

Original Research Article

Clinical and laboratory profile of COVID-19 in children below 15 years

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19), in children has varied clinical presentations from asymptomatic infection to severe pneumonia, multi system inflammatory syndrome in children (MIS-C) and rarely death. To date, limited data has been published on the profile of COVID-19 infection among Indian children. The objective of this study was to analyze the clinical spectrum, laboratory parameters, treatment and its outcome in children less than 15 years admitted with COVID-19 infection.

Methods: This was a cross sectional study done in a tertiary care hospital. Children with COVID-19 infection detected by Reverse transcriptase polymerase chain reaction (RT-PCR) were included.

Results: Out of 167 children, 93 were males (55.6%) and median (Interquartile range- IQR) age of children admitted were 9 (4-13) years. Family cluster (71%) was the dominant source of infection. Majority were asymptomatic (60%, N=100). The predominant symptoms were fever (29%), cough (16%) and rhinorrhea (4.1%). Seven (4.1%) children had comorbidities and two (28%) among them had moderate to severe disease. Median (IQR) total leucocyte count was 7 (4-10) $\times 10^3 \mu\text{l}$ and platelet count was 390 (275-500) $\times 10^3 \mu\text{l}$. Leukopenia was observed in 58% (N=81), lymphocytosis in 32.8% (N=46) and thrombocytopenia in 3.5% (N=5). Inflammatory markers were raised in 10-15% of children. Peri-bronchial cuffing was the common abnormality (N=14, 17.5%) in chest X-ray (CXR) and peripheral heterogeneous opacities were noted in severe disease. Children with moderate to severe symptoms were treated with remdesivir and steroids.

Conclusions: COVID-19 infection in children was often benign and increased severity was noted among those with comorbidities. Leukopenia, lymphocytosis were commonly observed. High inflammatory markers were noted in severe disease. Nil fatality among our study group.

Keywords: COVID-19, Children, Chest X-ray, Leukopenia, Lymphocytosis, Laboratory profile

INTRODUCTION

In the pre-coronavirus disease-19 (COVID-19) era human coronavirus (HCoV) was one among the causes of bronchiolitis in infants and upper respiratory infection in children.¹ Previous outbreaks of Severe acute respiratory syndrome (SARS) and Middle east respiratory syndrome (MERS) caused by coronavirus were associated with less mortality in children.² Similarly COVID-19 which causes severe acute respiratory syndrome (SARS-CoV2) in adults causes milder illness in children. The incidence in children

is around 8.7% in below 19 years according to CDC.³ The hypothesis behind the less severe disease in children being differences in innate and adaptive immunity, pre-existing antibodies to corona virus, more frequent respiratory infections, protective effects of other live vaccines, different expression of angiotensin converting enzyme-2 (ACE-2) receptors and less intense exposure.⁴ Very rarely it may lead to Acute respiratory distress syndrome (ARDS), Multi organ dysfunction (MODS) and death. Multi system inflammatory syndrome in children (MIS-C), a post viral immune dysregulation following SARS-

CoV-2 infection is common among children and adolescents which may rarely lead to significant morbidity and mortality if not treated early.⁵

Hematological and biochemical markers of COVID-19 were well studied in adults. This cannot be extrapolated as such for children. The aim of the study was to present the detailed clinical, laboratory profile, treatment and outcome of 167 children below 15 years of age admitted with COVID-19 infection.

METHODS

This was a descriptive observational study and followed the Strengthening the reporting of observational studies in epidemiology (STROBE) guideline.

This study was done at PSG Institute of Medical Sciences and Research hospital which is one of the largest designated tertiary care hospitals in Coimbatore, India which caters to patients from around 250 km radius. Institutional ethics committee approval was obtained. Informed consent was taken from parents or patients included in prospective analysis (N=107) and waiver of consent was obtained for those taken retrospectively (N=60). All children less than 15 years admitted with COVID-19 infection between March 2020 to February 2021 were included in our study. Positive cases were confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) validated as per ICMR standards. Both nasopharyngeal and oropharyngeal swabs were taken for confirmation. The severity of illness were categorized into mild, moderate, severe and critical as per the COVID-19 clinical management-Interim guidance.⁶ Mild illness is defined as symptomatic COVID-19 positive patients without evidence of pneumonia, moderate as with clinical signs of pneumonia and no signs of hypoxia and severe as clinical signs of pneumonia and SpO₂<90%. Critical disease is with ARDS, sepsis or septic shock and MODS.

Fever was defined when the temperature was >38°C, the source of infection was identified by recording which family member developed the symptoms first. Basic hematological and radiological investigations were taken for most of the patients admitted except in few because of logistical issues. Investigations were repeated in patients showing persistent symptoms.

All the necessary information was collected from electronic records on the hospital database. Chest X-ray findings were analyzed and reported by a single radiologist. Information on baseline demographics, clinical features, symptoms, signs, laboratory reports, imaging, treatment and outcome were recorded. Laboratory values were interpreted with age specific reference ranges. If the patient had a serial investigation for a particular parameter, the highest value was taken into consideration. Asymptomatic and mildly symptomatic children were given supportive care. Those presented with sore throat, fever beyond 3 days, lower respiratory

symptoms, pneumonia (confirmed by clinical and radiological signs) were treated with antibiotics. Steroids were used only in severe cases.

Statistical analysis

Data was entered in Microsoft excel (Microsoft corporation, Redmond, USA) sheet and analyzed using SPSS software version 24. Descriptive statistics were used to summarize the data. Continuous variables were described as median and interquartile range. Categorical variables were described as frequencies and percentages. Chi square test was used to assess the relationship between gender and incidence of COVID-19. Mann-Whitney U-test was used to assess the correlation between severity of illness and inflammatory markers. A p value of <0.05 was considered significant.

RESULTS

A total of 167 children admitted with COVID-19 positive reports were included in our analysis. The baseline demographic and clinical characteristics of these children are shown in Table 1.

Demographic and clinical characteristics

The median age (IQR) of children admitted were 9 (4-13 years) and male children (N=93, 55.6%) outnumber females with a male: female ratio of 1.25:1. There was no relationship between gender and incidence of COVID infection in children (p=0.12, Chi square test). Family cluster as the source of infection was identified in 71% (N=119) (Table 1).

Fever was the predominant symptom in 29.3% (N=49) followed by cough (N=27, 16.1%) and rhinorrhea (N=7, 4.1%). Diarrhoea was noted in 3.5%, abdominal pain in 1.1% and loss of taste was present in 1.1%. Very few had fever beyond 24-48 hours after hospital admission. Among the admitted, 7 (4.1%) had preexisting comorbid conditions (Table 2). In them, a child with a germ cell tumor and a hemolytic anemia had moderate to severe illness. More than half were asymptomatic, 38% (N=64) had mild symptoms, 0.5% (N=1) had moderate symptoms and 1.1% (N=2) had severe symptoms. Out of 4 children admitted in ICU, 2 had comorbidities (hemolytic anemia and germ cell tumor) one among them required oxygen support by mask (germ cell tumor), a 2-months-old without any comorbidity had respiratory distress and hypoxemia supported by mechanical ventilation and a child with head injury was admitted for monitoring (Table 3). There was a significant association between comorbidity and severe illness (p=0.014, Fisher's exact test).

Radiological and laboratory finding

CXR was performed in 48% (N=80) of children and out of which 78% (N=63) were normal. Few had prominent

central peri bronchial cuffing (N=14, 17.5%) and peripheral heterogeneous opacities were noted in 3.7% (N=3). CT was done only in patients with moderate to severe illness which showed ground glass opacities (Table 4). On admission, the median (IQR) WBC count was 7 (4-10)×10³/μl. Leukopenia, lymphopenia and lymphocytosis were noted in 58%, 11.4% and 32.8% respectively. Thrombocytopenia was seen only in 3.5%. Inflammatory markers IL-6, ferritin, D-dimer were raised in 10%, 6% and 13% respectively (Table 5). Moderate to severe group exhibited significantly higher IL-6, ferritin and D-dimer than milder group (p=0.04, p=0.04, p=0.06, Mann-Whitney U-test) (Figure 1-3). Hypoalbuminemia was noted in 3.5% and liver enzymes were elevated in 7-8%.

Treatment and outcome

Intravenous antibiotics and remdesivir were given in 3 children. Steroid was given only in a child with a Germ cell tumor. An infant with severe respiratory distress (0.5%) was treated with mechanical ventilatory support considering High frequency nasal cannula (HFNC) having high aerosolization risk during the initial phase of pandemic. In all others symptomatic treatment was given accordingly. Those with severe illness have recovered and discharged by 2nd to 3rd week of admission. There was nil mortality among our study group (Table 6).

Table 1: Demographic characteristics.

Total patients (N=167)	
Age (years) median (IQR)	9 (4-13)
Distribution (years) N (%)	
<1	19/167 (11)
1-5	39/167 (23.3)
6-10	47/167 (28.5)
10-15	62/167 (37)
Sex N (%)	
Male	93/167 (55.6)
Female	74/167 (44.3)
Exposure to source N (%)	
Family cluster	119/167 (71)
Other exposure	28/167 (17)
Unknown	20/167 (12)

Note: Data presented are in numbers (%) or median (interquartile range).

Table 5: Laboratory investigations.

Parameters	Observations	
Total white cell count (10 ³ cells/mm ³), median (IQR)	7 (4-10)	4-10×10 ³ cells/μl
Leukocytosis, N (%)	17/140 (12.1)	>10×10 ³ cells/μl
Leukopenia, N (%)	81/140 (58)	<4×10 ³ cells/μl
Absolute lymphocyte count (10 ³ cells/μl), median (IQR)	3.0 (0.8-5.2)	1.5-3 cells/μl
Lymphocytopenia N (%)	16/140 (11.4)	ALC <1.5×10 ³ cells/μl
Lymphocytosis N (%)	46/140 (32.8)	>4×10 ³ cells/μl
Neutrophilcount (10 ³ cells/mm ³) median (IQR)	2.5(0.5-4.5)	1-8 ×10 ³ cells/μl
Platelet count (10 ³ cells/mm ³), median (IQR)	390 (275-500)	150-400×10 ³ cells/μl
Thrombocytopenia n(%)	5/140 (3.5)	<150 ×10 ³ cells/μl

Continued.

Table 2: Clinical characteristics.

Symptoms N (%)	Value
Fever >38° C	49 (29.3)
Cough	27 (16.1)
Breathlessness	4 (2.3)
Rhinorrhea	7 (4.1)
Feeding difficulty	1 (0.5)
Nausea/vomiting	3 (1.7)
Fatigue	3 (1.7)
Diarrhea	6 (3.5)
Abdominal pain	2 (1.1)
Headache	2 (1.1)
Sore throat	6 (3.5)
Loss of taste	2 (1.1)

Table 3: Coexisting disorder and severity.

Coexisting disorder N (%)	7 (4.1)
Asthma	1
VSD	1
Hemolytic anemia	1
Seizure disorder	1
Germ cell tumor on chemotherapy	1
Congenital hypothyroid	1
Hirschsprung disease with dysmorphic facies	1
Illness severity N (%)	
Asymptomatic	100/167 (60)
Mild	64/167 (38)
Moderate	1/167 (0.5)
Severe	2/167 (1.1)

Table 4: Radiological findings.

Investigations	N (%)
CXR N (%)	80/167 (48)
Normal	63/80 (78)
Peribronchial cuffing	14/80 (17.5)
Peripheral heterogeneous opacity	3/80 (3.7)
CT N (%)	3/167 (1.7)
Ground glass opacity	3/3 (100)

Note: CXR- Chest X-ray, CT-Computed tomography.

Parameters	Observations	
Elevated CRP	4/38 (10.5)	>0.6 mg/dl
Elevated ESR	4/30 (10)	≥40 mm/hour
Elevated LDH	1/40 (2.5)	>500 u/l
Hypoproteinemia	1/85 (1.2)	<4 mg/dl
Hypoalbuminemia	3/85 (3.5)	<3.5 mg/dl
Elevated AST	7/85 (8)	>50 u/l
Elevated ALT	6/85 (7)	>45 u/l
Elevated creatinine	3/106 (2.8)	As per age-based cut-off mg/dl
Elevated IL-6	5/50 (10)	≥7 pg/ml
Elevated ferritin	3/50 (6)	>500 ng/ml
Elevated D-dimer	4/31 (13)	≥0.5 mg/l FEU

Note: IQR- interquartilerange, CRP- C-reactiveprotein, ESR- Erythrocyte sedimentation rate, LDH-lactatedehydrogenase, AST- aspartate amino transferase, ALT- alanineaminotransferase, IL-6-interleukin 6.

Table 6: Treatment and outcome.

Complications	N (%)
Respiratory failure	1/167(0.5)
Treatment	
IV antibiotics	4/167 (2.3)
Remdesivir	3/167 (1.8)
Oral azithromycin	10/167 (5.9)
Systemic glucocorticoid	1/167 (0.5)
Oxygen by mask	1/167 (0.5)
Mechanical ventilation	1/167 (0.5)
Admission to ICU	4/167 (2.3)
Clinical outcome	
Discharge	167/167 (100)
Mortality	Nil

Note: Reference ranges as per from Nelson textbook of paediatrics.

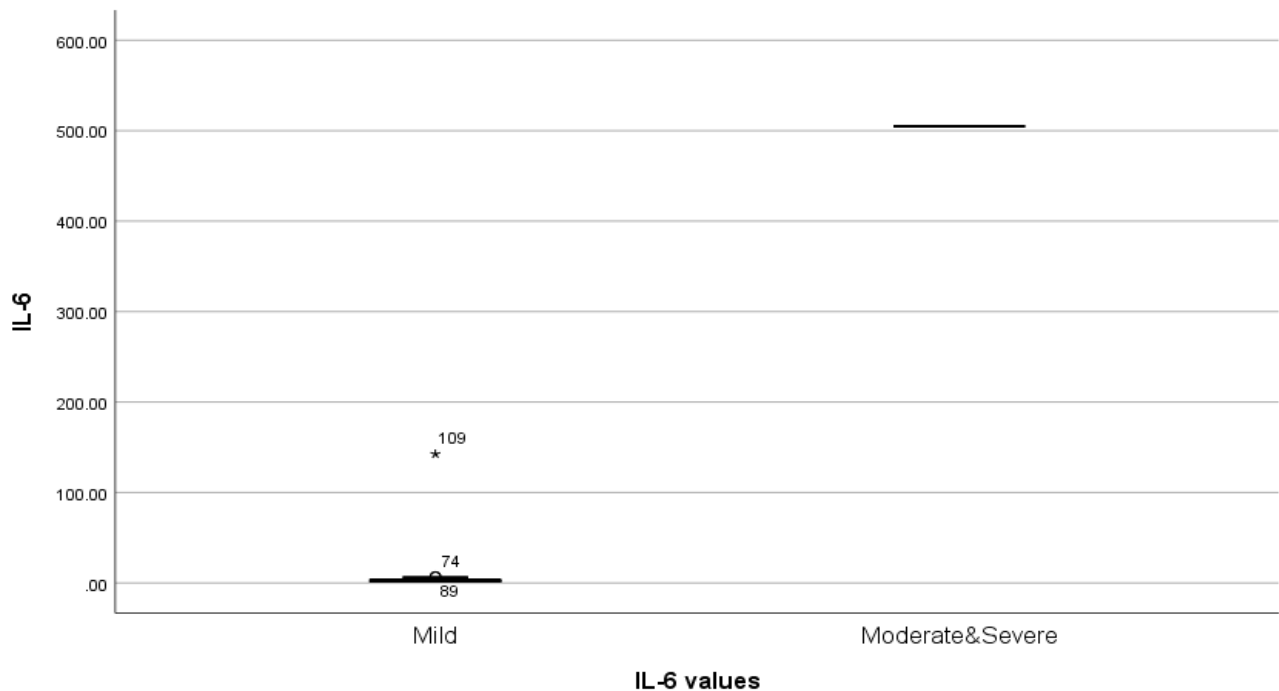


Figure 1: IL-6 value and severity of illness.

Note: Data were expressed in median. P=0.04 by Mann-Whitney U test.

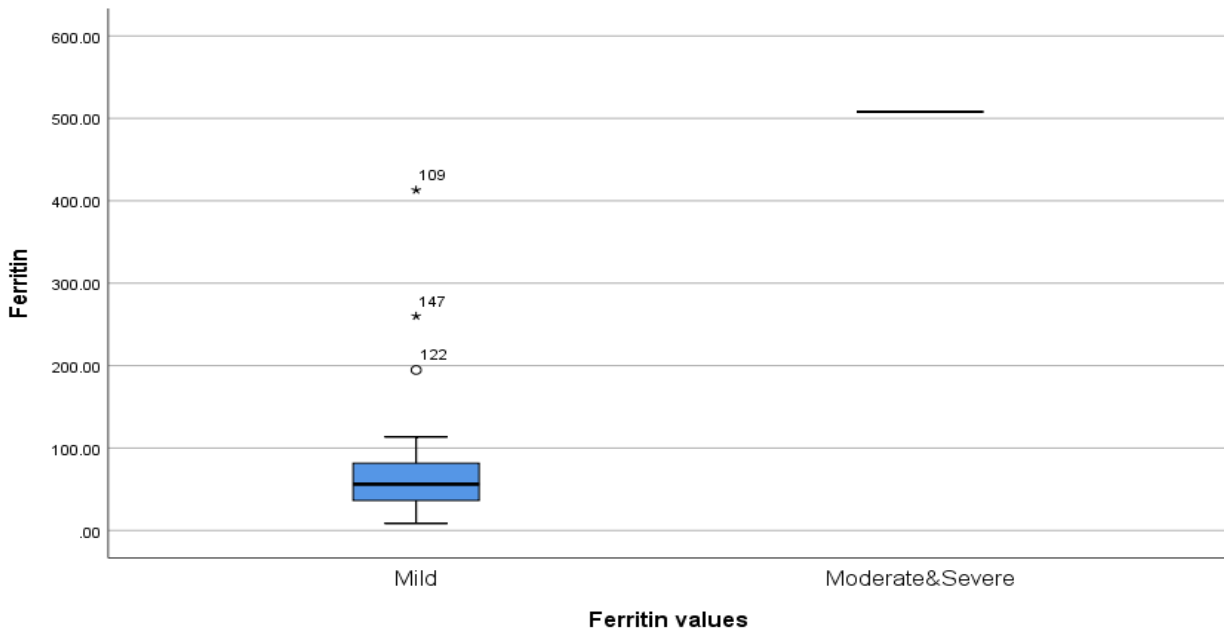


Figure 2: Ferritin value and severity of illness.

Note: Data were expressed in median. $P=0.04$ by Mann-Whitney U test.

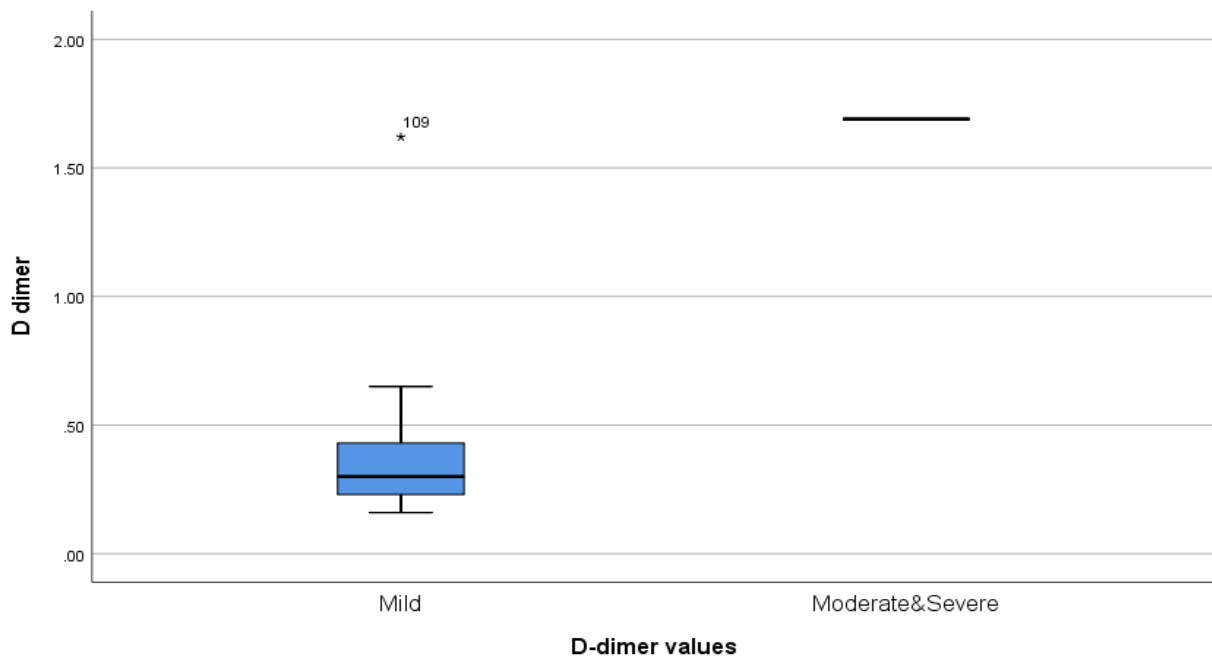


Figure 3: D-dimer and severity of illness.

Note: Data were expressed in median. $P=0.06$ by Mann-Whitney U test.

DISCUSSION

The main focus of this study was to analyze the clinical, laboratory profile, treatment and its outcome of 167 children admitted in the designated tertiary care COVID unit which admits children from asymptomatic infection to critical disease. When compared to adults, paediatric age

groups were reported with less severe disease. As the schools were closed and outdoor activities were restricted the primary source of infection in children were household contacts. Majority of children in our cohort were asymptomatic (60%), and few had variable severity of symptoms from mild to severe. As per WHO-China joint mission on COVID-19, 2.5% of cases under 19 years had severe infection and 0.2% had critical disease.⁷ A large

report from China stated that 10.6%, 7.3% and 4.2% children between 0-1, 1-5, 6-10 years had severe infection respectively.⁸ High risk groups for severe infection are infants below 1 year and those with underlying medical conditions like neurological problems, metabolic disorders, congenital heart disease, diabetes, asthma, chronic lung disease, sickle cell disease and obesity.⁹ Similarly, in this study a 2-months old infant and a child with comorbidity developed severe disease. Incidence of severe disease among comorbid children was high (14%) in this study. This is in accordance with a systematic review of 42 studies on severe COVID-19 infection where the clinical manifestations were severe in 5.1% of children with comorbidities and 0.2% without comorbidities.¹⁰ Among children admitted in US and Canadian PICU with COVID-19, 83% had pre-existing comorbidities and out of which 73% had respiratory symptoms and 38% required mechanical ventilation.¹¹ Hence, children with comorbidities need careful monitoring during the first 2 weeks of illness.

Most common symptoms in our patients were fever, cough and rhinorrhoea followed by gastrointestinal symptoms which were consistent with previous reports.^{6,12} Dermatological and neurological manifestations were not observed in our children.

Central peri bronchial cuffing was the common CXR abnormality noted in our study. 92% of them with the above finding neither had respiratory symptoms at admission nor during hospital stay. Hence, the central peri bronchial cuffing may be a nonspecific finding and further evaluation may be required only if there are worsening symptoms and signs. Another study from Spain had shown similar findings in CXR in 86% of its patients.¹³ In our study those with peripheral heterogeneous opacity in CXR had significant clinical symptoms and ground glass opacities in CT. This was identical to COVID pneumonia causing diffuse interstitial infiltrates involving the periphery of the lung.¹⁴

Similar to few meta-analysis and systematic review on COVID-19, leukopenia (58%) and lymphocytosis (32.8%) were most commonly observed in our study.¹⁵ Lymphopenia (11.4%) and thrombocytopenia (3.5%) were comparable to that of study by Meena et al.¹² Though lymphopenia was frequently seen in adults with severe disease and high mortality, it was rarely observed in children. It may be because of milder illnesses in children.¹⁶ Hence, these hematological findings along with clinical features similar to COVID should raise a strong suspicion of COVID-19 infection and it will be a useful predictor for planning treatment in children with moderate to severe illness.^{12,16}

Inflammatory markers were raised in 15-25% of our children. Studies found that higher the CRP, IL-6 and ferritin more severe was the disease.¹⁶ Liver enzymes were increased in 7-8% which is consistent with other studies and its prognostic significance is still uncertain.¹⁷

Children with severe infection can develop serious complications like acute respiratory distress syndrome, renal failure, myocarditis, shock, acute renal failure, coagulopathy, MODS and later MIS-C. In our study population only a single child developed respiratory failure and none had MODS. Antivirals and steroids were used in very few. Guidelines on COVID-19 treatment in children evolved only later and most were extrapolated from adult studies during our study period. Two children were readmitted with MIS-C manifestations after 3-4 weeks and both had very minimal symptoms during the 1st admission. More studies are needed to determine the children at risk for MIS-C. No mortality was encountered among the admissions in our study.

Hence our present study included the majority of asymptomatic children, these clinical and laboratory data may be helpful in supporting COVID-19 diagnosis in children when diagnostic tests are not available and it provides the true representation of disease spectrum of paediatric population. Limitations of this study was small sample size and single centre study.

CONCLUSION

COVID-19 infection was milder among the majority. Infants and children with comorbidities had increased risk of severe disease. Inflammatory markers were helpful in predicting the severity of illness. Antivirals and steroids were needed in very few children. Since the disease has many new variants it might present differently in future. Hence, clinicians need to have a high index of suspicion for early diagnosis and management to have a good outcome and recovery.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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