





Clinical Profile and Risk Factors for Severe Disease in 402 Children Hospitalized with SARS-CoV-2 from India: Collaborative Indian Pediatric COVID Study Group


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ABSTRACT

Introduction: There is a lack of large multicentric studies in children with COVID-19 from developing countries. We aimed to describe the clinical profile and risk factors for severe disease in children hospitalized with COVID-19 from India.

Methods: In this multicentric retrospective study, we retrieved data related to demographic details, clinical features, including the severity of disease, laboratory investigations and outcome.

Results: We included 402 children with a median (IQR) age of 7 (2–11) years. Fever was the most common symptom, present in 38.2% of children. About 44% had underlying comorbidity. The majority were asymptomatic (144, 35.8%) or mildly symptomatic (219, 54.5%). There were 39 (9.7%) moderate-severe cases and 13 (3.2%) deaths. The laboratory abnormalities included lymphopenia 25.4%, thrombocytopenia 22.1%, transaminitis 26.4%, low total serum protein 34.7%, low serum albumin 37.9% and low alkaline phosphatase 40%. Out of those who were tested, raised inflammatory markers were ferritin 58.9% (56/95), c-reactive protein 33.3% (41/123), procalcitonin 53.5% (46/86) and interleukin-6 (IL-6) 76%. The presence of fever, rash, vomiting, underlying comorbidity, increased total leucocyte count, thrombocytopenia, high urea, low total serum protein and raised c-reactive protein was factors associated with moderate to severe disease.

Conclusion: Fever was the commonest symptom. We identified additional laboratory abnormalities, namely lymphopenia, low total serum protein and albumin and low alkaline phosphatase. The majority of the children were asymptomatic or mildly symptomatic. We found high urea and low total serum protein as risk factors for moderate to severe disease for the first time.

KEYWORDS: COVID-19, SRAS-CoV-2, children, ferritin, IL-6

INTRODUCTION

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in Wuhan, China, in December 2019 [1]. Globally, about 134 million of people were affected and about 2.8 million died by 10 April 2021 [2]. Children contribute to a small proportion of the caseload as well mortality; however, with the pandemic entering into its peak, many children are getting diagnosed with COVID-19 [3, 4]. As per the available literature, children have a relatively mild disease as compared to adults with better prognosis and lower mortality (<0.1% vs. 5–15%) [5, 6]. In a systematic review including children beyond the neonatal period, the authors concluded that screening algorithm in adults using fever and cough as important manifestations (present in >80% cases) is likely to miss 40–50% of children with COVID-19 [6]. Therefore, screening algorithm for children should include both respiratory and gastrointestinal symptoms. In a study from Eastern India ($n = 41$), 27% of children were asymptomatic, fever was seen in only

21% and 15% of children required intensive care with only one death (2.5%) [7]. There have been few single-centre studies from India with small sample sizes that have tried to evaluate the clinical profile and outcome of COVID-19 in children during the early or mid-part of the pandemic [7, 8]. Another single-centre small study reported severe and fatal cases of COVID-19 in children [9]. There is a lack of large multicentric studies describing the clinical profile of children infected with SARS-CoV-2 from India. Further, there are limited studies assessing risk factors for severe disease, particularly from developing countries. This multicentric study aimed to describe the clinical profile and risk factors for severe disease in children hospitalized with COVID-19 from India.

METHODS

Study population

In this retrospective study, we retrieved children's data from birth to 12 years of age infected with SARS-CoV-2 from March to November 2020.

Children with a positive RT-PCR or cartridge-based nucleic acid amplification test (CBNAAT) for SARS-CoV-2 from secretions of the upper or lower respiratory tract were eligible for inclusion in the study. We also included children with clinical profile suggestive of COVID-19 and positive for SARS-CoV-2 antibody. Tests for SARS-CoV-2 were performed as per Indian Council of Medical Research (ICMR) guidelines [10]. In brief, the following were tested: persons with influenza-like illness (ILI) symptoms (fever and cough) who had international travel in the last 14 days, had contacts with confirmed COVID-19 case, or are health care workers; all patients with a severe acute respiratory infection, asymptomatic high-risk contact and hospitalized patients developing ILI [10]. Besides, all hospitalized children were tested for SARS-CoV-2 as per institutional policy. A few children were also tested as part of family screening. The study included children who were hospitalized with COVID-19. Initially, all cases of COVID-19 were being hospitalized. The Government of India recommended home isolation for patients who were asymptomatic or mildly symptomatic without any comorbidity from July 2020 onwards. After that, only moderate to severe cases, children with comorbidities and those for whom home isolation was not feasible were hospitalized. We did not include children who were home isolated. We did not include cases of multisystem inflammatory syndrome of children (MIS-C) in this report.

Data collection

We collected data from five centres of India: All India Institute of Medical Sciences, New Delhi (site 1); All India Institute of Medical Sciences, Bhubaneswar, Odisha (site 2); Karnataka Institute of Medical Sciences Hubli, Karnataka (site 3); All India Institute of Medical Sciences, Jodhpur, Rajasthan (site 4); and Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Jammu and Kashmir (site 5), representing different zones of India. Investigations were performed as decided by the treating team as per the clinical condition. There were no specific national guidelines for the treatment of COVID-19 in the paediatric age group, though some guidelines exist in literature [11]. In most

cases, supportive treatment was used, and medications were used on case to case basis.

A data collection form was created using Microsoft office access and circulated to all centres for uniform data collection. We compiled all data at site 1. Data were collected regarding demographic details, source of contact, family history, clinical features with duration, various laboratory parameters, imaging findings and children's outcome if known. Outcome measures were descriptive statistics related to demographic, clinical and laboratory parameters in children. We classified the severity of the disease as per WHO guidelines [12]. To assess risk factors, we grouped all children into two groups: one with asymptomatic and mildly symptomatic children and the other group with a moderate, severe and critical illness (moderate to severe group).

Definitions of laboratory abnormalities

We defined the abnormal laboratory parameters as follows [13]: anaemia-haemoglobin <11.5 gm/dl, severe anaemia-haemoglobin <7 g/dl, leukopenia-total leukocyte counts (TLC) <4000 cells/mm³, leucocytosis-TLC >12 000 cells/cm²; low % of lymphocytes <25%; lymphopenia-absolute lymphocyte count <1500 cells/cm²; thrombocytopenia <150 000/mm³; transaminitis-serum glutamic-oxaloacetic transaminase (SGOT) or serum glutamic-pyruvic transaminase (SGPT) >45 IU/l; hypoalbuminaemia-albumin < 3.5 g/dl; hyperbilirubinaemia >1.0 mg/dl except neonates; raised C-reactive protein (CRP) >6 mg/l; raised urea >40 mg/dl; raised creatinine >0.9 mg/dl; increased ferritin >60 ng/ml (till 9 years) and >300 ng/ml (10–12 years); increased lactase dehydrogenase (LDH) >500 U/l; alkaline phosphatase-low <140 U/l, high >560 U/l; hyponatraemia-sodium <134 mmol/l; hypernatraemia-sodium >144 mmol/l; hypokalaemia-potassium <3.3 mmol/l; hyperkalaemia-potassium >4.6 mmol/l; low total protein <6.1 g/dl; deranged international normalized ratio >1.5; raised aPTT > 40 s; raised procalcitonin (PCT) ≥0.5 ng/ml, raised IL-6 >7 pg/ml; raised D-dimer >1 µg/ml; high triglyceride >300 mg/dl; and low fibrinogen levels <150 mg/dl.

The study was approved by the institute ethics committee (IEC) at each site.

Statistical analysis

We analysed data using STATA version 12.0 (StataCorp LP, College Station, TX, USA). We reported categorical data as a percentage (%) and continuous parameters as mean \pm SD if data were normally distributed or median (IQR) if data had a skewed distribution. We classified the patients into two groups to assess risk factors for severe disease: one group with asymptomatic and mildly symptomatic and second group with moderate, severe and critical illness. We compared clinical and laboratory parameters among both groups using bivariate analysis. We compared means using Student's *t*-test and medians using Mann–Whitney test. We did logistic regression to identify risk factors for moderate to severe disease. We considered factors for logistic regression those were significant in bivariate analysis. As many data were missing, we used multiple imputation method for logistic regression. We used standardized *z*-score for parameters that had multiple zeroes after decibel in coefficient. We considered a *p*-value of <0.05 as significant.

RESULTS

Demography

We enrolled a total of 402 children in the study. There were 190 (47.3%) children from site 1 and 74 (18.4%), 68 (16.9%), 60 (14.9%) and 10 (2.5%) from sites 2, 3, 4 and 5, respectively. Demographic details of included children are shown in Table 1. Eleven (2.8%) were neonates, and 45 (11.4%), 118 (29.9%) and 221 (55.9%) were 1 month to <12 months, 1–5 years and more than 5 years of age, respectively. More than 50% of children had contact with known COVID-19 patients, and about 44% of children had some underlying comorbidity. Malignancy (leukaemia and other malignancy) followed by cardiac disease was the most common underlying comorbidity (Table 1).

Clinical features

Fever was the most common clinical presentation, but it was present only in 38.2% of children. Other common symptoms were cough and sore throat, present in about 20% of children. Pain abdomen, vomiting and loose motions each were present in $<10\%$ of

children (Table 1). The median duration of symptoms at presentation was 2–4 days.

Table 2 shows the laboratory investigations in included children with the proportion of children having abnormal values. About 18% of children (21 out of 113 in whom chest X-ray was performed) had abnormal chest X-ray findings, and there were bilateral infiltrates in most of the abnormal X-rays. One child had right lung collapse (having a foreign body in the right main bronchus) and infiltrates on the left side. Computed tomography chest findings were available for the same child with foreign body aspiration, and it showed ground-glass opacities on the left side suggestive of COVID-19 pneumonia. Serum fibrinogen and triglyceride levels were available in 28 and 24 children, and all were within normal limits.

Treatment and outcome

The majority of symptomatic children received supportive therapy. Asymptomatic children did not receive any treatment. Some children received additional therapy, as shown in Table 3. Forty children received azithromycin, mainly from site 2.

The severity of disease and outcome of children are shown in Table 4. The majority of children had mild disease, and about 10% had moderate to severe disease. The average duration of hospital stay was ten days. The majority of children survived; 13 (3.2%) children died; all were having an underlying comorbidity [five CNS disease (tubercular meningitis, seizure disorder, glioma, West syndrome and GM1 gangliosidosis), three congenital cyanotic heart disease (one was the case of Down syndrome), two rheumatic heart disease, one acute leukaemia, one Wilson disease and one steroid-resistant nephrotic syndrome with type 1 diabetes].

Risk factors for moderate-severe disease

In bivariate analysis, the presence of fever, rash, diarrhoea, vomiting and underlying illness were risk factors for moderate-severe disease (Table 5). Children with severe disease have significantly high total leukocyte counts, urea, high SGOT, ferritin, CRP, PCT, PT, aPTT and LDH and low lymphocyte percentage, platelet counts, low serum sodium, total serum protein and serum albumin compared to mild cases (Table 6). The results of logistic regression are

TABLE 1. Demographic and clinical characteristics of children with SARS-CoV-2

Characteristics ^a	Value
Age (years), median (IQR)	7 (2–11)
Gender, M:F	247:155
History of foreign travel (<i>N</i> = 268), <i>n</i> (%)	12 (4.5)
Contact with known COVID patient (<i>N</i> = 227), <i>n</i> (%)	134 (59.0)
Coming from hot spot (<i>N</i> = 93), <i>n</i> (%)	27 (29.0)
Presence of underlying disease (<i>N</i> = 318), <i>n</i> (%)	142 (44.7)
Type of underlying disease, <i>n</i> (%), out of all underlying disease)	
Cardiac disease	24 (16.9)
Leukaemia	23 (16.2)
Gastrointestinal disease	17 (11.8)
Malignancy, other than leukaemia	13 (9.1)
Renal disease	13 (9.1)
Haematological disease	10 (7.0)
CNS disease	10 (7.0)
Rheumatologic disease	8 (5.6)
Respiratory disease	7 (4.9)
Immunodeficiency	4 (2.8)
Others (miscellaneous)	13 (9.1)
Clinical features	
Fever (<i>N</i> = 366), <i>n</i> (%)	140 (38.2)
Cough (<i>N</i> = 365), <i>n</i> (%)	76 (20.8)
Coryza (<i>N</i> = 252), <i>n</i> (%)	32 (12.7)
Sore throat (<i>N</i> = 250), <i>n</i> (%)	49 (19.6)
Breathing difficulty (<i>N</i> = 385), <i>n</i> (%)	30 (7.8)
Rash (<i>N</i> = 243), <i>n</i> (%)	13 (5.4)
Pain abdomen (<i>N</i> = 177), <i>n</i> (%)	10 (5.6)
Loose stools (<i>N</i> = 387), <i>n</i> (%)	24 (6.2)
Vomiting (<i>N</i> = 386), <i>n</i> (%)	34 (8.8)
Loss of taste (<i>N</i> = 182), <i>n</i> (%)	3 (1.6)
Loss of smell (<i>N</i> = 182), <i>n</i> (%)	2 (1.1)
Feeding difficulty (<i>N</i> = 190), <i>n</i> (%)	5 (2.6)

^aIn the first column, *N* indicates the number of children for which that particular data are available.

shown in Table 7. On regression analysis, fever, rash, vomiting, underlying illness, TLC, serum urea, total serum protein, CRP and LDH were significant risk factors for severe disease.

DISCUSSION

In this multicentric study, we described the clinical and laboratory profile of 402 children infected with SARS-CoV-2. It affected all age groups, and fever

was the most common presenting complaint. Lymphopenia, thrombocytopenia, transaminitis, low total serum protein and albumin and low alkaline phosphatase were common laboratory abnormalities. Among inflammatory markers, IL-6 and PCT were predominantly raised. The majority had mild disease, and there was 3.2% mortality. The presence of fever, rash, vomiting, underlying comorbidity, increased TLC, thrombocytopenia, high urea, low total serum

TABLE 2. Laboratory parameters in children infected with SARS-CoV-2 (N = 402)

Laboratory parameter ^a	Median (IQR)/mean (SD) ^b	Proportion of children having abnormal values, n (%)
Haemoglobin (Hb), g/dl (N = 268)	11.2 (2.8) ^b	Hb <11.5 132 (49.3) Hb <7 19 (7.1)
Total leucocyte counts/mm ³ (N = 262)	7975 (5300–12 200)	TLC <4000 25 (9.5) TLC >12 000 67 (25.6)
Neutrophil, % (N = 196)	58 (39.1–67)	Neutrophils <1500 29 (14.8)
Lymphocytes, % (N = 196)	32 (21.5–46.2)	Lymphocytes <25% 60 (30.6) Lymphocytes <1500 48 (25.4)
Platelet counts/mm ³ (N = 263)	260 000 (159 000–340 000)	Platelets <150 000 58 (22.1)
Urea, mg/dl (N = 270)	21.2 (16–28)	Urea >40 26 (9.6)
Creatinine, mg/dl (N = 208)	0.5 (0.4–0.6)	Creatinine >0.9 13 (6.3)
Total bilirubin, mg/dl (N = 196)	0.6 (0.37–0.8)	Bilirubin >1 (N = 188 after excluding neonate) 32 (17.0)
SGOT, IU/dl (N = 169)	33 (24–46)	SGOT >45 45 (26.8)
SGPT, IU/dl (N = 173)	24 (16–36)	SGPT >45 29 (16.9)
Total protein, g/dl (N = 173)	6.4 (1.0) ^b	Total protein <6.1 60 (34.7)
Serum albumin, g/dl (N = 177)	3.6 (0.8) ^b	Albumin <3.5 67 (37.9)
Alkaline phosphatase, IU/dl (N = 95)	172 (105–248)	ALP <140 38 (40) ALP >560 4 (4.2)
Ferritin, ng/ml (N = 95)	144 (80.1–290)	Ferritin >60 56 (58.9)
C-reactive protein, mg/dl (N = 123)	1 (0.5–13.8)	CRP >6 41 (33.3)
Procalcitonin (PCT), ng/ml (N = 86)	0.5 (0.04–0.7)	PCT >0.5 46 (53.5)
PT, s (N = 53)	14 (12.9–16.7)	PT >14.5 22 (41.5)
INR (N = 49)	1.1(1.02–1.27)	INR >1.5 6 (12.2)
aPTT, s (N = 48)	30 (27–33.8)	aPTT >40 6 (12.5)
LDH (N = 63)	243 (190–318)	
D-dimer, µg/ml (N = 73)	0.3 (0–0.46)	D-dimer >1 13 (17.8)
IL-6, pg/ml (N = 50)	32.7 (7.7–103.9)	IL-6 >7 38 (76%)

SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; PT, prothrombin time; INR, international normalized ratio; LDH, lactate dehydrogenase; IL-6, interleukin-6.

^aIn the first column, N indicates the number of children for which that particular data are available. ^bmean(SD)

protein and raised CRP were significant features for moderate to severe disease.

In a study from West Bengal, India (N = 41), the median age was 1 year [7], whereas we had a median age of 7 years. But, fever was the most common symptom as in our study. A recent systematic review, including 27 paediatric studies, reported fever and cough in about 50% of children [6], but we

documented fever in about 38% and cough in about 20% of children. Another systematic review had reported fever and cough in 48% (95% CI 39–56%) and 39% (95% CI 30–48%) children, respectively [14]. A few studies from China reported fever in 30–100% of children with SARS-CoV-2 infection [15]. Studies from the USA and European countries had reported fever in about 50% of children [16–18]. A

TABLE 3. Treatment received in children infected with SARS-CoV-2

Nature of treatment (data available) ^a	Number (%) of children, received the treatment
Medications	
Antibiotics, other than azithromycin (<i>N</i> = 64)	5 (7.8)
Azithromycin (<i>N</i> = 84)	40 (47.6)
Respiratory support	
Oxygen (<i>N</i> = 131)	11 (8.4)
Non-invasive ventilation (<i>N</i> = 69)	2 (2.9)
HHHFNC (<i>N</i> = 68)	3 (4.4)
Mechanical ventilation (<i>N</i> = 233)	14 (6.0)
Vasoactive support	
Inotropes (<i>N</i> = 174)	19 (10.9)
Immune modulators	
HCQ (<i>N</i> = 201)	11 (5.5)
Remdesivir (<i>N</i> = 129)	3 (2.3)
IVIg (<i>N</i> = 142)	4 (2.8)
Steroids (<i>N</i> = 136)	11 (8.1)

HHHFNC, heated humidified high flow nasal cannula; HCQ, hydroxychloroquine.

^aIn the first column, *N* indicates the number of children for which that particular data are available.

TABLE 4. Severity of disease and outcome of children infected with SARS-CoV-2

Characteristics ^a	Values
Severity of disease (<i>N</i> = 402)	
Asymptomatic, <i>n</i> (%)	144 (35.8)
Mild disease, <i>n</i> (%)	219 (54.5)
Moderate to severe disease, <i>n</i> (%)	39 (9.7)
Duration of hospital stay, days, median (IQR), <i>N</i> = 305	10 (7–12), range 1–40
Outcome (<i>N</i> = 402)	
Survived, <i>n</i> (%)	385 (95.8)
Died, <i>n</i> (%)	13 (3.2)
LAMA, <i>n</i> (%)	4 (1)

LAMA, left against medical advice.

^aIn the first column, *N* indicates the number of children for which that particular data are available.

systematic review reported fever and cough in 59.1% and 55.9% children, respectively [19]. Another systematic review reported fever and cough in 53% (95% CI 45–61%) and 39% (95% CI 30–47%), respectively [20]. The two systematic reviews reported asymptomatic infection in 19.3% [19] and 18% [20] children, respectively. To summarize, fever and

cough are most common symptoms of COVID-19 in children, but these are present only in about half of the patients, suggesting that children may be asymptomatic or may present without fever and cough. Further, the variability of symptoms may be due to different geography and differences in the testing strategy. Some centres or countries might be

TABLE 5. Clinical features for moderate-severe disease in children infected with SARS-CoV-2

Parameter	Asymptomatic/mildly symptomatica (N = 363)	Moderate to severea (N = 39)	p-value
Age, years, median (IQR)	6 (2–10.8)	8 (2–12.9)	0.310
Male:female	221:142	26:13	0.481
Fever, n (%)	117 (35.5)	25 (69.4)	<0.001
Cough, n (%)	70 (21.2)	8 (22.9)	0.821
Coryza, n (%)	30 (13.4) (N = 224)	2 (7.1) (N = 28)	0.349
Sore throat, n (%)	47 (21.1) (N = 223)	2 (7.4) (N = 27)	0.091
Rash, n (%)	8 (3.8) (N = 213)	5 (16.7) (N = 30)	0.003
Pain abdomen, n (%)	8 (5.2) (N = 153)	2 (8.3) (N = 24)	0.540
Diarrhoea, n (%)	17 (4.8) (N = 351)	7 (19.4) (N = 36)	0.001
Vomiting, n (%)	22 (6.3) (N = 351)	12 (34.3) (N = 35)	<0.001
Underlying illness, n (%)	112 (39.7) (N = 282)	31 (83.8) (N = 37)	<0.001

^aIn second and third columns, N indicates the number of children for which that particular data are available. Bold p-value indicates significant p-value

testing only symptomatic children with history of exposure to COVID patients, whereas others might be testing all children with exposure to COVID patients irrespective of symptoms.

We had about 30% of children who were asymptomatic when detected. About 4–27% of asymptomatic cases among children have been reported from different countries [21, 22]. It suggests that percentage of asymptomatic children varies depending on test strategy: testing on symptomatic children or all exposed children.

In a systematic review, the most common laboratory abnormalities were leukopenia in 16% (95% CI 11–22) children, followed by raised SGOT in 15% (95% CI 9–21) [6]. Our study showed more lymphopenia than leukopenia, and we have low total serum protein, albumin and ALP in the large number of children, and it was a new finding in our study. The same systematic review reported raised CRP and PCT in 16% (95% CI 10–22) and 25% (95% CI 9–42) children [6]. Another systematic review reported raised PCT, IL-6, creatine kinase and D-dimer levels in children with COVID-19 [19]. Our study revealed raised CRP and PCT in a high proportion of children tested (Table 2). Increased inflammatory parameters in this study may be explained by the fact that we included on hospitalized children. There were only 5 deaths out of 4476

included patients in the review [6]. Our study had higher mortality (13, 3.2%). The possible explanation for high mortality may be that we included only hospitalized children. Further, all five centres are tertiary care referral centres where we got mostly referred cases due to sickness. Lastly, many children had underlying comorbidity in our cohort and contributed high mortality. Clinical and laboratory features for severe disease COVID-19 are sparingly described. We identified that fever, rash, vomiting, underlying illness, increased TLC, thrombocytopenia, high urea, low total serum protein and raised CRP were significant risk factors for severe disease. Dong, *et al.* [21] reported younger (age <1 year) as a risk factor for severe disease. Oualha, *et al.* [9] and Shekerdemian, *et al.* [23] also found the presence of underlying disease as a risk factor for severe disease as in this study. Bhumbra, *et al.* [24] reported younger (<2 years) and older (15–18 years) age, Hispanic children, males, thrombocytopenia and raised CRP as risk factors for severe disease. A recent review summarized the risk factors for severe disease in children; most of the studies in the review reported young age and underlying medical condition as risk factors, whereas a few studies reported adolescents and young adults, higher levels of CRP, PCT and pro-BNP, lower platelet counts, increased ferritin, increased D-dimer, decrease lymphocyte count, transaminitis, cytokine

TABLE 6. Laboratory parameters for severe disease in children infected with SARS-CoV-2

Parameter	Asymptomatic/mildly symptomatic (N = 363)	Moderate to severe (N = 39)	p-value
Haemoglobin, g/dl, mean ± SD	11.3 ± 2.8 (N = 241)	10.6 ± 3.2 (N = 27)	0.263
TLC/cm ² , median (IQR)	7731 (5120–11 900) (N = 236)	10 970 (9100–18 600) (N = 26)	<0.001
Lymphocyte %, median (IQR)	33 (24–46.5) (N = 171)	19.5 (12–41) (N = 25)	0.024
Platelet counts/cm ² , median (IQR)	267 000 (170 000–340 000) (N = 237)	150 000 (79 000–268 000) (N = 26)	0.032
Urea, mg/dl, median (IQR)	20 (16–27) (N = 236)	29.5 (21–49) (N = 34)	<0.001
Creatinine, mg/dl, median (IQR)	0.5 (0.4–0.6) (N = 174)	0.51 (0.4–0.9) (N = 34)	0.145
Sodium, mEq/l, mean ± SD	136.9 ± 4.7 (N = 111)	134.7 ± 6.9	0.046
Total bilirubin, mg/dl, median (IQR)	0.6 (0.37–0.8) (N = 163)	0.62 (0.31–1.38) (N = 33)	0.292
SGOT, IU/l, median (IQR)	33 (24–44) (N = 145)	40.5 (28.0–87) (N = 24)	0.042
SGPT, IU/l, median (IQR)	23.6 (16–34) (N = 148)	28 (18–69) (N = 25)	0.132
Total serum protein, g/dl, mean ± SD	6.6 ± 0.9 (N = 150)	5.3 ± 1.2 (N = 23)	<0.001
Serum albumin, g/dl, mean ± SD	3.7 ± 0.8 (N = 152)	2.8 ± 0.8 (N = 25)	<0.001
Ferritin, ng/ml, median (IQR)	132 (80.1–196) (N = 77)	397.9 (148–879.2) (N = 18)	0.002
C-reactive protein, mg/dl median (IQR)	0.52 (0.45–12) (N = 106)	4.6 (1.4–30.4) (N = 17)	0.005
PCT, ng/dl, median (IQR)	0.3 (0.02–0.5) (N = 72)	0.8 (0.5–1.5) (N = 14)	<0.001
PT, s, median (IQR)	13.8 (12.8–15) (N = 38)	16.7 (13–20.5) (N = 15)	0.035
INR, median (IQR)	1.1 (1.0–1.2) (N = 36)	1.2 (1.1–1.5) (N = 13)	0.107
aPTT, s, median (IQR)	30 (27–32.2) (N = 35)	34.1 (31.6–53.1) (N = 13)	0.012
LDH, median (IQR)	233 (185.5–299.5) (N = 52)	291 (228–531) (N = 11)	0.037
D-dimer, µg/ml, median (IQR)	0.3 (0.28–0.44) (N = 64)	0.34 (0.3–1.1) (N = 9)	0.435
IL-6, pg/ml	21.8 (7.7–103.9) (N = 38)	59.7 (10.2–108.8) (N = 12)	0.733

TLC, total leucocyte counts; SGOT, serum glutamic-oxalacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; PCT, procalcitonin; PT, prothrombin time; INR, international normalized ratio; aPTT, activated partial thromboplastin time; LDH, lactate dehydrogenase; IL-6, interleukin-6.

^aIn the second and third column, N indicates the number of children for which particular data are available. Bold p-value indicates significant p-value

storm, imaging abnormalities and co-infection with RSV as the risk factors for severe disease [25]. Based on our study and literature, underlying comorbidity, thrombocytopenia and raised inflammatory markers are associated with severe disease in children. High urea and low total serum protein were not reported as risk factors for the severe disease till now. Poor nutrition in developing countries may be a possible reason for low

total serum protein and serum albumin in children with COVID-19.

The strength of this study is that it is one of the largest series on COVID-19 in the paediatric age group. Second, we have a variety of laboratory investigations in our cohort. Inflammatory markers in paediatric age group had been reported sparingly. The study had a few limitations also. Being a

TABLE 7. Logistic regression of features associated with moderate-severe disease in children with SARS-CoV-2

Risk factor	Coefficient (95% CI)	Odds ratio (95% CI)	p-value
Fever	1.47 (1.20 to 1.73)	4.36 (3.33–5.67)	<0.001
Rash	1.85 (1.49 to 2.21)	6.39 (4.48–9.13)	<0.001
Diarrhoea	0.22 (–0.26 to 0.69)	1.24 (0.77–2.00)	0.367
Vomiting	1.74 (1.42 to 2.06)	5.74 (4.17–7.92)	<0.001
Underlying illness	2.18 (1.80 to 2.56)	8.85 (6.07–12.91)	<0.001
TLC ^a	0.20 (0.08 to 0.31)	1.21 (1.08–1.37)	0.001
Lymphocyte % ^a	0.02 (–0.08 to 0.13)	1.02 (0.92–1.14)	0.670
Platelet count ^a	–0.06 (–0.18 to 0.05)	0.94 (0.83–1.05)	0.270
Urea	0.03 (0.02 to 0.04)	1.03 (1.02–1.04)	<0.001
Sodium	–0.02 (–0.04 to 0.01)	0.98 (0.96–1.01)	0.134
SGOT ^a	–0.02 (–0.17 to 0.13)	0.98 (0.84–1.15)	0.814
Total protein	–0.45 (–0.65 to –0.26)	0.64 (0.52–0.77)	<0.001
Albumin	0.13 (–0.12 to 0.37)	1.14 (0.89–1.45)	0.283
Ferritin ^a	0.16 (–0.01 to 0.32)	1.17 (0.99–1.38)	0.057
C-reactive protein ^a	0.17 (0.01 to 0.33)	1.19 (1.01–1.39)	0.033
PCT ^a	0.05 (–0.06 to 0.15)	1.05 (0.94–1.17)	0.390
PT ^a	–0.20 (–0.79 to 0.38)	0.81 (0.45–1.47)	0.499
aPTT ^a	0.57 (–0.03 to 1.17)	1.76 (0.97–3.22)	0.062
LDH ^a	–0.20 (–0.33 to –0.07)	0.81 (0.72–0.93)	0.003

TLC, total leucocyte counts; SGOT, serum glutamic-oxalacetic transaminase; PCT, procalcitonin; PT, prothrombin time; aPTT, activated partial thromboplastin time; LDH, lactase dehydrogenase.

^aWe used standardized z-score for these parameters as there were multiple zeroes after decimal. Bold p-value indicates significant p-value

retrospective study, few clinical and laboratory data were missing. Further, laboratory tests were performed mostly in sick patients. It may overestimate the prevalence of observations in this study compared to community based studies or studies enrolling both hospitalized and non-hospitalized children.

CONCLUSION

COVID-19 can affect children of all age group. Fever was the most common clinical feature. The majority of children were asymptomatic or mildly symptomatic. Lymphopenia, thrombocytopenia, transaminitis, low total serum protein and albumin and low alkaline phosphatase were common laboratory abnormalities. Fever, rash, vomiting, underlying illness, high urea, increased TLC, thrombocytopenia, high urea, low total serum protein and raised CRP were significant features for moderate-severe disease.

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