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Clinical profile of children with SARS-CoV-2 infection from a dedicated COVID-19 hospital in India.

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Abstract

Objective: To determine the demography and clinical profile including severity, radiology, therapy, complications and outcome in hospitalized children with SARS-CoV-2 infection.
Methods: This observational study enrolled 100 children, aged 1 month to 12 year with confirmed SARS-CoV-2 infection, admitted consecutively from 21st April to 19th August 2020. The above parameters were described, analyzed and the association of age, gender and underlying comorbidity with the severity of disease was assessed.
Results: The study enrolled 100 children, 63 boys (boys:girls ratio=1.7:1) with median age of presentation being 2 year (IQR: 0.64 years to 7.25 years). Thirty-three children were below the age of 1 year, 32 were between 1 and 5 years while 35 were >5 years. Sixty-three children had non-severe and 37 had severe disease. Thirty children had underlying comorbidities. The most common symptom was fever and the most common systems involved were respiratory system followed by gastro-intestinal. Twenty-two children had abnormal chest radiograph. Eighty-two children received antibiotics. Fifteen children suffered from complications of COVID-19. The median duration of hospital stay for children with severe disease was 8 d (IQR 5-12 d). There were 3 deaths and 97 were discharged. Age and gender had no association with severity of disease. The severity of disease had significant association with co morbidities and number of underlying comorbidities (p-value<0.01).
Conclusion: Children can have varied presentation of SARS-CoV-2 infection and need monitoring with optimum care.

Keywords: SARS-CoV-2, COVID-19, Children, Severe disease.

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Introduction

Corona virus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), which originated in Wuhan, China and has now spread across the globe [1]. Epidemiological studies from across the world have shown that data on occurrence of COVID-19 in children is scarce due to containment measures as shown by a systematic review on 27 studies in children across the globe [2]. Unlike adults, children present with milder disease with deaths being rare [3,4]. However, as the number of cases with SARS-CoV-2 infection continues to rise, there is need for studies to revisit the clinical characteristics in children, after relaxation of containment measures. There have been few guidelines on management of children with SARS-CoV-2 like the World Health Organization guidelines, especially, as the data on clinical spectrum of SARS-CoV-2 in children is limited by a small cohort. Hence, we intend to contribute our experience on 100 children (excluding children from 0-29 d) with SARS-CoV-2 infection, from a single dedicated COVID-19 hospital located in a metropolitan city of India. This is an observational study, undertaken to determine the clinical spectrum, extent of severity in children with SARS-CoV-2 infection and to study the association of age, gender and underlying comorbidity with respect to severity of disease.

Methods

We conducted a retrospective review of inpatient medical records of 100 successive pediatric patients aged 1 month to 12 years with confirmed SARS-CoV-2 infection admitted to pediatric ward and intensive care unit in a dedicated COVID-19 tertiary health care centre from 21st April 2020 till 19th August 2020. Children aged more than 12 years were admitted in the medicine ward and hence have been excluded from the study.

The data was analyzed after seeking approval from the ethics committee of the institute. We included children who had positive result for SARS-CoV-2 on the nasopharyngeal and/or pharyngeal swab by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), with or without symptoms and with reconfirmation of the result by RT-PCR repeated from a designated laboratory of the Indian Council of Medical Research.

A clinical proforma comprising of detailed history, clinical course, investigations and treatment, was made. Age group wise stratification was done into; <1 year, 1-5 years and >5 years. Children were categorized into asymptomatic, mild, moderate, severe and critical cases as per the diagnostic criteria used by Eastin et al. [5].

Asymptomatic cases were children with SARS-CoV-2 infection but without any symptoms, admitted as per the local

government isolation policy. Mild cases included children with fever, sore throat, myalgia, nasal congestion, diarrhoea or vomiting without dehydration and without dyspnoea. Moderate cases included children with symptoms and signs of pneumonia without hypoxemia, with or without evidence on chest radiograph or High Resolution Computerized Tomography (HRCT). Severe cases included children with severe pneumonia associated with either cyanosis (oxygen saturation <90%), lethargy or increased respiratory efforts and other symptoms like diarrhoea causing severe dehydration, lethargy and or seizures. Critical cases included children with either respiratory failure requiring invasive ventilation like endotracheal intubation, Acute Respiratory Distress Syndrome (ARDS), shock with or without inotrope support, disseminated intravascular coagulation with or without sepsis and organ failure (single or multiple).

ARDS, sepsis and shock were defined as per World Health Organization criteria [6]. For the ease of comparison, we further regrouped children based on the above categories into 2, severe disease (severe and critical cases) and non-severe disease (asymptomatic, mild and moderate cases). Multisystem inflammatory syndrome in children with COVID-19 was defined as per World Health Organization (WHO) criteria [7]. Acute kidney injury was defined as per kidney disease improving global outcomes, 2012, criteria [8]. Laboratory parameters were assessed wherever required. Chest radiograph was done in all and HRCT thorax was done in selected children, when they had increase in severity of the disease.

Children were given symptomatic treatment with paracetamol and nasal decongestants for mild respiratory symptoms, oral rehydration solution and anti-emetics for mild gastrointestinal symptoms. Empirical antibiotics were given wherever there was possibility of bacterial co-infection or secondary infection. Oseltamivir was given empirically to children with respiratory system involvement as children could not be tested for co-infection with H1N1 influenza virus. Steroids were given to children with MISc and for specific underlying conditions like nephrotic syndrome as per the recommendations of WHO [6,7]. The clinical outcomes with respect to duration of hospital stay, oxygen therapy and survival were described.

Statistical Analysis

Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi-Square test and by Fisher's exact test for all 2 × 2 tables where Chi-Square test was not valid due to small counts. Quantitative data was represented using mean ± SD (Standard Deviation) or median and IQR (Inter Quartile Range). Comparison of quantitative data measured between binomial qualitative variable was done using unpaired t-test, if the data passed 'normality test' or by Mann-Whitney Test if the data failed 'normality' test. Binary logistic regression was used to assess predictors of severity status. Appropriate statistical software, including but not restricted to MS Excel, PSPP version 1.0.1 was used for statistical analysis. P-value of <0.05 was considered significant.

Results

Demographic profile

A total of 100 children with COVID-19 were evaluated. There were 63 boys and 37 girls with the boy to girl ratio of 1.7:1. The median age of presentation was 2 year (IQR: 0.64 years to 7.25 years). The demographic profile is shown in (Table 1). Division of children into 2 groups showed that 63 children had non severe disease and 37 had severe disease.

The median age of children with severe disease was 2 year (IQR: 0.6 year-8.6 years) and that of children without severe disease was 2 year (IQR 0.75-6.75 years). When compared, there was no statistical association of age with severity of disease (p-value 0.750). Forty three percent of boys (27/63) as compared to 27% girls (10/37) had severe disease. However, there was no statistically significant association between gender and severity of disease (p-value 0.113) (Table 2).

Thirty children had underlying comorbidities (Table 1). Of the 30 children with comorbidities, 60% (18/30) had severe and 40% (12/30) did not have severe disease. The severity of disease had statistically significant association with the presence of underlying comorbidities (p-value<0.01). Also, on application of binary logistic regression, it was found that only the number of comorbidities was statistical significant predictor of severity of the disease (p value<0.01) (Table 3).

	n (%)
Age group wise stratification	
<1 y	33 (33)
1-5 y	32 (32)
>5 y	35 (35)
Symptoms	
Fever	41 (41)

Fever with nasal congestion	12 (12)
Diarrhoea	8 (8)
Dyspnoea	8 (8)
Fever with cough	7 (7)
Seizures	7 (7)
Others	17 (17)
Category of severity	
Asymptomatic infection	9 (9)
Mild	33 (33)
Moderate	21 (21)
Severe	27 (27)
Critical	10 (10)
System wise involvement	
Respiratory	36 (36)
Gastro-intestinal	16 (16)
Central nervous system	10 (10)
Hematology	6 (6)
Renal	5 (5)
Others	19(19)
Comorbidities	
Malignancy	6 (20)
Tuberculosis	3 (10)
Congenital heart disease	2 (7)
Failure to thrive	2 (7)
Obesity	2 (7)
Severe acute malnutrition	2 (7)
Thalassemia	2 (7)
Others	12 (40)
No comorbidity	70 (70)

Table 1. Clinical characteristics and demographic profile.

Clinical parameters	**Severe**	**Non Severe**	**p value**
Age at presentation, median in y (IQR) ^	2 (8)	2 (6)	0.75
Gender			
Male	27 (43)	36 (57)	0.113
Female	10 (27)	27 (73)	
Abnormal findings on chest radiograph, n (%)	15 (41)	7 (11)	<0.01
Duration of antibiotics, median in d (IQR) ^	7 (5)	5 (5)	<0.01
Duration of hospital stay, median in d (IQR) ^	8 (7)	6 (4)	0.083

Table 2. Comparison of clinical parameters in two groups. ^: Data failed normality Test. Hence Mann-Whitney Test applied.

Severe disease	Comorbidity			p value
	Yes	No		
Yes	18 (60)	19 (27.1)		0.004
No	12 (40)	51 (72.9)		
	No. of comorbidities			p value
	0	1	2	
Yes	19 (27)	16 (57)	2 (100)	0.004
No	51 (73)	12 (43)	0 (0)	

Table 3. Severity of the disease.

Symptoms

The most common COVID-19 related symptom at presentation was fever in 41 children, while 17 children had other symptoms not specific for COVID-19.

Upper respiratory tract infection was the most common clinical manifestation and the most common system involved was respiratory system (Table 1). Hundred percent children (10/10) with Central Nervous System (CNS) involvement had severe disease while 35%(12/34) of children with respiratory and 19% (3/16) with Gastrointestinal (GI) system involvement, had severe disease.

Radiological investigations, co-infections and treatment

Chest x-ray was done in all children and 22 children had abnormal findings. Fifty nine percent (13/22) children had unilateral and 41% (9/22) had bilateral lung involvement (Table 4).

The association between presence of abnormal chest radiograph and severity of disease was statistically significant (p-value<0.01) (Table 2). Seventeen children had evidence of infection with other co-pathogens. Mycobacterium tuberculosis was the most common bacterial pathogen in 27% (4/15) of children. Eighty two children received antibiotics in either oral or intravenous form.

The median duration of antibiotic therapy was 7 d (IQR: 5-10 d) in the group with severe disease, as compared to median of 5 d (IQR: 2.5-7.5 d) in the group without severe disease. Children with severe disease required longer duration of antibiotics as compared to those with non-severe disease (p-value 0.003). In our study, 3 children with MIS-c were given steroids.

Steroids were given in 6 other children for underlying specific conditions. Intravenous immunoglobulin was given to 2 children, 1 with MIS-c and second to a child with severe sepsis due to klebsiella pneumonia. Low molecular weight heparin was given to 1 patient having MIS-c and raised D-dimer. Overall, there were 21 children on oxygen therapy. Sixteen children required non-invasive and 5 required invasive ventilation (Table 4). Forty eight percent (18/37) children with severe disease required oxygen therapy and the mean duration of oxygen therapy was 3.28 d (SD 3.31 d).

Abnormal findings on chest radiographs	n (%)
Unilateral	
Diffuse opacities	6 (46)
Localised opacities	5 (38)
Pleural effusion	2 (15)
Bilateral	
Diffuse opacities	7 (78)
Localised opacities	1 (11)
Pleural effusion	1 (11)
HRCT findings	

Ground glass opacities	
Bilateral lower zones	4(33)
Bilateral diffuse	2(17)
Consolidation	5(41)
Empyema	1(8)
Upper lobe fibrosis	1(8)
Oxygen therapy	
CPAP	1(1)
Intubation with ventilation	5(5)
Nasal prongs	15(15)
None	79 (79)
Complications	
Acute kidney injury	8 (8)
Circulating shock requiring Inotropes	6 (6)
Acute Respiratory Distress Syndrome (ARDS)	2 (2)
Multiple organ system failure	5 (5)
Multisystem inflammatory syndrome in children	4 (4)
Pharmacotherapy	
Antibiotics	82(82)
Oseltamivir	51 (51)
Azithromycin	41 (41)
Steroids	9 (9)
IVIG	2 (2)
Low molecular weight heparin	1 (1)
Outcome	
Discharged	97(97)
Death	3(3)

Table 4. Radiological investigations, treatment, complications and outcome.

Complications and outcomes

Fifteen Children developed one or more than one complication during the course of hospitalization (Table 4). The median duration of hospital stay for children with severe disease was 8 d (IQR 5-12 d) and for children without severe disease was 6 d (IQR 4-8 d). Ninety seven percent (97/100) children were discharged, and 3% (3/100) died.

Discussion

Our centre in Mumbai city, India, was the first dedicated COVID-19 hospital for children with SARS-CoV-2 infection, since April 2020. It has received a significant number of children with the infection compared to other centres in the city; hence we present a study depicting the clinical spectrum of SARS-CoV-2 infection in the first 100 children at our centre. In our study, there was similar representation of SARS-CoV-2 infection in all age groups with no particular age group more susceptible to severity of the disease. This is in contrary to some studies showing that infants and adolescents account for more number of hospitalized children [9]. There were more number of boys than girls with SARS-CoV-2 infection, but there was no association of gender with severity of the disease. In our study, of the 30 children with comorbidities, 1 died. The most common underlying comorbidity was malignancy. In a series by DeBiasi et al. it was found that 39% hospitalized children had underlying medical conditions with asthma being most common, however, it did not affect the course or outcome when critically ill children were compared to the non-critical [9]. In contrary to this,in our series, children with co-morbidities were prone for severe clinical course and greater

the number of comorbidities, greater was the probability of having severe disease, but not mortality. Shekerdemian et al. showed that 80% children had comorbidities in their series but emphasized that despite comorbidities children fare better than adults with the same [10]. This statement has also been supported by Dhochak et al. and Mantovani et al. [3,11].

Most common COVID-19 symptomatology was fever in 41% children and respiratory was most common system to be involved. Children also presented with atypical symptoms like diarrhoea in 8% and neurological symptoms like seizures in 7%. A meta-analysis of 27 studies on 4857 children showed that fever is the most common symptom of SARS-CoV-2 infection followed by respiratory symptoms but 4%-9% children can have gastrointestinal manifestations [2]. Similar findings were reported by Mantovani et al. in their meta-analysis [11]. However, children can present with only GI or CNS system manifestations, like acute hepatitis or seizures, respectively [10]. Our study showed that 15% children had concomitant or secondary bacterial infection and 82% were given antibiotics, whereas overall 37% children had severe disease. There is insufficient evidence to support the role of empirical antibiotics to prevent either co-infections or secondary bacterial infections in patients without severe COVID-19 diseases, hence further studies are required. Twenty two percent children had abnormalities on baseline chest radiographs. In children, as compared to adults, radiological features are less common [12,13].

Of the 37 children admitted to PICU, 40% (15/37) had a critical course complicated by shock, AKI, ARDS and multiple organ system failure (Table 4). During early COVID-19 pandemic, it was seen that very small percentage of hospitalized children in PICU developed organ system failure, unlike adults. However, from our study, it was observed that this scenario can change with a greater number of children having severe disease. MIS-c is now a known feature in children and was also seen in our study, in 4% of children [14,15]. One of the patients with MIS-c was a 9 year old girl with catecholamine refractory shock, AKI which required peritoneal dialysis and she died of pulmonary hemorrhage due to disseminated intravascular coagulation. Her Interleukin-6 level was 4632 pg/ml and D-dimer of 3 µg/ml. Another child was a 5 year old boy with familial hemophagocytic lymphohistiocytosis type 4 with MIS-c triggered by SARS-CoV-2 infection. His IL-6 was 3650 pg/ml, serum Ferritin 1567 µg/litre, had lymphopenia and thrombocytopenia. He responded well to Intravenous Immunoglobulin (IVIG) and steroid therapy. Third MIS-c patient was a 10 year old boy with fever, pleural effusion, and congestive cardiac failure, IL-6 of 5500 pg/ml and serum ferritin of 1086 µg/litre. He responded well to intravenous methylprednisolone and did not require IVIG. Our 4th patient with MIS-c was an 8 year old boy with fever, ARDS, circulatory shock, hepatosplenomegaly, who required intubation and mechanical ventilation. His C-reactive protein was 173 mg/litre, serum ferritin of 780 µg/litre, D-dimer of 19.4 µg/ml. He responded to intravenous methylprednisolone and low molecular weight heparin.

There is a lack of formal clinical trial in children regarding pharmacotherapy of COVID-19 [16,17]. We used azithromycin as an antiviral therapy in 41% children with symptoms typical for COVID-19 infection and oseltamivir empirically in 55% children with respiratory symptoms. Our study, predominantly enrolled children in the initial few months of the pandemic when there were no clear guidelines or trials on the use of steroid therapy in COVID-19. As there were limited recommendations, the usage of steroids in our study had specific indications like meningitis, miliary tuberculosis, nephrotic syndrome, leukemia, interstitial pneumonia, MISc and severe ARDS, in accordance with WHO guidelines and as proposed by Sankar et al. [6,7,18]. Intravenous immunoglobulins with or without steroid therapy is recommended in children with pediatric inflammatory syndromes [14].

Forty-eight (18/37) percent children with severe disease required oxygen support and of them, 82% children were successfully weaned from the oxygen therapy in a short duration of time with total of 3 deaths. The duration of hospital stay was longer in children with severe disease. Out of the 3 deaths, 1 child had AKI, one had ARDS with sepsis and one had pneumonia with hepatic abscess along with a thrombus in the accessory hepatic vein.

Conclusions

Our study highlights that children with SARS-CoV-2 infection have fever and respiratory symptoms commonly but can have varied and severe clinical presentation of the same irrespective of any gender or age-group predilection. Presence of underlying comorbidities can result in severe clinical course. Our study shows that children have good recovery despite having a severe disease and with lesser duration of hospital stay, when compared to adults. As the pandemic continues, this study can provide a reference to detect any new paradigm shift in the clinical spectrum of COVID-19 in children, especially with emergent strains of the virus. Our study emphasizes on the awareness of the atypical and severe presentation of COVID-19 disease in children, especially with underlying comorbidities. Also, it stresses upon the need for optimum care and definite pharmacotherapy for children with COVID-19 disease.

Limitations

Our study was retrospective, and it depicted the clinical spectrum of SARS-CoV-2 infection in only hospitalized children. Hence, we cannot generalize our findings to the children with SARS-CoV-2 in the community or any other region.

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