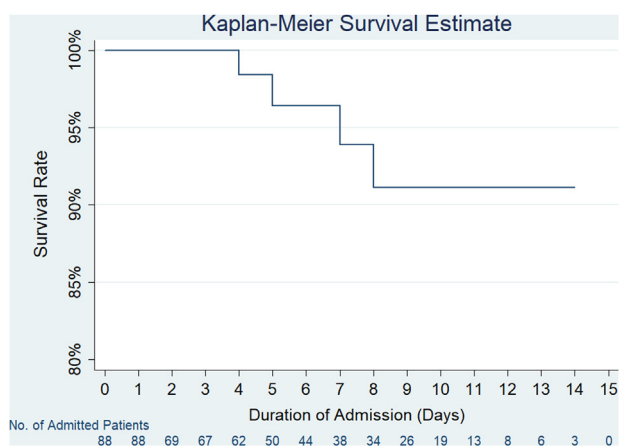


Fig. 3. In-hospital survival of children admitted with a confirmed diagnosis of COVID-19.

Table 2
Physical signs of children admitted with confirmed diagnosis of COVID-19.

Physical signs	PICU no. (%)	Regular ward no. (%)	Total no. (%)
Fever (%)	5 (71.4)	40 (49.4)	45 (51.1)
Tonsillitis (%)	1 (14.3)	2 (2.5)	3 (3.4)
Severe respiratory distress (%)	2 (28.6)	1 (1.2)	3 (3.4)
Dehydration (%)	3 (42.9)	12 (14.8)	15 (17.1)
Heart failure (%)	1 (14.3)	0 (0)	1 (1.1)

Abbreviations: CI, confidence interval; PICU, paediatric intensive care unit.

Table 3
Type of PCR sampling specimens and their results.

PCR sampling	Estimate (95% CI)
Type of specimen	
Nasopharyngeal (%)	98.9 (93.8–100)
Endotracheal Aspiration (%)	1.1 (0.03–6.2)
Initial positive result (%) ^a	97.7 (92.0–99.7)
Duration from positive to negative results (mean in days) ^b	7.9 (5.2–10.5)

^a The remaining were confirmed positive by a second test.

^b In a subgroup of patients, repeated RCR test was performed.

Factors associated with mortality included skin rash, hypotension, heart failure signs, high troponin I, and abnormal liver enzymes, which are of clinical and laboratory characteristics of paediatric multi-system inflammatory syndrome. Other risk factors for mortality included hypoxia, chest radiograph suggestive of acute respiratory distress syndrome, anaemia, leucocytosis, and hyperna-

tremia. Factors associated with a prolonged LOS (<7 d) included the presence of comorbidities, leucopenia, hyponatraemia, and high serum level of CRP (Table 4).

The most common medications used as COVID-19 regimen in PICU was hydroxychloroquine, followed by low molecular weight heparin and antiviral therapy (lopinavir and ritonavir). However, these medications were not commonly used in the general medical ward. Table 5 shows the medications that had been used among patients admitted to the regular ward and PICU.

Discussion

To the best of our knowledge, this is the first multicentre study on paediatric COVID-19 to be conducted in KSA. However, there was a multicenter ten case series of MIS-C from Al-Ahsa region of KSA [25]. The majority of the cases had mild to moderate symptoms and did not require critical care. This is somewhat similar to the 2 previous major meta-analysis where 98% and 96% of cases had mild to moderate [30,31] infection. This slightly lower percentage may be due to the strict protocol endorsed by the Ministry of Health in Saudi Arabia, in which asymptomatic children were quarantined in hotels and were not managed in the hospital. The LOS for all cases was 5.9 days (1–14 days). Factors associated with prolonged LOS were leukopenia, high CRP, positive blood culture, and comorbidities (Table 3). Of note, the mean LOS for all non-critical care patients who did not require oxygen at presentation was 5 days, and 29.5% of cases required <3 days. In a case series from the UK, the average LOS for 45 patients was 3 days [32]. In another study, the average LOS was 12.9 days [33]. In a systematic review and data synthesis of 52 studies, the median hospital LOS ranged from 4 to 53 days within China, and 4–21 days outside of China [34].

At presentation, fever was the most prevalent symptom in our cohort followed by respiratory and gastrointestinal symptoms. Previous studies showed fever was observed in 41% and 59% of all series while cough was noted between 37% and 46% [27,28,30–34,35–39]. Fever was found in 50% of patients with mild to moderate disease compared with 71% who needed critical care. In contrast, the mean saturation of all cases was 96%. Sixteen patients required oxygen on admission and their mean baseline saturation was 90% with a minimum saturation of 80%. Furthermore, 6 out of the 7 cases which required critical care had hypoxemia at presentation. Therefore, hypoxemia was a factor that influenced the outcome (Table 3). One of the first published studies about children from China reported that 4 (2.3%) out of 171 confirmed cases had saturation <92% [38].

A previous report that summarised clinical findings in 171 PCR-confirmed cases in Wuhan suggested that approximately 20% of children and adolescents with SARS-CoV-2 infection did not have symptoms [36]. During the period when this study was conducted, the testing capacity for SARS-CoV-2 in KSA had not been ramped up. Therefore many cases of paediatric COVID-19 were not identified in the community. While younger children (<3 years) were more affected, it is reassuring that our data indicate that children are generally less severely affected by the SARS-CoV-2 virus, which probably could be due to the age-associated changes in their immune systems [40]. These results were obtained even though infants, whose immune systems are relatively immature [41], comprised a considerable proportion of our sample.

The rate of critical disease requiring PICU admission in this study was 8%, with case fatality rate of 4.5%. Given that many children with asymptomatic or mild disease were probably never brought for medical examination and consequently were not screened for COVID-19, it is highly likely that the case fatality rate is considerably lower than 4.5%. Our data showed that underlying comorbidity, high WBC count, high serum sodium, and high CRP significantly influenced outcomes. Furthermore, factors such as comorbidities,

Table 4
Factors associated with in-hospital mortality and a prolonged length hospitalisation.

Factor	(%)	In-hospital mortality		Prolonged LOS ^a	
		p-Value	(%)	p-Value	(%)
Age			0.224		0.810
≥5 years		2.1		37.5	
<5 years		7.5		40.0	
Sex			0.172		0.755
Male		8.1		40.5	
Female		2.0		37.3	
Nationality			0.889		0.343
Saudi		4.3		34.0	
Non-Saudi		4.9		43.9	
Comorbidities			0.296		<0.001
No		3.1		21.9	
Yes		8.3		83.3	
Dyspnoea			0.633		0.198
No		3.7		33.3	
Yes		5.9		47.1	
GI symptoms ^b			0.917		0.893
No		4.7		39.1	
Yes		4.2		37.5	
Skin rash			<0.001		0.162
No		2.4		40.0	
Yes		66.7		0	
Arterial BP			<0.001		0.343
Normal		0		40.3	
High		9.1		45.5	
Low		100		0	
Hypoxia			<0.001		
No		0			
Yes		25			
Dehydration			0.073		0.905
No		2.7		38.4	
Yes		13.3		40.0	
Heart failure			<0.001		0.425
No		3.5		39.1	
Yes		100		0	
Chest radiograph			<0.001		0.307
Normal		0		36.4	
Mild pneumonia		5.9		52.9	
Severe pneumonia		0		50.0	
ARDS		100		0	
Anaemia			0.006		0.639
No		0		36.8	
Yes		12.9		41.9	
WBC			0.011		0.004
Normal		0		26.0	
Low		0		80.0	
High		14.3		46.4	
Serum Sodium			<0.001		0.009
Normal		0		32.9	
Low		0		100	
High		50		62.5	
Hyperkalaemia			0.140		0.554
No		3.7		37.8	
Yes		16.7		50.0	
GFR (baseline)			0.335		0.302
≥ 90		5.6	0.335	36.1	0.302
< 90		0		50.0	
LFT			<0.001		0.665
Normal		0		38.8	
Abnormal		22.2		44.4	
CRP			0.132		0.003
Normal		1.9		26.4	
High		8.8		58.8	
Troponin I			<0.001		0.359
Normal		0		43.4	
High		28.6		57.1	
Blood culture			0.083		0.511
Negative		2.7		36.5	
Positive		16.7		50.0	

Abbreviations: CRP, C-reactive protein; GI, gastrointestinal; GFR, glomerular filtration rate; LFT, liver function test; LOS, length of stay; WBC, white blood cells.

^a >7 days.

^b Diarrhoea or vomiting.

Table 5
COVID treatment regimens used during the hospitalisation among children diagnosed with COVID-19.

Treatment	PICU no. (%)	Regular ward no. (%)	Total no. (%)
Azithromycin (%)	0 (0)	30 (37.0)	30 (34.1)
Hydroxychloroquine (%)	4 (57.1)	3 (3.7)	7 (8.0)
Lopinavir/ritonavir (%)	1 (14.3)	0 (0)	1 (1.1)
LMWH (%)	1 (14.3)	1 (1.2)	2 (2.3)

Abbreviations: LMWH, low molecular weight heparin; PICU, paediatric intensive care unit.

leukopenia, hyponatraemia, and high serum CRP levels were associated with prolonged LOS (>7 days). In a previous report, age <1-month, male sex, signs or symptoms of lower respiratory tract infection at presentation, and underlying comorbidity were associated with a higher likelihood of ICU admission. The investigators also reported that most intubated children due to respiratory failure required prolonged ventilation, usually for >1 week. We were unable to perform subgroup analyses among children who required intubation due to the small sample size. A recent multinational study revealed that more severe form of COVID-19 and a high number of MIS-C in people of lower socioeconomic level and in Latin American children, compared with those from China, Europe and North America [42].

There is considerable uncertainty about the effectiveness of the available treatment options for COVID-19. In our setting, hydroxychloroquine, lopinavir/ritonavir, and low-molecular-weight heparin were the most frequently used treatment in PICU patients. However, azithromycin was the most used treatment in patients admitted to the regular wards. In countries such as Italy and Spain, hydroxychloroquine has been widely used. Furthermore, guidelines were enacted to administer antiviral agents due to the lack of robust human data [43]. A panel from the United States-based paediatric infectious diseases recommended physicians and pharmacists, healthcare practitioners should reserve antivirals for patients with severe disease, preferably within a clinical trial [44]. The panel of experts seemed to favour the administration of remdesivir over other antivirals. However, they had differing opinions regarding the use of lopinavir/ritonavir, mainly because recent data from a randomised controlled trial showed inconsistent clinical outcomes in patients who received a combination of lopinavir/ritonavir [43].

Of the four patients with a fatal disease, three satisfied the diagnostic criteria for paediatric multisystem inflammatory syndrome with a high PRISM IV score on admission. This suggests that the mortality may have been due to paediatric multisystem inflammatory syndrome, which has been described as a severe manifestation of paediatric COVID-19 [17–20].

Our study has several limitations, including its retrospective design and small sample size. Consequently, we are unable to conclude on the effectiveness of hydroxychloroquine or antivirals on treatment outcomes. We did not collect comprehensive data on laboratory investigations or intensive care interventions to avoid distracting front-line healthcare workers from their primary duties during the ongoing pandemic. Nevertheless, this study is the first to provide an account of the clinical characteristics of the SARS-CoV-2 infection in children and adolescents from the largest tertiary centres of KSA. In addition we recruited affected children living in KSA, including children of expatriates who live in KSA. The policy of the Ministry of Health in KSA is free treatment for all nationalities affected with COVID19 who live in the KSA.

Conclusion

Fever is the most prevalent presenting sign of COVID-19 in children requiring hospitalisation. The majority acquired mild dis-

ease, but a small proportion of children and adolescents developed severe disease requiring PICU admission. The presence of clinical manifestations of paediatric multisystem inflammatory syndrome at the time of presentation was associated with a poor prognosis; however, most children were hospitalised for less than seven days and made a full recovery. A larger study is warranted to determine factors that are associated with an increased risk of PICU admission and to determine the effectiveness of currently available treatments.

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Competing interests

None declared.

Ethical approval

Not required.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jiph.2021.01.011>.

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