

Clinical and laboratory profile of children with COVID-19 admitted at a tertiary care hospital in Karnataka, Southern India

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Abstract

Objectives: To assess the clinical characteristics, laboratory parameters and outcomes in paediatric patients with COVID-19.

Method: Case records of all paediatric patients admitted with COVID-19 were included in the study. Data regarding mode of presentation, presence of comorbid conditions, severity of COVID-19, laboratory investigations and management were noted.

Results: A total of 32 children was admitted with COVID-19 infection in our institute. COVID-19 infection was mild in 16 (50%) patients, moderate in 6 (18.8%) and severe in 10 (31.3%). Ages of the children ranged from 6 months to 16 years with a mean age of 10.75 years. Of them 17 (53%) were boys and 15 (47%) were girls. Pre-existing comorbidities were present in 8 (25%) children. Respiratory symptoms were the commonest presenting complaints, being observed in 18 (59%) cases. Atypical presentation of COVID-19 (other than respiratory) was seen in 31% of cases. Presence of undernutrition and elevated C-reactive protein (CRP) were associated with severe Covid-19 illness ($p < 0.05$). Eleven (34%) cases required intensive care and mechanical ventilation was required in 2 (6.3%) cases. Out of the 32 cases only 1 patient expired giving a case fatality rate of 3.1%.

Conclusions: Atypical presentation of COVID-19 with varied manifestations involving systems other than respiratory was observed in children as a separate entity from hyper-inflammatory syndrome. Presence of undernutrition and elevated CRP was associated with severe illness.

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(Key words: COVID-19, paediatric, atypical presentation)

Introduction

Coronavirus disease-19 (COVID-19) is caused by severe acute respiratory syndrome-corona virus [SARS-CoV-2], a beta coronavirus, mainly involving adults, and known to cause milder or asymptomatic infection in children as noted during the initial phase of the pandemic¹. However, recently it has been shown that Coronavirus can cause problems in children including multisystem inflammatory syndrome (MIS-C) which can be life threatening. Many children may require hospitalisation, including intensive care management and ventilation². Children under one year of age and children with other underlying conditions like asthma, diabetes, congenital heart disease, immune-suppression, genetic, metabolic or neurological conditions are more likely to get affected with severe COVID-19 illness³.

The common symptoms of COVID-19 in children are fever and cough, similar to adults, as reported in other studies but may also include sore throat, difficulty in breathing, myalgia, and gastrointestinal symptoms including poor feeding in infants. Children with severe COVID-19 may develop respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, encephalopathy and multi-organ system failure. Typical laboratory findings in children with COVID-19 include mild abnormalities in white blood cell count, mildly elevated inflammatory markers and mildly elevated liver enzymes. Radiologic findings in children with COVID-19 include unilateral or bilateral infiltrates on chest radiograph or computed tomography (CT), ground-glass opacities on CT and consolidation. Inflammatory markers are closely monitored in sick children and are very important in the early identification of hyper-inflammatory syndromes^{3,4}.

Treatment of COVID-19 remains largely supportive and includes prevention and management of complications. World Health Organisation (WHO) and United States National Institute of Health (US NIH) provide guidelines regarding usage of steroids and anticoagulants applicable to the paediatric age group^{5,6}. Though Remdesivir is not recommended

by the Drugs Controller General of India (DGCI) below 12 years of age, the United States Food and Drug Administration (US FDA) and US NIH allow emergency usage of the drug in children⁶. Mortality rate due to COVID-19 in children is very low. While in countries like Canada it is around 4.2%⁷, it was found to be 11.4% in an analysis done in Mumbai which included neonates in contrast to initial perception of low mortality rate in the paediatric population⁸. Limited data is available regarding varied clinical manifestations seen in children especially from Karnataka.

Objectives

To assess the clinical characteristics, laboratory parameters, management and outcomes of paediatric patients with COVID-19.

Method

Case records of all paediatric patients admitted with COVID-19 from March 2020 to November 2020 were included in the study. All children were diagnosed with COVID-19 either by Reverse Transcription – Polymerase Chain Reaction (RT-PCR) or rapid antigen test. Data regarding mode of presentation, the presence of comorbid conditions, severity of COVID-19 disease, laboratory investigations, including blood and imaging studies and management of the patients during their stay in the hospital was noted in a pre-structured proforma. Paediatric patients presenting with MIS-C were also considered under the severe category due to the seriousness of the illness. Correlation between severity of the COVID-19 disease with clinical risk factors and laboratory parameters was done. Outcomes, including requirement of intensive care unit care, mechanical ventilation, duration of hospital stay and mortality were noted.

Ethical issues: Approval for the study was obtained from the Yenepoya Ethics Committee - 1, Mangalore, India (No. YEC-1/2020/074). As this was a retrospective study, written informed consent could not be obtained.

Statistical analysis: Descriptive analysis was done by IBM SPSS software version 23. ANOVA was used to test the mean difference of all continuous study parameters among all categories of severity. Chi square test was used to assess the distribution of severity among categorical study parameters.

Results

A total of 32 children were admitted with COVID-19 infection in our institute. Ages of admitted children ranged from 6 months to 16 years with a

mean age of 10.8 years. Of them 17 (53%) were boys and 15 (47%) were girls. Eight (25%) children had pre-existing comorbidities. Of them, 5 had chronic neurological conditions and congenital heart disease, chronic pancreatitis and chronic kidney disease were present in one each. Distribution of presenting symptoms and signs is given in Table 1.

Table I: Symptoms and signs in admitted COVID-19 patients (n=32)

Symptom/Sign	Number (%)
Cough	09 (32.0)
Fever	15 (46.0)
Breathlessness	06 (18.8)
Gastrointestinal symptoms	05 (15.0)
Atypical presentation	12 (37.5)
Presence of co-morbidities	08 (25.0)
Respiratory distress	06 (18.8)
Shock	05 (15.0)
Impaired consciousness	06 (18.8)
Underweight	09 (28.0)
Pallor	05 (15.0)
Oedema	04 (12.5)
Organomegaly	02 (06.3)

Respiratory symptoms were the commonest presenting complaints, being observed in 18 (59%) cases. Cough was the commonest respiratory symptom observed followed by breathlessness while sore throat and rhinorrhoea were present in only 2 patients each. Fever was the next common symptom observed but it was present in less than 50% of cases. Gastrointestinal tract symptoms, including abdominal pain, vomiting and diarrhoea, were present in 15% of cases. On examination, 18.8% of patients had respiratory distress with oxygen saturation (SpO₂) less than 94%. Shock was present in 5 (15%) patients while hypertension was seen in 2 patients who had associated renal abnormalities. Underweight was seen in 28% patients but none of the cases had obesity. Oedema was present in 4 patients due to renal and cardiac involvement. None of the patients had conjunctival suffusion or any skin rash. Organomegaly was present in 2 hyper-inflammatory syndrome cases.

Patients presenting with symptoms other than Severe Acute Respiratory Infection (SARI) / Influenza-Like Illness (ILI) contributed 10 (31%) cases which included neurological, cardiovascular, acute kidney injury (AKI) and chronic pancreatitis exacerbation, haematological and hyper-inflammatory syndromes details of which are given in Table 2.

Table 2: Details of atypical COVID-19 presentation

Case presentation	D dimer (ng/ml)	LDH (U/L)	Ferritin (µg/L)	Treatment
<i>Guillain-Barre syndrome</i> 13Y/M	3009	176	57.3	IVIG
<i>Chronic pancreatitis exacerbation with pseudo-aneurysm and pseudocyst</i> 14Y/F	2580	168	3.1	Stent grafting of gastro-duodenal artery
<i>Right sided empyema with underlying lower lobe consolidation</i> 5Y/F	583	365	300	Antibiotics, Inj. Remdesevir anticoagulants
<i>Aicardi syndrome with shock</i> 6Y/F	751	1072	127	Inotropes, dexamethasone anticoagulants, antibiotics
<i>Acute kidney injury Stage 3</i>	3512	259	12.7	Dialysis, dexamethasone heparin
<i>Para-infectious autoimmune encephalitis</i>	96	207	39.8	Pulse therapy of steroids, anticoagulants
<i>SARI due to COVID-19 associated with seizures</i>	667	233	23.4	Inj. Remdesevir, Inj. enoxaparin, Anticonvulsants.
<i>COVID-19 with thrombocytopenia</i>	5540	641	967	Dexamethasone
<i>Cerebral palsy with seizure disorder with encephalitis with refractory status epilepticus</i>	6000	345	677	Multiple anticonvulsants, antibiotics, acyclovir
<i>Pulmonary arterial hypertension with right atrial and right ventricular dilation [?Heart failure with preserved ejection fraction]</i>	62	184	156	Inj. furosemide.

Mean haemoglobin (Hb) was 11.03g/dl with 2 patients being severely anaemic with Hb of 1.4g and 6.9g in haemophagocytic lymphohistiocytosis (HLH) and in a known case of atypical haemolytic uraemic syndrome (HUS) with chronic kidney disease (CKD) on maintenance dialysis respectively. Majority of the patients had normal leucocyte counts (mean 8636/cu mm, range 2860 to 20,500/cu mm) except 3 patients out of which 2 had leucocytosis (neutrophilic in severe COVID-19 cases) and 1 had leucopenia. Mean neutrophil to lymphocyte ratio was 1.99:1 while in severe cases it was found to be 2.5:1. Majority of the children had normal platelet counts (mean 240,000/cu mm, range 10,000 to 580,000/cu mm) except for 4 children who had thrombocytopenia and 1 who had thrombocytosis. CRP ranged from 5 to 90mg/L with a mean value of 20mg/L. Four children had abnormal renal function tests out of which 1 case was stage 3 AKI requiring dialysis. Three children had abnormal liver function tests with evidence of coagulopathy present in 1 child. Abnormal x ray was seen in 12 patients out of which computed tomography (CT) of chest was done in 4 patients. Abnormalities in CT chest were seen bilaterally, predominantly involving the lower lobe. Lactate dehydrogenase (LDH), D dimer and ferritin levels were done in severe cases or in any atypical presentation. Mean LDH was 635 U/L and ranged from 176 to 1817 U/L. Mean D dimer was 3,154 ng/ml and ranged from 96 to 10,000ng/ml. Mean ferritin was 233.5 µg/L. Though troponin I was done for a few patients, depending on the clinical indication, none of them had values higher than 2ng/ml. Echocardiography was abnormal in 3 patients with global hypokinesia noted in 2 patients and the other child with dilated right atrium and right ventricle with dilated and congested inferior vena cava with preserved ejection fraction. The latter had COVID-19 IgG positive and child was suspected to

have heart failure with preserved ejection fraction (HEpEF).

All patients received symptomatic treatment as per Ministry of Health guidelines available at that time⁹. Inj. Remdesevir was used in 3 patients after consultation with the Institutional Medical Board. Azithromycin and chloroquine combination was used in 3 patients above 12 years of age. Anti-inflammatory drugs were used in 10 (31%) patients and anticoagulants in 8 (25%) patients. Antibiotics were used in 10 (31%) patients. Oxygen was required in 15 (46%) patients with high flow nasal cannula (HFNC) in 2 patients and mechanical ventilation in 2 patients out of which 1 patient expired. Inotropes were required in 5 patients.

Out of 2 patients with hyper-inflammatory syndromes, 1 child presented with fever, seizures, altered sensorium, bleeding from nose, oral cavity, rectal bleeding along with respiratory distress requiring oxygen. Child had pallor and hepatomegaly. She had bicytopenia with leucocytosis and bone marrow showed increased destruction of cells due to HLH. She also had altered liver function tests, renal function tests and echocardiographic abnormality with persistent sinus tachycardia even after resolution of the fever. Her D dimer was more than 10,000 ng/ml and ferritin more than 1000µg/L. Child responded to dexamethasone as per HLH regimen. COVID-19 IgG was positive and magnetic resonance imaging (MRI) of the brain was normal.

Mild COVID-19 cases were seen in 16 (50%) patients, moderate in 6 (18.8%) and severe in 10 (31.3%). Mild cases were seen in children less than 10 years but moderate and severe cases were seen in children above 10 years. Severe COVID-19 was

seen in 6 (18%) girls compared to 4 (12%) boys. Severe COVID-19 cases were seen in undernourished children which was statistically

significant (p=0.012), but other comorbidities were not significantly associated with severity as shown in Table 3.

Table 3: showing association between comorbid conditions and severity of illness

Comorbid conditions		Severity			Total
		Mild	Moderate	Severe	
No	Count	14	04	06	24
	% of total	43.8	12.5	18.8	75.0
Yes	Count	02	02	04	08
	% of total	06.3	06.3	12.5	25.0
Total	Count	16	06	10	32
	% of total	50.0	18.8	31.3	100.0
Weight					
Normal	Count	15	04	04	23
	% of total	46.9	12.5	12.5	71.9
Underweight	Count	01	02	06	09
	% of total	03.1	06.3	18.8	28.1
Total	Count	16	06	10	32
	% of total	50.0	18.8	31.3	100.0

Mean CRP was 39.3 in severe cases and was found to be statistically significant compared to mild and

moderate cases with a p value of 0.025 which is shown in Table 4.

Table 4: showing association between laboratory parameters and severity of COVID-19 disease

Study parameter	Severity	Mean	Standard. error	95% Confidence interval for mean		p-value
				Lower bound	Upper bound	
Total count	Mild	7875.00	393.012	7037.32	8712.68	0.267
	Moderate	7178.33	410.726	6122.53	8234.14	
	Severe	9561.00	1611.918	5914.59	13207.41	
	Total	8271.25	552.021	7145.40	9397.10	
Platelet count	Mild	268375.00	14179.173	238152.81	298597.19	0.366
	Moderate	248500.00	78796.679	45946.69	451053.31	
	Severe	199400.00	44206.133	99398.78	299401.22	
	Total	243093.75	21057.925	200145.83	286041.67	
Erythrocyte sedimentation rate	Mild	13.906	2.938	7.643	20.169	0.052
	Moderate	17.167	3.497	8.178	26.156	
	Severe	33.100	9.407	11.819	54.381	
	Total	20.516	3.586	13.203	27.829	
C- reactive protein	Mild	11.644	4.066	2.976	20.321	0.025
	Moderate	11.667	2.376	5.599	17.774	
	Severe	39.320	12.449	11.157	67.483	
	Total	20.297	4.852	10.402	30.192	

Eleven (34%) cases required intensive care and mechanical ventilation was required in 2 (6.3%) cases. Nine (28%) patients exceeded the benchmark stay of 14 days. Out of 32 cases only 1 patient expired giving a case fatality rate of 3.1%.

Discussion

This study included 32 children who were admitted with COVID-19 at a tertiary care hospital from Karnataka, South India, with a varied spectrum of COVID-19 infection. Though boys were affected more compared to girls with the COVID-19, severity of COVID-19 was more in girls and in older children above 10 years which is in contrast to the study done by Rao S, *et al*⁸ from Mumbai. Of the 32 children 25% were noted to have pre-existing co morbidities which is lower compared to the study from

Mexico¹⁰. While many studies have noted malignancy as one of the common pre-existing comorbidities, we observed chronic neurological conditions as the most common entity. Obesity was not observed as a risk factor but instead undernutrition was associated with severe cases.

Respiratory symptoms were the commonest presenting symptoms, cough being the main symptom seen in more than 59% of cases followed by fever and gastrointestinal symptoms. In Spain, it was observed that fever and respiratory symptoms were predominant in children who had an uncomplicated course compared to those who had a complicated course¹¹. Of the 32 children 31% had atypical presentation of COVID-19 involving neurological, cardiovascular, renal, gastrointestinal

and haematopoietic systems. The reason for more percentage of atypical presentation in our study may be because the severity of the illness was forcing them to take hospital care. Though hyper-inflammatory syndromes are well recognised in children, involvement of other systems is infrequently reported¹². None of the patients had olfactory or gustatory symptoms.

Among neurological manifestations, seizures were observed more commonly, with 1 patient having refractory status epilepticus. There are few case reports about the association of seizures including febrile seizures and COVID-19 infection and it is noted that patients can have either new onset seizures or breakthrough seizures in a previously well controlled patient^{13,14}. Para-infectious complications like Guillain-Barre syndrome and autoimmune encephalitis noted in our case series were first reported by Curtis M, *et al*¹⁵ and Burr T, *et al*¹⁶. Madaan P, *et al*¹⁷ mentioned that we need to be more vigilant about these neurological manifestations as COVID-19 induced inflammation can trigger varied neurological disorders and early consideration of immunotherapy will be beneficial in such scenarios.

AKI developed in 9.3% of children. In a study done by Basalely A, *et al*¹⁸, AKI developed in 11.8% of children which is slightly higher compared to our study. AKI can be a part of MIS-C syndromes in children but it can occur even with acute COVID-19 infection as an isolated entity and it is associated with significant morbidity and mortality. One case of acute exacerbation of chronic pancreatitis leading to pseudo-aneurysm with pseudo-cyst was noted who presented with haematemesis and severe anaemia. The temporal association between acute pancreatitis and COVID-19 has been suggested over the past several months with a few case reports¹⁹. If patient is presenting with significant pain in the abdomen in COVID-19 infection, the possibility of pancreatitis should be considered. Bhattacharjee S, *et al*²⁰, in their study noticed that 7% of paediatric patients had immune thrombocytopenic purpura (ITP) compared to 1 case in our study who presented with gum bleeding and severe thrombocytopenia. Among haematological complications ITP has emerged as an important complication and can be delayed by 2 to 3 weeks after COVID-19 infection.

Among 2 children with MIS-C, one child was very sick requiring intensive care for a prolonged period with involvement respiratory, nervous, cardiovascular, renal, hepatic and haematological systems with bone marrow showing evidence of HLH. Tang Y, *et al*²¹ have done a systematic review of MIS-C cases and observed that fever and gastrointestinal symptoms were the most common symptoms and that the outcome was favourable.

Neutrophil lymphocyte ratio, though it is increased in severe cases, has not corresponded with the adult cut off values (<3.2 for mild, >3.2 for moderate and >5.5 for severe cases) but CRP was found to be significantly elevated in children with severe disease. Henry BM, *et al*²² recommended that instead of leucocyte indices CRP, procalcitonin and LDH were better markers to monitor the course in children. In our study, though D dimer, LDH and Ferritin were elevated in patients with severe cases and atypically presented cases, comparison with mild to moderate cases was not done as the values were not available for all.

Anti-inflammatory drugs and anticoagulants were used more frequently compared to antivirals in our study which was based on Centres for Disease Control and Prevention (CDC), WHO and US NIH guidelines and a favourable outcome was noted. Case fatality in our study was 3.1% which is higher compared to 0.5% case fatality rate observed in England during the first wave²³. That may be because only admitted patients were taken into account in our study but Ladhani SL, *et al*²³ have taken all COVID-19 positive paediatric cases into account.

Conclusions

Atypical presentation of COVID-19 was observed in children with varied manifestations involving systems other than respiratory as a separate entity apart from hyper-inflammatory syndrome. Presence of undernutrition and elevated CRP were associated with severe illness.

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