Original Article

A cross-sectional study on clinical characteristics and severity of children with COVID-19 admitted to a teaching institute in North India

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Abstract

Background: SARS-CoV-2 infection presentation in children is usually milder than in adults but can be severe and fatal as well. Data on the pediatric population regarding severity and clinical presentation are still limited, and there is a need to have a better understanding of clinical features, severity, and laboratory parameters. **Aims and Objective:** To document clinical and laboratory characteristics and outcomes of children with SARS-CoV-2 in a low-middle-income country and to evaluate clinicodemographic factors and biochemical markers associated with severity and mortality. **Materials and Methods:** A hospital-based cross-sectional study was conducted among 112 COVID-19-positive children at a designated Level-3 center in North India. Clinical characteristics, laboratory parameters, and severity of COVID-19 cases as well as factors associated with the severity of the disease, were analyzed by descriptive statistics and a Chi-square test. **Results:** The adolescent age group (age 12-18 years) was affected most (64.3%). Male patients accounted for 56.3% of total cases. Fever was the most common symptom (41.1%) followed by cough. Presenting complaints were highest from the respiratory system (32.1%) followed by the gastrointestinal (8.9%) and the neurological system (7.1%). Majority of patients had mild disease (87%) while 13% had the moderate-severe disease. $Spo_2 < 95\%$ ($P = 0.00001$), neutrophilia ($P < 0.000001$), lymphopenia ($P < 0.000001$), elevated values of C-reactive protein ($P < 0.00001$), Interleukin-6 ($P = 0.002$), D- dimer ($P = 0.00014$) and respiratory symptoms as presenting complaints ($P < 0.000001$) were found to be significantly associated with severity of disease. **Conclusion:** The male and adolescent age group was affected most. Presenting complaints were highest from the respiratory system. Unusual presentation may have gastrointestinal or neurological presentation. Most children with COVID-19 had mild disease. Moderate to severe disease was not uncommon. Factors including neutrophilia, lymphopenia, elevated lab values of C-reactive protein, D-dimer, and interleukin-6 had a significant association with the severity of the disease. These biomarkers can help predict the severity of the disease.

Keywords: Children, clinical spectrum, COVID-19, SARS-CoV-2, severity biomarkers

Introduction

A cluster of cases of pneumonia due to severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) was declared a pandemic by WHO on March 11, 2020.[1,2] First pediatric case of COVID-19 was detected on January 28, 2020, in China.[3,4] Understanding of the disease and its management is still evolving,

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Received: 25-10-2023 **Revised:** 08-01-2024
Accepted: 17-01-2024 **Published:** 28-06-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1734_23

How to cite this article: Nauriyal D, Dubey R, Agrawal P, Kumar D, Punj A, Nasser K. A cross-sectional study on clinical characteristics and severity of children with COVID-19 admitted to a teaching institute in North India. J Family Med Prim Care 2024;13:2653-62.

and there is a lack of clarity about the presentation, severity, and management of COVID-19 cases in children, especially in middle-income countries like India.[5] Pediatric vaccination against COVID-19 is still in the preliminary stage only, thus making them selectively vulnerable and a potential source of adult infections.

The magnitude of illness in children has been variously reported from 0.39%[6] to 12.3%[7] and of total cases positive for COVID-19, depending on local isolation and reporting protocols. In India, 2.5% of children tested positive for COVID-19 in the second wave,[8] with the death of 1500 children.[9] Further, data on pediatric patients are still limited regarding severity and clinical presentation, and there is a need to have a better understanding of clinical features, severity, and laboratory parameters.

COVID-19 disease has a wide spectrum of presentations. Patients can have mild disease only or severe disease with complications like multi-organ failure.[10] SARS-CoV-2 infects cells, entering via angiotensin-converting enzyme 2 receptors. The host immune system responds to this infection through increased inflammatory markers that can become deregulated and exaggerated. In COVID-19, there is the interplay of deregulated inflammation, immunological, and coagulation cascade, which may eventually cause multi-organ failure and death.[11,12] Timely identification of laboratory parameters deranged during this dysregulation of immunity, inflammation, and coagulation cascade could help in timely clinical intervention and improve disease outcomes.

In this study, we attempted to assess various clinical presentations, laboratory findings, severity, and outcome of disease. We also attempted to analyze the association between disease severity and clinicodemographic factors. As very few Indian studies have been conducted to analyze the association between inflammatory markers and/or other biomarkers and the severity of COVID-19 disease, we attempted to analyze the same in this study.

Awareness of primary physicians on clinical presentation of COVID-19 in children will help in early detection and prompt treatment of the disease. Also, knowledge of factors that are associated with severity of disease and can be evaluated easily, like $spo_2 < 95\%$, and simple tests like complete blood picture suggestive of neutrophilia and lymphopenia could help in the prompt referral of cases.

Materials and Methods

Case enrollment

It was a hospital-based prospective observational study conducted from April 2020 to May 2021 in a tertiary care hospital in North India. A reverse transcriptase polymerase chain reaction (RT-PCR) test was performed on all children coming to OPD/emergency for any complaints as well as on children having a history of contact with a COVID-positive person. Children under and up to 18 years of age who were documented positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) test on nasal and nasopharyngeal swabs were included in the study, irrespective of the severity of the disease. A total of 112 children were included and were categorized as per age into categories of less than 1 year, 1-5 years, 6-11 years, and 12-18 years. Patients whose RT-PCR was negative, whose parents refused consent, and patients with incomplete data were excluded from the study.

Written informed consent was obtained in Vernacular (Hindi)/ English language from parents in all cases. Children above five years of age were explained as well, and assent was obtained in the presence of parents/legal guardians.

Detailed information was taken regarding contact with positive cases, travel history, symptoms, and demographic details. Clinical presentation, laboratory, and radioimaging findings within the first 48 hours of admission were recorded in the data. Response to treatment and outcome were recorded and then analyzed. The study was approved by the Institutional Ethics Committee.

Case definition[13-17]

All those children who were positive for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR) test on nasal and nasopharyngeal swabs were taken as COVID-positive.

Grading of Disease Severity.

Mild COVID Disease: features of upper respiratory infection like sore throat, runny nose, cough, fever, and easy fatiguability.

No tachypnea (age-based) and normal auscultatory findings.

No hypoxia ($SpO_2 > 95\%$ on room air).

Pain in the abdomen. Diarrhea, vomiting.

Moderate COVID Disease: Tachypnea (age-based).

Hypoxia (resting SpO_2 90-94% on room air).

Asymptomatic pneumonia with lesions seen on chest CT scan signs of severe disease absent.

Severe COVID Disease: Pneumonia with either severe retractions or grunting, tachypnea, or $SpO_2 < 90\%$ on room air.

Severe abdominal pain, diarrhea, vomiting.

Seizures, lethargy, or Somnolence.

Multi-organ dysfunction, acute thrombosis, shock, acute respiratory distress syndrome (ARDS).

For common laboratory values, cut-off points that are widely accepted in clinical practice were used. Leukopenia was defined as white blood cell count $< 4.0 \times 10^9$/L. Thrombocytopenia was defined as platelet count $< 150 \times 10^9$/L, and Lymhopenia

was defined as lymphocyte count < 1×10^9/L. Deranged kidney function test (KFT) was defined as an absolute increase in serum creatinine of >0.3 mg/dl or >50% increase from baseline. Using WHO-recommended cut-off values, Hb > 10 g/dl to <11 g/dl was considered mild anemia, while Hb 7 to 11 g/dl was moderate anemia, and Hb < 7 g/dl was severe anemia. Neutrophilia was defined as neutrophil values above two standard deviations for that age group.

Statistical analysis

Data obtained was tabulated on an Excel sheet based on a Proforma and statistically analyzed. A comparison of demographic, clinical, and laboratory values for mild and moderate to severe disease was conducted using the Chi-square test. Using a two-tailed distribution, a *P* value of < 0.05 was considered statistically significant.

Results

A total of 112 children up to 18 years of age were enrolled in the study. Demographic and clinical parameters are summarized in Table 1.

Out of 112 cases, 56.3% (63/112) were male, and the largest percentage of patients were in the 12-18 years age group (64.3%, 72/112). Percentage of patients in other age groups was 10.7% (12/112) in <1 year, 11.6% (13/112) in 1-5 years, and 13.4% (15/112) in the 6-11 years age group. History of contact was present in 80.4% (90/112).

The common symptoms of children with COVID-19 disease are mentioned in Table 1 and Figure 1. The most common symptom was fever (41.1%, 46/112), followed by cough (13.4%, 15/112). Respiratory distress was seen in 12.5% (14/112) of cases. Gastrointestinal manifestations like vomiting, pain in the abdomen, and diarrhea were present in 8.9% (10/112) of cases. Neurological manifestations (headache, dizziness, altered sensorium, seizures) were found in 7.1% (8/112) cases. Comorbidity was present in two cases. One case was a known case of miliary tuberculosis and other tuberculosis meningitis. 82.1% (92/112) of patients were allocated to the mild degree group, while 15.2% (17/112) of patients were classified as moderate and 2.7% (3/112) as severe disease [Figure 2]. Combined, 17.9% (20/112) of patients were assigned to the moderate-severe degree of disease group.

Table 2 shows the hematological, biochemical, and radiological parameters of patients. The most common abnormality in hematology was neutrophilia, seen in 9.8% (11/112) of cases. In contrast, leucopenia was seen in 5.4% (6/112) cases only. Among deranged coagulation profiles, Prolonged Prothrombin Time (PT)/aPTT/INR was seen in one case only; however, D-dimer was elevated in 6.2% (7/112) of cases. Abnormal radio imaging was found in 3.6% (4/112) cases only. All cases had ground glass opacity, and chest computerized tomography had no additional advantage over plain radiography.

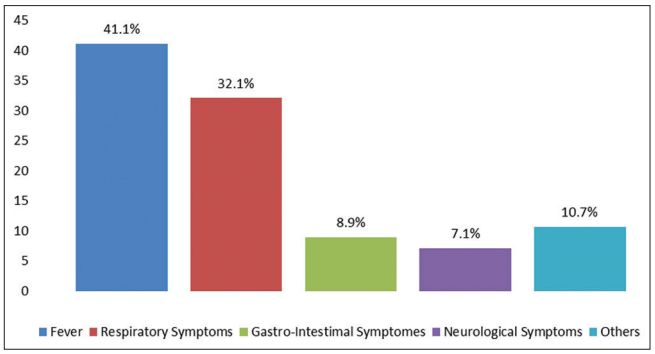

Figure 1: Main presenting complaints of children with COVID-19 disease

Table 1: Sociodemographic and clinical parameters of children with COVID-19 disease

Characteristics	*n* (%)
Age groups (age in year)	
<1 year	12 (10.7%)
1-5 year	13 (11.6%)
6-11	15 (13.4%)
12-18	72 (64.3%)
Gender	
Male	63 (56.3%)
Female	49 (43.7%)
History of contact	
Present	90 (80.4%)
Absent	22 (19.6%)
Clinical characteristics	
Fever	46 (41.1%)
Respiratory symptoms	36 (32.1%)
Cough	15 (13.4%)
Respiratory distress	14 (12.5%)
Cold (nose running and nasal blockage)	7 (6.2%)
Gastrointestinal symptoms	10 (8.9%)
Pain abdomen, vomiting, diarrhea	9 (8%)
GI bleeding (bleeding P/R)	1 (0.9%)
Neurological manifestations	8 (7.1%)
Headache	3 (2.7%)
Dizziness	2 (1.8%)
Altered sensorium	2 (1.8%)
Seizures	1 (0.9%)
Others (Fatigue, decreased appetite, myalgia, arthralgia, skin rash, red eyes, and general feeling of discomfort)	12 (10.7%)
Total	112 (100%)

Further, as Table 3 shows, 9.8% (11/112) of patients needed oxygen via mask/nasal prongs while 2.7% (3/112) needed invasive ventilation. Drugs like steroids, Remdesivir, and low molecular weight heparin were given to 6% (7/112), 4.5% (5/112) and 1.8% (2/112) cases only. 98.2% (110/112) of patients were successfully discharged. The mortality rate among children with COVID-19 was reported as 1.8% (2/112).

As shown in Table 4, the adolescent age group (12-18 years) was affected most, but there was no association between the severity of the disease and age group ($P = 0.14$ by Chi-square

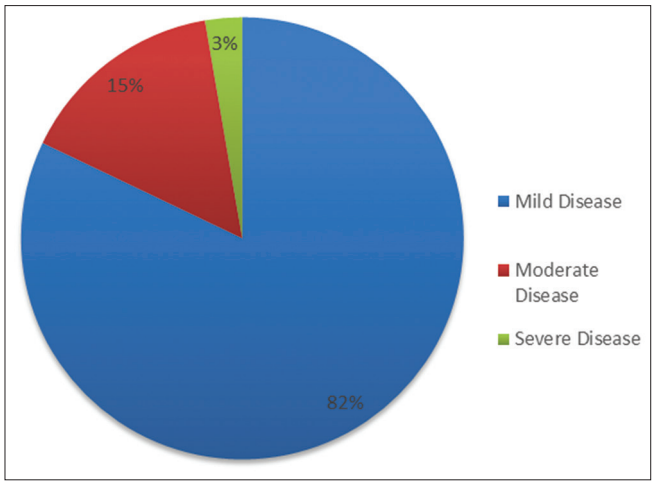

Figure 2: Distribution of severity of disease in children with COVID-19

test). Also, no association was found between disease severity and gender of patients ($P = 0.70$). On analyzing the association between disease severity and the system affected primarily, that presented as presenting complaints, a significant association was found between the respiratory system and COVID severity ($P < 0.000001$), while other presenting complaints like fever ($P = 0.36$), or other systems affected primarily including Digestive system ($P = 0.20$) and neurological ($P = 0.13$) did not affect the severity of disease significantly. There was a highly significant association ($P = 0.000001$) between $spo_2 < 95\%$ on room air at presentation and the severity of COVID-19. Leucopenia was not found to have a significant association with disease severity ($P = 0.24$), while neutrophilia ($P < 0.000001$), lymphopenia ($P < 0.000001$), and CrP > 10 mg/l ($P < 0.000001$) had a highly significant association with disease severity. IL-6 > 32 pg/L also had a significant association with disease severity ($P = 0.002$)

Table 2: Laboratory and radiological findings of children with COVID-19 disease

Investigations	*n* (%)
CBC	
Leucopenia	6 (5.4%)
Neutrophilia	11 (9.8%)
Lymphopenia	10 (8.9%)
Anemia	
Mild	6 (5.3%)
Moderate	4 (3.5%)
Thrombocytopenia (mild)	2 (1.8%)
Deranged coagulation profile	8 (7.1%)
↑ PT/aPTT/INR	1 (0.89%)
Elevated D-dimer (>1 ug/L)	7 (6.2%)
Deranged KFT	1 (0.89%)
Abnormal chest x-ray	
Ground glass opacity	4 (3.6%)
Abnormal chest CT-findings	
Ground glass opacity	4 (3.6%)

Table 3: Treatment and outcome of children with COVID-19 disease

Treatment and outcome	*n* (%)
Conservative (paracetamol, oral fluids, oral antibiotics)	87 (77.7%)
Oxygen via mask/nasal prongs	11 (9.8%)
Invasive ventilation	3 (2.7%)
Drugs used	
Steroids	7 (6%)
Remdesivir	5 (4.5%)
Tocilizumab	3 (2.7%)
Low molecular weight heparin	3 (2.7%)
Outcome	
Discharge	110 (98.2%)
Mortality	2 (1.8%)

Discussion

In this study, which comprised 112 children, the maximum percentage was adolescents (12-18 years), followed by young children and infants. These results are in tune with studies that showed that with increasing age, more children became COVID-positive.[18] The male gender was affected more than the female. Fever followed by cough were the two most common symptoms, like most other studies in children.[19] Though fever is considered to be an important clue to COVID-19 infection, many COVID-19-positive children were afebrile also. This suggests that body temperature alone may not be a sufficient indicator of SARS-CoV-2 infection.[20]

Like other studies, in our study, the respiratory system was affected most commonly.[21] Patients presented with various respiratory manifestations like cough, cold, and shortness of breath.

COVID-19 virus has a very high affinity for ACE-2 receptors. These receptors are like entry and replication ports for the virus and are present most abundantly in airway epithelium, type I, and type II alveolar cells. Studies have shown this distribution pattern of ACE -2 receptors as a cause of the respiratory system being the most common clinical presentation of symptomatic patients.[21]

Recently, there has been a focus on gastrointestinal (GIT) manifestations in COVID-positive children. COVID virus is known to bind to the Angiotensin-converting enzyme 2 receptor of not only the lung but kidney, pancreas, nervous system as well as GIT epithelium. The binding of the virus to GIT epithelium causes a variety of symptoms including nausea, vomiting, diarrhea, and pain in the abdomen.[22] In our study, gastrointestinal manifestations were the commonest extra-pulmonary manifestations of COVID-19, followed by neurological manifestations. Studies have also shown that in COVID-positive children with GIT symptoms, rectal swabs were persistently positive even though nasopharyngeal swabs became negative, and this persistent shedding of virus can increase chances of fecal-oral transmission.[8]

Table 4: Relationship between demographic profile, presenting complaints, laboratory parameters, and severity of COVID-19

Variables predicting the severity of COVID-19	Mild COVID-19 disease (*n*=92)	Moderate –severe COVID-19 disease (*n*=20)	*n* (%)	*P* (Chi-square test)
Age				
<1 year	8 (8.7%)	4 (20%)	12 (10.7%)	
1-5 years	10 (10.9%)	3 (15%)	13 (11.6%)	0.14
6-11 years	15 (16.3%)	(0%)	15 (13.4%)	
12-18 years	59 (64.1%)	13 (65%)	72 (64.3%)	
Sex				
Male	51 (55.4%)	12 (60%)	63 (56.3%)	
Female	41 (44.6%)	8 (40%)	49 (43.7%)	0.71
Presenting complaints				
Fever	36 (39.1%)	10 (50%)	46 (41.1%)	0.37
Respiratory (cough, cold, and dyspnea)	20 (21.7%)	16 (80%)	36 (32.1%)	0.00001
Digestive (pain in the abdomen, nausea, vomiting, diarrhea, and PR bleeding)	7 (7.6)	3 (15%)	10 (8.9%)	0.29
Neurological (headache, altered sensorium, and seizures)	5 (5.4%)	3 (15%)	8 (7.1%)	0.13
Laboratory parameters				
Spo_2 <95%	1	14	15 (13.4)	0.00001
Leucopenia (TLC <4000/mm^3)	6 (6.5%)	0 (0%)	6	0.24
Neutrophilia[15]	4 (4.3%)	7 (35%)	11	<0.00001
Lymphopenia**	3 (3.3%)	7 (35%)	10	<0.00001
CrP >10 mg/l	0	6 (30%)	6	<0.00001
IL-6 >32 pg/l	1 (1.1%)	4 (20%)	5	0.002
D-Dimer				
>1 ug/l	2 (2.2.%)	5 (25%)	7 (6.2)	0.00014

**Lymphocyte <20% of total leukocyte count or <1,100/microliter

One important observation of our study was lower GI bleeding in one COVID-19-positive child. It was a fresh bleed or hematochezia, without any hematemesis or melena. There were a few episodes of hematochezia, with decreasing amounts and frequency. The child had a normal coagulation profile and normal platelet counts and was not on low molecular weight heparin, NSAIDs, or Aspirin. Based on clinical and laboratory parameters, bleeding was attributed to mucosal erosions as has been documented in other studies also.[23]

Neurological manifestations were also not uncommon and had a varied spectrum from mild symptoms like a headache to severe ones, i.e. altered sensorium and seizures. As standardized, well-defined case definitions and diagnostic criteria for neurological manifestations of COVID are lacking, there are high discrepancies in rates of neurological involvement in different studies. Neurological manifestations include central (dizziness, altered sensorium, and seizure) and peripheral (loss of taste and smell) nervous system involvement. Though very frequent in adult COVID-19 patients, none of the patients in our study had complaints of an altered sense of smell.[24] Multiple mechanisms including cytokine storm, hypoxic and metabolic changes, direct neuroinvasion by virus, and hypercoagulability have been proposed,[25,26] Yet pathophysiology of nervous system involvement in COVID disease is still not clear.

In our study, underlying comorbidity was present in two cases only. One child had Miliary tuberculosis while the other had tubercular meningitis. Both children were successfully discharged. The majority of children had mild disease, like most of the other studies.[19,20] Moderate-severe disease was not uncommon in our study. In this study, there were two mortality. The mortality rate in our study was 1.8%.

Studies on hematological changes due to COVID-19 in the pediatric population are very few. Therefore, we attempted to observe the same. Leucopenia was not characteristically found in our study, and these results are consistent with a few other such studies.[27,28] Neutrophilia was present in 9.8% of cases. Neutrophils are part of innate immunity and are among Leukocytes that are recruited first during any inflammation.[29] Studies have already proven that the dysregulated immune system that causes excessive inflammation plays a major role in the pathogenesis of COVID-19. Neutrophilia is part of that dysregulated immune system, and many studies have documented neutrophilia in COVID-19 patients.[30-32] Lymphopenia was seen in 8.9% of cases. Though the mechanism of lymhopenia is still not well understood, it has been proposed that the presence of ACE 2 receptors, which is a main binding receptor for COVID-19, in T-lymphocytes, could lead to lymphocyte destruction and lymphopenia.[33] Anemia like some other studies was also not commonly observed finding[34] mild and moderate anemia was observed in a few cases while no case had severe anemia. Causes for anemia include destruction of RBC membrane by SARS-COV-2 after attaching to ACE -receptors of RBC, gastrointestinal bleeding due to coagulopathy or mucosal erosions, dysregulated iron metabolism, and autoimmune hemolytic anemia during cytokine storm.[35] Thrombocytopenia was of mild degree only observed in a smaller percentage.

Deranged coagulation profile with prolonged PT and activated partial thromboplastin time (aPTT) and international normalized ratio was seen in one case. Increased D-dimer was seen in 6.2% of cases. D-dimer is a fibrinogen degradation product present in blood after fibrinolysis of the blood clot. It is due to the activation of coagulation and, hence, secondary fibrinolysis.[36] Determining cut-off values of D-dimer is a challenge, and values that have been widely adopted are 0.5 microgram/l, 1 microgram/l, and 2 microgram/l.[36] For our study, we used a cut-off of 1 microgram/l. Though D-dimer was elevated in a good number of cases, deranged PT/aPTT and thrombocytopenia were seen in only one case. Thus, coagulation derangement in our study is not consumptive coagulopathy. These results differ from studies where patients with deranged coagulation profile primarily had Disseminated Intra-vascular Coagulation.[37] However, in a few other studies also, COVID-19 patients had hypercoagulability but not consumptive coagulopathy.[38] Many mechanisms that have been proposed for this hypercoagulability include increased levels of pro-coagulant factors, reduced levels of anti-coagulants, COVID-19 induced anti-phospholipid antibodies and complements causing microthrombosis and vasculitis.[39]

Abnormal lung imaging was observed in three cases with respiratory distress. The only radiological abnormality seen in the X-ray as well as CT scan of these patients was ground glass opacity. Few other major studies have shown ground glass opacity as the most frequent radiological abnormality in patients with COVID-19 disease.[40] Though Studies have shown that radiological features can appear before clinical signs/symptoms and can be present in asymptomatic patients.[41] None of the patients without respiratory distress had abnormal CT chest in our study. Thus, we do not recommend routine use of CT scan for screening purposes.

The majority of patients had mild severity of disease and hence were treated symptomatically. Patients in respiratory distress were treated with oxygen supplementation via nasal prong or mask, while in more severe cases of respiratory distress or respiratory failure, early intubation and gentle mechanical ventilation were preferred. Continuous Positive Airway Pressure, Bi-level positive airway pressure (Bi–PAP), and high-frequency nasal cannula were avoided due to the risk of generation of aerosols and putting other admitted patients and healthcare staff at risk of getting infected.

In our study, we used drugs like steroids, Tocilijumab, low molecular weight heparin, and Remdesivir in a small percentage of patients from the moderate-severe disease category. Randomized Evaluation of COVID-19 therapy (RECOVERY) trial conducted in June 2020 in the UK showed the benefits of immunomodulation with steroid use in severe COVID-19 disease.[42] However, this study also showed the potential harm that steroids can cause in patients who were not on oxygen supplementation. COVID-19 treatment guidelines issued by the National Institutes of Health in October 2020 also advised avoiding systemic steroids in patients with mild-moderate COVID-19 disease.[43,44]

Only a small percentage of patients in our study, who either had severe disease, extensive lung lesions, or elevated laboratory values of IL-6, were started on Tocilizumab along with steroids or Remdesivir and supportive treatment. Tocilizumab is a monoclonal antibody that selectively and competitively binds to the IL-6 receptor. This blocks further IL-6 signaling which is responsible for cytokine storm and lung injury.[45] Studies have advocated the use of Tocilizumab in severe patients only.[46] However, whether it can be used solely and what time it should be added is still a matter of debate. It is an expensive drug and comes in limited supply. Hence, its use should be very judicial.

We used Remdesivir in a small percentage of cases only. Till now, no anti-viral drug has been shown to have proven benefits against COVID-19 disease, and treatment is primarily targeted toward immunomodulation. Remdesivir is the first anti-viral drug approved by the US Food and Drug Administration for COVID-19 disease.[47] However, various clinical trials have shown conflicting results regarding the use of Remdesivir and its impact on morbidity, mortality, or hospital stay.[48]

Low molecular weight heparin was used in a small percentage of patients with severe respiratory distress and elevated D-dimer. Studies have shown that micro and macro-thrombosis due to exaggerated pro-coagulation in COVID-19 is more pronounced in the lungs. Therefore, giving low molecular weight heparin in such cases can prevent progression to ARDS, respiratory failure, and death. 43 Anti-viral drugs have not been proven to be very effective in COVID-19 disease, and more studies have documented the favorable role of immunomodulation.[43] Therefore, more studies should be dedicated to understanding the role of immunomodulation and especially drugs acting via IL-6 inhibition in COVID-19 disease.

Though many studies have been performed on COVID-19, data on predicting the severity of its infection are still limited. We attempted to find a relationship between clinicodemographic, laboratory parameters, and severity of COVID-19.

In our study, age group and gender did not have any significant association with the severity of COVID-19. These results are in tune with a few other studies.[49]

We also attempted to find an association between presenting complaints and the severity of COVID-19. Among various presenting complaints, symptoms of the respiratory system only as presenting complaint had a significant association with the severity of the disease. Few other studies have observed similar results.[50]

In our study, we also documented spo2 < 95% in room air at initial presentation to be significantly higher in moderate to severe COVID-19 disease patients as compared to patients with

mild disease. It has been well documented that COVID-19 can present with asymptomatic hypoxia initially, which progresses to breathlessness. By that time, the patient usually develops significant hypoxia.[51] Pulse oximeter can be a very valuable tool for primary physician who can monitor initial oxygen saturation (SpO_2) on room air, and detect such asymptomatic hypoxic patients earlier, refer them promptly to higher center, where treatment can be started before pneumonia advances to the critical stage. Many studies have also shown a significant association between dropping levels of initial Spo_2 in room air and the severity of COVID-19 disease.[52-54]

Further, we analyzed the association between various hematological parameters and the severity of COVID-19. It was observed that Leucopenia was not significantly associated with the severity of the disease. Few other studies have also documented no significant association between both.[55,56]

Neutrophil count was elevated significantly in moderate to severe COVID-19 disease as compared to mild disease. Neutrophils are part of innate immunity and are recruited first during host-viral interaction. As a part of the defensive mechanism, neutrophils make neutrophil extracellular traps (NETs), a web-like structure of nucleic acids wrapped with histones that detain virus particles and protect against viral infection.[57] However, neutrophilia and excessive production of NETs have been found to promote microthrombosis and damage multiple organs including the lung, heart, and kidney.[58] Studies have also shown elevated neutrophil count and elevated neutrophil to lymphocyte ratio are significantly associated with the severity of COVID-19.[59]

In our study, lymphopenia was significantly higher in moderate and severe disease than in mild disease. Similar findings were observed in other studies.[55,56] Various hypotheses that have been proposed as explanations of lymphopenia in COVID-19 include

(a) a high level of inflammatory markers like IL-6 that could cause lymphopenia as well as decreased cytotoxic activity of T-lymphocytes.[60]
(b) Exhaustion of T cells due to increased cell surface expression of Programmed cell death protein1(PD-1) and T cell immunoglobulin and mucin domain 3 (markers of T cell exhaustion).[61]
(c) Destruction of T cells due to abundance of ACE-2 receptors in T-lymphocytes.[62]
(d) Down-regulation of genes responsible for T cell activation and function in COVID-19 disease.[63]

In our study, we documented elevated CrP in moderate-severe COVID-19 disease that was significantly higher than in mild disease. C-reactive protein is an acute phase protein produced by hepatocytes in response to various inflammatory mediators like Interleukin-6 (IL-6), and its values are normally less than 10 mg/l in healthy people.[27,28] Hence, being a cheap and easily available laboratory test, C-RP levels testing of COVID-19 patients on and during admission could help assess the severity and progression of COVID-19 disease.

Our study demonstrated significantly elevated IL-6 in moderate-severe COVID disease. This result is in accordance with other studies where elevated IL-6 is significantly associated with the severity of COVID-19 disease Interestingly, few studies have documented IL-6 as a better biomarker for predicting COVID-19 severity than C-RP levels.[64-66]

We attempted to analyze the association between elevated D-dimer and the severity of COVID-19 disease. Our study documented a significant association between values of D-dimer > 1 microgram/l and severity of COVID-19 disease. Studies have shown a significant association between higher D-dimer values and the severity of COVID-19 disease.[64] This result shows that D-dimer can be a valuable biomarker for predicting COVID-19 disease severity.

Most of the above-mentioned blood tests are cheap, readily available, and easy to interpret. Primary physicians can also easily get these tests performed and treat patients with mild disease while referring cases in which laboratory tests are alarming.

Conclusion

In this study**,** children of all age groups were affected by COVID-19. Male and adolescent age groups were affected more. The majority of the children had mild disease. Symptoms in children had a wide range of spectrum. Fever and cough were the most common symptoms. The gastrointestinal system was the most common extra-pulmonary system to be affected. Severe disease and mortality were not uncommon. Factors like respiratory symptoms as presenting complaint, $SP0_2$ < 95% on room air on admission, neutrophilia, lymphopenia, C-reactive Protein (CrP) >10 mg/L, IL-6 > 32 pg/L, and D-dimer > 1 ug/L were significantly associated with the severity of COVID-19. While understanding of COVID-19 is still evolving, its spectrum in children is much less explored than that of adults. In these modern times, when an evidence-based approach is increasingly required to make decisions based on the best available evidence, more studies with larger sample sizes should be dedicated to studying the complete spectrum (epidemiology, clinical features, lab parameters, drugs, and final outcome) of COVID-19 in children.

Acknowledgments

Authors are thankful to all scholars whose articles have been cited in this manuscript and included in references as well as immensely grateful to patients whose data has been used in this study. The authors acknowledge all healthcare workers and front-line warriors for their pivotal role, directly or indirectly, in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, *et al.* Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: Experts' consensus statement. World J Pediatr 2020;16:223-31. doi: 10.1007/s12519-020-00343-7.
2. Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. JAMA 2020;323:1335. doi: 10.1001/jama. 2020.4344.
3. Yang P, Liu P, Li D, Zhao D. Corona Virus Disease 2019, a growing threat to children? J Infect 2020;80:671-93. doi: 10.1016/j.jinf. 2020.02.024.
4. Choi SH, Kim HW, Kang JM, Kim DH, Cho EY. Epidemiology and clinical features of coronavirus disease 2019 in children. Clin Exp Pediatr 2020;63:125-32. doi: 10.3345/cep.2020.00535.
5. Singh P, Attri K, Mahto D, Kumar V, Kapoor D, Seth A, *et al.* Clinical profile of COVID-19 illness in children—Experience from a tertiary care hospital. Indian J Pediatr 2022;89:45-51. https://doi.org/10.1007/s12098-021-03822-5.
6. Li Y, Guo F, Cao Y, Li L, Guo Y. Insight into COVID-2019 for pediatricians. Pediatr Pulmonol 2020;55:E1-4. doi: 10.1002/ppul. 24734.
7. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, *et al.* SARS-CoV-2 infection in children. N Engl J Med 2020;382:1663-5. doi: 10.1056/NEJMc2005073.
8. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, *et al.* Epidemiology of COVID-19 among children in China. Pediatrics 2020;145:e20200702. doi: 10.1542/peds.2020-0702.
9. Ministry of Health and Family Welfare. Total vaccination. 2021. https://www.mohfw.gov.in
10. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, *et al.* Genomic characterization and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 2020;395:565-74. doi: 10.1016/S0140-6736 (20) 30251-8.
11. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-7. doi: 10.1111/jth. 14768.
12. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 2020;383:2451-60. doi: 10.1056/NEJMcp2009575.
13. COVID-19 Management for 1 month-19 years old: Statement by Indian Academy of Pediatrics (April 2021) Guidelines On Clinical Management Of COVID-19. Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division), p. 3-5. Available from: https://www.mohfw.gov.in/pdf/GuidelinesonClinicalManagementofCOVID1912020.pdf.
14. American Heart Assosciation. Pediatric Advanced Life Support Provider Manual. American Heart Assosciation; 2020.
15. WHO, UNICEF, UNU. Iron deficiency anemia: Assessment, prevention and control, a guide for programme managers. Geneva, World Health Organization, 2001. Available from: http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/WHO_NHD_01.3/en/index.html.
16. Obiagwu PN, Morrow B, Mc Culloch M, Argent A. Burden and severity of deranged electrolytes and Kidney function in children seen in a tertiary hospital in Kano, northern Nigeria. PLos one 2023;18:e0283220. doi: 10.1371/ journal.pone.0283220.
17. Gallagher PG. Anemia in the pediatric patient. Blood 2022;140:571-93 doi: 10.1182/blood. 2020006479.
18. Parcha V, Booker KS, Kalra R, Kuranz S, Berra L, Arora G, *et al.* A retrospective cohort study of 12,306 pediatric COVID-19 patients in the United States. Sci Rep 2021;11:10231. doi: 10.1038/s41598-021-89553-1.
19. Pereka R, Shalini MB, Reddy J. Predictors of severity in COVID-19. J Clin Sci Res 2023;12:18-23.
20. Schneider A, Kirsten H, Lordick F, Lordick F, Lübbert C, von Braun A. Covid-19 in outpatients-Is fever a useful indicator for SARS-CoV-2 infection? PLoS One 2021;16:e0246312. doi: 10.1371/journal.pone. 0246312.
21. Johnson KD, Harris C, Cain JK, Hummer C, Goyal H, Perisetti A. Pulmonary and extra-pulmonary clinical manifestations of COVID-19. Front Med (Lausanne) 2020;7:526. doi: 10.3389/fmed. 2020.00526.
22. Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, *et al.* Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 2002;417:822-8. doi: 10.1038/nature00786.
23. Barrett LF, Lo KB, Stanek SR, Walter JW. Self-limited gastrointestinal bleeding in COVID-19. Clin Res Hepatol Gastroenterol 2020;44:e77-80.
24. Lechien JR, Chiesa-Estomba CM, Beckers E, Mustin V, Ducarme M, Journe F, *et al.* Prevalence and 6-month recovery of olfactory dysfunction: A multicentre study of 1363 COVID-19 patients. J Intern Med 2021;290:451-61.
25. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci 2020;11:995-8.
26. Urbano M, Costa E, Geraldes C. Hematological changes in SARS-COV-2 positive patients. Hematol Transfus Cell Ther 2022;44:218-24. doi: 10.1016/j.htct.2021.12.001.
27. Bari A, Ch A, Bano I, Saqlain N. Is leukopenia and lymphopenia a characteristic feature of COVID-19 in children? Pak J Med Sci 2021;37:869-73. doi: 10.12669/pjms. 37.3.3848.
28. Lamichhane PP, Samarasinghe AE. The role of innate leukocytes during influenza virus infection. J Immunol Res 2019;2019:8028725.
29. Mortensen RF. C-reactive protein, inflammation, and innate immunity. Immunol Res 2001;24:163-76. doi: 10.1385/IR:24:2:163.
30. Chen R, Sang L, Jiang M , *et al.* Longitudinal, hematologic and immunologic variations associated with the progression of COVID-19 patients in China [J]. Allergy Clin Immunol 2020;146:89-100.
31. Jenne CN, Wong CH, Zemp FJ, McDonald B, Rahman MM, Forsyth PA, *et al.* Neutrophils recruited to sites of infection protect from virus challenge by releasing neutrophil extracellular traps. Cell Host Microbe 2013;13:169-80.
32. Parackova Z, Bloomfield M, Klocperk A, Sedvia A. Neutrophils mediate Th17 promotion in COVID-19 patients. J Leukoc Biol 2021;109:73-6. doi: 10.1002/JLB.4COVCRA0820-481RRR.
33. Gajendra S. Spectrum of hematological changes in COVID-19. Am J Blood Res 2022;12:43-53.
34. Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D, *et al.* Autoimmune haemolytic anaemia associated with COVID-19 infection. Br J Haematol 2020;190:29-31.

doi: 10.1111/bjh. 16794.

35. Bergamaschi G, Borrelli de Andreis F, Aronico N, Lenti MV, Barteselli C, Merli S, *et al.* Anemia in patients with Covid-19: Pathogenesis and clinical significance. Clin Exp Med 2021;21:239-46. doi: 10.1007/s10238-020-00679-4.
36. Li Y, Deng Y, Ye L, Sun H, Du S, Huang H, *et al.* Clinical significance of plasma D-dimer in COVID-19 mortality. Front Med (Lausanne) 2021;8:638097. doi: 10.3389/fmed. 2021.638097.
37. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-7.
38. Panigada M, Bottino N, Tagliabue P, Grasselli G, Novembrino C, Chantarangkul V, *et al.* Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020;18:1738-42.
39. Kichloo A, Dettloff K, Aljadah M, Albosta M, Jamal S, Singh J, *et al.* COVID-19 and hypercoagulability: A review. Clin Appl Thromb Hemost 2020;26:1076029620962853. doi: 10.1177/1076029620962853.
40. Medcalf RL, Keragala CB, Myles PS. Fibrinolysis and COVID-19: A plasmin paradox. J Thromb Haemost 2020;18:2118-22.
41. Kumar J, Meena J, Yadav A, Yadav J. Radiological findings of COVID-19 in children: A systematic review and meta-analysis. J Trop Pediatr 2021;67:fmaa045. doi: 10.1093/tropej/fmaa045.
42. RECOVERY: Randomised Evaluation of COVID-19 Therapy. Low-cost dexamethasone reduces death by up to one-third in hospitalized patients with severe respiratory complications of COVID-19. Available from: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19. [Last accessed on 2022 February 18].
43. National Institutes of Health. Therapeutic management of non-hospitalized adults with COVID-19. Updated February 1, 2022. Available from: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management/. [Last accessed on 2022 March 30].
44. Ray A, Goel A, Wig N. Corticosteroids for treating mild COVID-19: Opening the floodgates of therapeutic misadventure. QJM 2021;114:541-2.
45. Herold T, Jurinovic V, Arnreich C, Lipworth BJ, Hellmuth JC, von Bergwelt-Baildon M, *et al.* Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. J Allergy Clin Immunol 2020;146:128-36.e4.
46. Song SN, Yoshizaki K. Tocilizumab for treating rheumatoid arthritis: An evaluation of pharmacokinetics/pharmacodynamics and clinical efficacy. Expert Opin Drug Metab Toxicol 2015;11:307-16. doi: 10.1517/17425255.2015.992779.
47. U.S. Food and Drug Administration, 2020 FDA Approves First Treatment for COVID-19. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19. [Last accessed on 2021 May 22].
48. Rezagholizadeh A, Khiali S, Sarbakhsh P, Entezari-Maleki T. Remdesivir for treatment of COVID-19; an updated systematic review and meta-analysis. Eur J Pharmacol 2021;897:173926.
49. Najafinejad M, Cheraghali F, Aghcheli B, Rajabi A, Barati L, Naziri H, *et al.* COVID-19 in pediatrics: Demographic, clinical, laboratory, and radiological characteristics of infected patients with SARS-CoV-2. Front Pediatr 2021;9:808187. doi: 10.3389/fped. 2021.808187.
50. Nakagawara K, Chubachi S, Namkoong H, Tanaka H, Lee H, Azekawa S, *et al.* Impact of upper and lower respiratory symptoms on COVID-19 outcomes: A multicenter retrospective cohort study. Respir Res 2022;23:315. doi: 10.1186/s12931-022-02222-3.
51. Bickler PE, Feiner JR, Lipnick MS, McKleroy W. "Silent" presentation of hypoxemia and cardiorespiratory compensation in COVID-19. Anesthesiology 2021;134:262-9.
52. Gidari A, De Socio GV, Sabbatini S, Francisci D. Predictive value of National Early Warning Score 2 (NEWS2) for intensive care unit admission in patients with SARS-CoV-2 infection. Infect Dis (Lond) 2020;52:698-704.
53. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, *et al.* Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. BMJ 2020;369:m1966.
54. Berdahl CT, Glennon NC, Henreid AJ, Torbati SS. The safety of home discharge for low-risk emergency department patients presenting with coronavirus-like symptoms during the COVID-19 pandemic: A retrospective cohort study. J Am Coll Emerg Physicians Open 2020;1:1380-5. doi: 10.1002/emp2.12230.
55. Jafarzadeh A, Jafarzadeh S, Nozari P, Mokhtari P, Nemati M. Lymphopenia an important immunological abnormality in patients with COVID-19: Possible mechanisms. Scand J immunol 2021;93:e12967.
56. Wong RS, Wu A, To KF, Lee N, Lam CW, Wong CK, *et al.* Haematological manifestations in patients with severe acute respiratory syndrome: Retrospective analysis. BMJ 2003;326:1358-62.
57. Jenne CN, Wong CH, Zemp FJ, McDonald B, Rahman MM, Forsyth PA, *et al.* Neutrophils recruited to sites of infection protect from virus challenge by releasing neutrophil extracellular traps. Cell Host Microbe 2013;13:169-80.
58. Nicolai L, Leunig A, Brambs S, Kaiser R, Weinberger T, Weigand M, *et al.* Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. Circulation 2020;142:1176-89. doi: 10.1161/CIRCULATIONAHA.120.048488.
59. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical Characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9. doi: 10.1001/jama. 2020.1585.
60. Mazzoni A, Salvati L, Maggi L, Capone M, Vanni A, Spinicci M, *et al.* Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. J Clin Invest 2020;130:4694-703.
61. Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, *et al.* Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 2020;11:827.
62. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, *et al.* Transplantation of ACE2(-) mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020;11:216-8.
63. Ouyang Y, Yin J, Wang W, Shi H, Shi Y, Xu B, *et al.* Downregulated gene expression spectrum and immune responses changed

during the disease progression in patients with COVID-19. Clin Infect Dis 2020;71:2052-60.

64. Santa Cruz A, Mendes-Frias A, Oliveira AI, Dias L, Matos AR, Carvalho A, *et al.* Interleukin-6 is a biomarker for the development of fatal severe acute respiratory syndrome coronavirus 2 pneumonia. Front Immunol 2021;12:613422. doi: 10.3389/fimmu.2021.613422.
65. Mahmood SBZ, Majid H, Arshad A, Zaib-Un-Nisa, Niazali N, Kazi K, *et al.* Interleukin-6 (IL-6) as a predictor of clinical outcomes in patients with COVID-19. Clin Lab 2023;69:1126. doi: 10.7754/Clin.Lab.2022.220741.
66. Hafez W, Nasa P, Khairy A, Jose M, Abdelshakour M, Ahmed S, *et al.* Interleukin-6 and the determinants of severe COVID-19: A retrospective cohort study. Medicine (Baltimore) 2023;102:e36037. doi: 10.1097/MD.0000000000036037.