

Original Research Article

Profile, risk factors for severe disease and predictors of mortality in children with COVID-19: Experience from a tertiary COVID-care center in India

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ABSTRACT

Background: Knowledge of pediatric COVID-19 is important to determine those at risk for severe disease and mortality. There is limited data on risk factors for development of severe disease and predictors of mortality amongst children with COVID-19, especially from the developing nations. We aimed to study the profile, risk factors for severe COVID-19 and predictors of mortality in children with laboratory confirmed COVID-19.

Methods: This prospective observational study was conducted from April to September 2020 in the Department of Pediatrics of a referral COVID-care hospital in Northern-India. All children 1 month to 18 years of age, hospitalized in the Pediatrics Department and having a positive Reverse Transcriptase-Polymerase chain reaction (RT-PCR) for SARS-CoV-2 infection on their combined oro-nasopharyngeal swab were enrolled.

Results: A total of 335 SARS-CoV-2 positive children were enrolled with median age of 6 years, slight male predominance (54%) and 24.4% infants. Commonest presentations were respiratory (47.7%), gastrointestinal (33.3%) and neurological (14.9%) with moderate/severe disease in 24%, mortality in 4.8%, co-morbidities in 20.5% and co-infections in 17.9%. Risk factors for severe disease were underlying co-infection ($p=0.017$), associated tuberculosis ($p=0.0015$), associated culture positive bacterial sepsis ($p<0.001$) and being underweight ($p<0.001$). Overweight/obese children had less severe COVID-19 ($p=0.0016$). Predictors of mortality were co-infections ($p=0.0019$), hypoxia ($p<0.001$), neurological manifestations ($p=0.016$), acute respiratory distress syndrome ($p<0.001$), acute kidney injury ($p=0.05$), shock ($p<0.001$), thrombocytopenia ($p=0.021$), leucopenia ($p=0.028$), lymphopenia ($p=0.021$), high Neutrophil:Lymphocyte ratio ($p=0.02$), coagulopathy ($p=0.02$), azotemia ($p=0.038$) and raised creatinine ($p=0.05$).

Conclusions: Children with identified risk factors for severe disease and mortality should receive prioritized treatment.

Keywords: Risk factors, Predictors, Pediatrics, COVID-19, Severity

INTRODUCTION

The (severe acute respiratory syndrome- Coronavirus-2) SARS-CoV-2 pandemic since its inception has caused extensive mortality and continuing morbidity. Children have comprised less than 5% of the total published COVID-19 cases.^[1] Majority of initially published pediatric studies from China and the developed nations

reported milder symptoms and better prognosis than adults.¹⁻⁴ However, studies from India and other developing countries have reported higher rates of severe disease and mortality amongst children with COVID-19 compared to the West.⁵⁻¹⁰ As newer variants of concern emerge, knowledge of COVID-19 infection among children during the previous waves is important to determine the group of children that are at risk for severe

disease and death. Previously identified risk factors for severe COVID-19 in children include extremes of age (≥ 10 years, age < 1 year), obesity and underlying co-morbidity.¹¹ However, majority of this data is from pediatric cohorts in the developed world. There are few studies from India and other developing nations that have focussed on risk factors for severe COVID-19 in children wherein additional factors like malnourishment have been identified.^{5,12} There are fewer studies which have focussed on predictors of mortality in children with moderate to severe COVID-19.⁵ They report hypoxia at admission, multi-organ dysfunction, presence of acute kidney injury, mechanical ventilation and need for inotropic support as clinical predictors of mortality. Most research on laboratory predictors of mortality has been done on adults and the elderly. Sparse pediatric studies have reported thrombocytopenia and raised serum C-reactive protein as predictors of mortality in children with COVID-19.⁵

Aim and objectives

In this study, we aimed to study the clinic-epidemiological, laboratory and radiological profile, risk factors for development of severe COVID-19 and predictors of mortality in children with laboratory confirmed COVID-19 infection.

METHODS

This prospective observational study was conducted from April to September 2021 in the Department of Pediatrics of Maulana Azad Medical College and Lok Nayak Hospital, New Delhi which was declared an exclusive COVID-care referral hospital in Northern-India during the COVID-19 pandemic.¹³ All children and adolescents 1 month to 18 years of age, hospitalised (as per government policy) in the Pediatrics department and having a positive Reverse Transcriptase-Polymerase chain reaction (RT-PCR) for SARS-CoV-2 infection on their combined oronasopharyngeal swab were enrolled after informed consent.^{13,14} There were no exclusion criteria.

Details regarding demographic, exposure history, underlying co-morbidities, clinical manifestations, nutritional status at admission, severity of disease at presentation, treatment received and outcomes were collected in a pre-designed proforma. Discharge was done as per prevailing hospital guidelines and government policy at the time. The laboratory (hemogram, renal function test, liver function test, coagulation profile) and radiological data (Chest X-ray for characterisation of lung lesions i.e., distribution, pattern, morphology, and accompanying manifestations) were collected for patients who underwent these investigations per the departmental policy i.e., those with moderate to severe disease or those in whom an alternate diagnosis was an initial possibility. All data were reviewed by the investigators post-compilation, and any inconsistencies and data queries were clarified.

Study definitions

Definitions of close contact, tachypnea and disease severity classification (mild, moderate and severe) was based on WHO guidelines.^{15,16} Acute respiratory distress syndrome or sepsis or septic shock were included in the severe disease category. In children with isolated gastrointestinal manifestations, we categorised acute gastroenteritis with no dehydration as mild and those with severe dehydration as severe.¹⁷ Those with isolated neurological manifestations of seizures, altered sensorium, meningitis were categorised into severe disease.¹⁷ All COVID-19 RTPCR positive children with isolated symptoms of fever, fatigue, headache or anorexia were categorised into mild disease.¹⁶ COVID-19 pneumonia: Lower respiratory tract infection (LRTI) attributed to SARS-CoV-2 infection in the absence of any identified clinical or laboratory or radiologically proven respiratory co-infection. COVID-19 gastroenteritis: Gastroenteritis attributed to SARS-CoV-2 infection in the absence of any identified clinical or laboratory proven gastrointestinal co-infection. Underweight: weight for age < 3 rd centile; overweight: weight for age between 75-90 centile; obese: weight for age > 90 centile as per IAP charts. Abnormal laboratory parameters were defined as per standard Pediatrics Textbook.¹⁸ Diagnosis of concomitant illnesses were as per standard diagnostic criteria.

Statistical analysis

The data was analysed using Statistical Package for the Social Sciences (SPSS) software, version 25. A p value of < 0.05 was considered significant. The categorical responses were expressed as percentages and significance level of differences between the proportions were tested by Chi square test or Fisher's exact test as applicable. Continuous variables were assessed for normal distribution by plotting a histogram and expressed as mean with SD (normal) or median with interquartile ranges (non-normal). Significant level of differences amongst non-normally distributed variables were tested by the Mann-Whitney U tests or Kruskal Wallis test as applicable.

RESULTS

A total of 335 SARS-CoV-2 positive children and adolescents were enrolled in the study. Demographic profile of enrolled patients is elucidated in (Table 1). A median of 1 (range: 0-8 members) additional household member was positive per family of children with close contact. Most (78.2%) admissions occurred during unlockdown (1 June, 2021 to 30 September 2021).

Clinical features at presentation

Respiratory complaints (47.7%) were predominant; 28.6% of them presented with upper respiratory tract infection and 19.1% had lower respiratory tract infection of which 12.5% were COVID-19 pneumonia.

Table 1: Demographic profile of the enrolled COVID-19 positive children and adolescents (n=335).

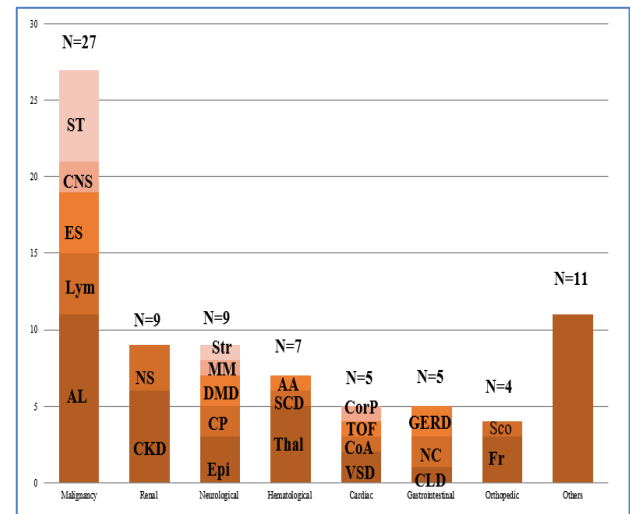
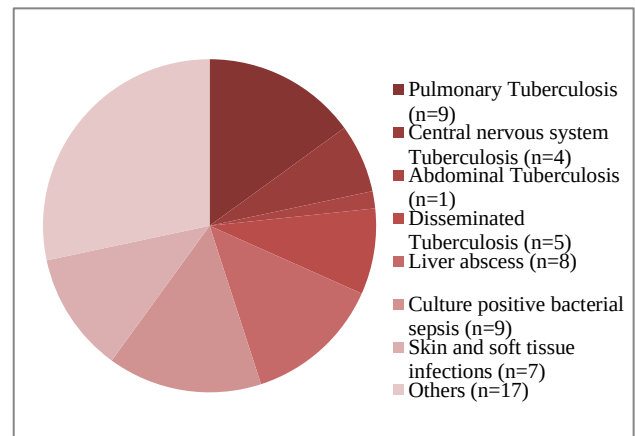
Demographic variables	Value, N (%)
Median age (years)	6 (IQR-1.5-11)
Proportion of males	181 (54)
Age (years)	
Less than 1	82 (24.4)
1-5	73 (21.7)
6-10	75 (22.4)
11-18	105 (31.3)
Reason for COVID-19 testing	
Close contact with COVID-19 positive family member with or without SARI	258 (77)
Endemic area exposure with or without SARI	33 (9.7)
Incidental detection due to pre-procedure testing	22 (6.5)
Presentation as SARI	22 (6.5)
Nutritional status (N=152)	
Underweight	51 (33.5)
Overweight	18 (11.8)
Obese	16 (10.5)

Parameter (N=335)	Number (%)	< 1 year (n=82)	1-5 years (n=73)	5-10 years (n=75)	11-18 years (n=105)	P value
Fever	204 (60.9)					0.58
Cough	119 (35.5)					0.16
Coryza	43 (12.8)					0.09
Anosmia	9 (2.7)					0.0004
Vomiting	55 (16.4)					0.94
Diarrhoea	38 (11.3)					<0.001
Pain abdomen	21 (6.2)					0.029
Anorexia	18 (5.4)					0.045
Dysgeusia	5 (1.5)					0.002
Lethargy	11 (3.9)					0.38
Excess irritability	17 (5.7)					0.96
Altered sensorium	5 (1.5)					0.81
Seizures	7 (2.1)					0.57
Headache	26 (7.8)					0.0003
Fatigue	46 (13.7)					0.0001
Bleeding	12 (3.5)					0.27
Rash	11 (3.3)					0.96
Respiratory manifestations	160 (47.7)					0.34
Upper respiratory infection	96 (28.6)					0.17
Lower respiratory infection	64 (19.1)					0.53
COVID-19 pneumonia	42 (12.5)					0.5
GIT manifestations	111 (33.1)					0.43
COVID-19 gastroenteritis	67 (20)					0.003
Neurological manifestations	50 (14.9)					0.007

Figure 1: Heat map depicting the symptom frequency in children with COVID-19 across various age groups. Deeper color depicts higher frequency of the symptom.

Gastrointestinal symptoms were present in 33% children, 20% had COVID-19 gastroenteritis and 11% had no associated respiratory manifestations. Neurological (14.9%), skin (3.3%) and bleeding manifestations (3.6%) were less common. Presentations as URTI (<5 years; p=0.03) and COVID-19 gastroenteritis (<5 years; p=0.001) were commoner in younger children. Neurological manifestations were commoner in older children (>10 years; p<0.001). The (Figure 1) depicts the frequency of symptoms of pediatric COVID-19 across various age groups. Amongst individual symptoms, fever was the commonest (60.5%) at presentation, with median duration of 3 days (IQR 1-5 days) followed by cough

(35.5%) and vomiting (15.5%). Fever (<1 year, p=0.008), cough (<5 years, p=0.04), coryza (<5 years, p=0.019) and diarrhoea (<5 years of age, p<0.001) were significantly more in younger children.

**Figure 2: Comorbidities and co-infections in enrolled children with COVID-19 (N=77).****Figure 3: Co-infections in enrolled children with COVID-19 (N=60).**

Pain abdomen (>5 years, p=0.009), anorexia (>10 years, p=0.005), headache (>10 years, p<0.001) and myalgias (>10 years, p<0.001) were commoner in the older age group. Dysgeusia (1.5%) and anosmia (2.7%) were rare and present only in children >5 years. About one-fifth children were asymptomatic. Atypical manifestations included isolated neurological manifestations in 6 children (1 Gullain Barre Syndrome, 1 febrile seizure, 1 meningitis, 3 encephalopathy), 1 isolated right shoulder arthritis, 1 newly diagnosed type 1 Diabetes mellitus with diabetic ketoacidosis, 2 children with first episode of wheeze associated lower respiratory infection, 1 child with COVID-19 hepatitis, 1 child with first episode nephrotic syndrome, 2 cases of COVID-19 dysentery. In these cases, clinical, laboratory and radiological evaluation per protocol ruled out other infections or underlying causes.

Table 2: Pediatric COVID-19 disease severity, comorbidities, co-infections, complications and outcomes (n=335).

Parameter	Total N (%)	≤1 yr (N=82)	1-5 yrs (N=73)	5-10 yrs (N=75)	10-18 yrs (N=105)	P value
Complications						
ARDS	14 (4.2)	4	1	3	6	0.54
AKI	6 (1.8)	2	1	0	3	0.51
Shock	15 (4.5)	5	1	3	6	0.46
CHF	4 (1.2)	0	1	1	2	0.68
Myocarditis	5 (1.5)	1	1	0	3	0.47
MISC	10 (2.9)	2	2	4	2	0.58
Super added bacterial infections	5 (1.5)	0	0	1	4	0.10
Co-morbidities	75 (22.4)	10	14	20	31	0.02
Co-infections	60 (17.9)	11	8	15	26	0.06
Disease severity						
Mild	185 (55.2)	45	40	43	57	0.98
Moderate	38 (11.3)	11	7	8	12	0.89
Severe	44 (13.1)	12	9	8	15	0.86
Outcomes						
Death	16 (4.7)	4	2	2	8	0.35

Co-morbidities and co-infections

There were 77 identified comorbidities present in 69 children (20.5%) with 6 children having more than 1 comorbidity. There were 60 identified co-infections of which tuberculosis was the commonest. Five of these 60 infections were acquired after 48 hours of hospital stay and were labelled as secondary bacterial co-infections. Co-morbidities ($p=0.03$), co-infections (<0.001) and super added bacterial infections (<0.018) were all significantly more in older children >10 years.

Disease severity and complications

In our cohort, 185 children had mild disease, 38 had moderate disease and 44 had severe disease. Complications included acute respiratory distress syndrome (ARDS) in 14 children, acute kidney injury (AKI) in 6 children, shock in 15, congestive heart failure (CHF) in 4, myocarditis in 5 and Multisystem inflammatory syndrome in children (MIS-C) in 10 children (Table 2).

Investigations

A complete blood count was done in 42.9%; anemia (69.4%), neutrophilia (39.5%), lymphocytosis (6.8%), thrombocytopenia (33.3%) were common findings. Leucocytosis was significantly more in younger children (<5 years, $p<0.001$). Leucopenia (>5 years, $p=0.023$) and neutrophilia (>5 years, $p=0.047$) were significantly more in older children. Older children also had significantly more hypoalbuminemia, coagulopathy and raised serum alkaline phosphatase (Table 3). Comparison of various laboratory parameters amongst children with mild, moderate and severe COVID-19 is elucidated in (Figure 3). Children with severe disease had significantly more

anemia, neutrophilia, hypoalbuminemia, azotemia and raised serum creatinine. A neutrophil: lymphocyte ratio of >3.03 was significantly more in children with severe COVID-19 ($p=0.03$) compared to those with mild and moderate disease.

Chest X-ray

A chest X-ray (CXR) was done in 133 children (39.7%), of which 70 had a radiological abnormality. Pattern of distribution was bilateral in 60% with diffuse involvement (all four zones) in 28.5% vs. localised in 71.4%. Isolated lower zone involvement was most common single site to be involved.

The most common findings included ground glass opacities in 28.5%, followed by patchy consolidation (24.3%), lobar consolidation (20%), and interstitial infiltrates (15.7%). Other findings included pleural effusion in 15.7%; although in 10 of these cases there was an underlying co-infection or co-morbidity, hilar adenopathy in 8.6%; 5 of whom had concomitant TB and 1 had Hodgkins lymphoma, miliary infiltrates in 4.3%; of these two had concomitant pulmonary TB, hyperinflation in 4.3%; none were known asthmatics and pneumothorax in 2.9% cases.

Treatment and outcomes

The median duration of hospital stay was 8 days (IQR-5-12 days). Most (91%) children were discharged, few (3%) transferred to other facilities (of own accord) and 2 (0.6%) children absconded. There were total 16 (4.8%) deaths of which 15 had severe disease and 1 had moderate disease; 14 deaths occurred in our hospital. Amongst the transferred children, 2 died in the transferred facility and remainder 8 were well at 1 month telephonic follow up.

Table 3: Laboratory parameter in mild, moderate and severe COVID-19 in children (n=335).

Parameters	Overall Median (IQR)	Mild (N=185)	Moderate (N=38)	Severe (N=44)	P value
Hb (gm/dl) (N=144)	10 (8.7-11.3)	10.4 (9.3-11.8)	9.3 (6.9-10.6)	9.6 (8.5-10.4)	0.009
TLC (/mm³) (N=144)	7400 (4960-12565)	7345 (5012-9750)	8600 (6517-11960)	9295 (4700-16090)	0.22
Polymorphs (%) (N=144)	58 (45-74)	56.5 (44-67)	58 (54-73)	64.5 (45-79.7)	0.21
ANC (/mm³) (N=144)	4073 (2490-7897)	3943 (2410-6075)	5294 (3224-9109)	6310 (3082-9436)	0.029
Lymphocytes (%) (N=144)	36 (22-47.2)	37 (24.8-50.2)	36.5 (23.5-43.5)	29 (17-47.5)	0.4
ALC (/mm³) (N=144)	2533 (1449-4115)	2509 (1527-3742)	2824 (2098-3966)	2652 (1282-6026.7)	0.79
Monocytes (%) (N=144)	2 (1-4)	2.5 (2-4)	2 (1-4)	1 (1-3)	0.06
AMC (/mm³) m (N=144)	159.7 (86.3-254)	176.6 (119.2-254)	211 (99-284)	127 (28-363)	0.59
Eosinophils (%) (N=144)	1 (0-3)	2 (1-4)	1 (0-2)	1 (0-4)	0.06
AEC (/mm³) (N=144)	98.5 (0-228.7)	147 (49.6-262.5)	92 (0-165.7)	93.5 (0-305)	0.21
Platelets (lacs/mm³) (N=144)	1.98 (1.30-2.95)	2.08 (1.38-2.82)	2.12 (1.61-3.07)	1.55 (1.01-2.89)	0.17
N:L RATIO (N=144)	1.45 (0.88-3.2)	1.55 (0.88-2.69)	1.52 (1.3-3.09)	2.3 (0.98-4.76)	0.34
P:L RATIO (N=144)	76.9 (47.5-130.5)	78.45 (48.23-130.4)	73.8 (51.04-165.7)	56.7 (37.7-102.2)	0.42
Blood urea (mg/dl) (N=113)	25 (21-32)	23 (19.5-26)	23 (22-30)	32 (24-55)	0.002
S.Creatinine (mg/dl) (N=113)	0.4 (0.3-0.6)	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.5 (0.4-0.8)	0.026
T.Bilirubin (mg/dl) (N=105)	0.6 (0.4-1.2)	0.5 (0.4-1)	0.8 (0.6-1.1)	0.9 (0.5-1.15)	0.12
AST (U/l)(N=105)	44 (26-89)	33 (25-75)	44 (25-58.5)	61 (33-101)	0.08
ALT (U/l) (N=105)	46 (24-81)	34 (25-69)	56 (25.5-74)	58 (24.7-115.7)	0.48
SAP (U/l) (N=79)	227 (166-302)	203 (145-272)	198 (167.5-272.5)	271 (202-324)	0.08
T protein (g/dl) (N=62)	6.5 (5.8-7.3)	6.5 (5.8-7.3)	6.2 (5.6-7.6)	6 (5.8-6.4)	0.59
S. Albumin (g/dl) (N=62)	3.5 (2.9-3.8)	3.6 (2.9-4)	3.2 (2.3-3.6)	3.15 (2.6-3.5)	0.011
INR (N=43)	1.2 (1-1.75)	1.1 (1.08-1.22)	1.42 (1.3-1.46)	1.3 (1-1.8)	0.59
D Dimer (N=20)	1331.5 (710-3221)	3111 (1088-5000)	1845 (1150-3375)	1257 (709-2143)	0.62

Hb: hemoglobin, TLC: total leucocyte count, ANC: absolute neutrophil count, ALC: absolute lymphocyte count, AMC: absolute monocyte count, AEC: absolute eosinophil count, N:L ratio: neutrophil:lymphocyte ratio; P:L ratio: platelet: lymphocyte ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase, SAP: serum alkaline phosphatase; T: total, S: serum, INR: international normalized ratio.

Seventeen percent children required oxygen with 10.4% requiring low flow oxygen, while 4.2% required high flow oxygen (9 by high flow nasal canula (HFNC), 3 by non-rebreathing mask (NRM), 2 by Bilevel positive airway pressure (BiPAP). Thirteen (3.9%) children required invasive ventilation (including 2 who initially received HFNC, one who received oxygen by mask and one escalated from nasal prongs to HFNC to ventilator. Almost one third (33.4%) children received intravenous antibiotics, 10.7% received oral antibiotics. Many (39.7%)

children received oral azithromycin, chloroquine (32.2%), and ivermectin (32.2%). Steroids were used in 9.8% children (Table 2).

Risk factors for severe disease

Children with underlying co-infection, associated tuberculosis, associated culture positive bacterial sepsis or were underweight had significantly more severe COVID-19. However, overweight and obese children had significantly less severe COVID-19 (Table 4).

Table 4: Risk factors for development of severe COVID-19 in children.

Parameter (N=335)	Mild (N=185)	Moderate (N=38)	Severe (N=44)	P value
Age (years)	72 (18-132)	78 (10.25-141)	72 (10.5-147)	0.96
Age groups (years)				
<1	45	11	12	0.80
1-5	40	7	9	0.90
5-10	43	8	8	0.75
>10	57	12	16	0.77
Gender	103	19	23	0.77
Co-morbidities	29	9	11	0.23
Malignancy	7	1	3	0.58
Neurological co-morbidity				0.07
Renal co-morbidity	3	3	2	0.09
Co-infections	24	9	13	0.017
Tuberculosis	7	6	6	0.0015
Liver abscess	5	2	2	0.65
Culture positive bacterial sepsis	0	2	7	<0.001
Underweight	4/53	10/38	23/44	<0.001
Overweight or obese	15/53	3/38	2/44	0.0016

Clinical and laboratory predictors of mortality in children with moderate to severe COVID-19

Amongst the 82 children with moderate to severe disease, there were 16 deaths and 66 survivors. Comparison between the survivors and non-survivors showed that presence of co-infections, hypoxia of <93% under room air at admission, severe COVID-19, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI) and shock at presentation were associated with higher mortality. Children with neurological manifestations of COVID-19 had higher risk of death. Children with COVID-19 gastroenteritis had significantly less mortality. Children with thrombocytopenia, leucopenia, lymphopenia, azotemia and raised creatinine were at higher risk of mortality. The proportion of non-survivors having high N:L ratio >3.03 ($p=0.02$) and raised INR >1.1 ($p=0.04$) was significantly more than the survivors (Table 5).

DISCUSSION

This is a large prospective study of Indian children and adolescents admitted with COVID-19 illness. Majority of our children acquired infection from a close contact. Hospital admissions increased in the period of un-lockdown likely due to restricted exposure of children outside their homes to infected symptomatic or asymptomatic adults. The age and gender distribution of infected children was similar to previously published studies with no particular age group or gender predisposed to develop symptomatic or severe disease.^{7,19} One-fifth of our children were asymptomatic compared to 4-70% reported previously.^{9,10,19-21} This wide variability may be attributed to difference in testing policy, inclusion and

admission criteria. Like previous studies, respiratory followed by gastrointestinal manifestations were the commonest. A larger proportion of our children had gastrointestinal (GI) manifestations (33%) compared to 6-19% reported previously.^{1,8,9} 11% of our children had isolated gastrointestinal compared to 4% reported previously.²² This may be due to ethnic and environmental differences.⁷ Nearly 15% of our cohort had neurological manifestations with 10.4% presenting with severe neurological manifestations (encephalopathy/seizures/paresis). Severe neurological manifestations have been sparingly reported in pediatric COVID-19 with stroke and encephalopathy as the commonest findings.²³ Identified associations have been MIS-C (38% cases) and postulated mechanisms include hypercoagulable state, direct viral neuronal injury and immune mediated damage. In majority of our cases, COVID-19 led to exacerbation of an already existing underlying neurological co-morbidity. While only 5 had associated MIS-C, 12 of them had elevated D dimers or thrombocytosis. Children with an underlying neurological co-morbidity who develop COVID-19 should be carefully monitored for development of neurological complications.

Risk factors for severe disease

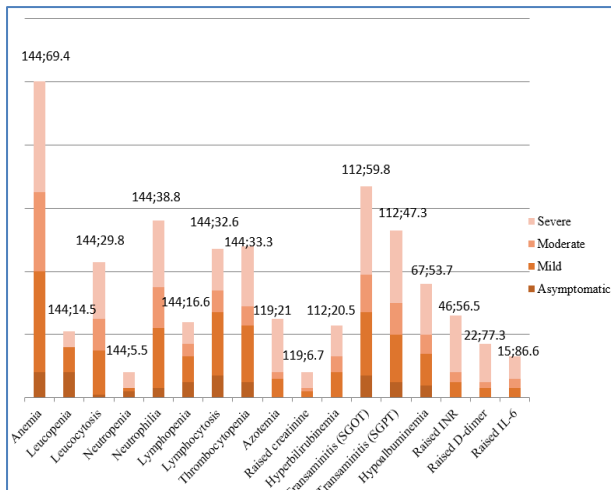
In our cohort, children with co-infections had higher risk of developing moderate to severe disease. Tuberculosis was the commonest co-infection followed by liver abscess. Western literature reports predominance of viral and bacterial infections; however another Indian study has reported TB as the commonest co-infection in moderate to severely ill COVID-19 positive children.⁷

Table 5: Predictors of mortality amongst children with moderate to severe COVID-19 (n=82).

Parameters	Survivors (N=66)	Non-survivors (N=16)	P value
Age (years) (Median, IQR)	66 (10-60)	126 (21-159)	0.21
<1	19	4	0.76
1-5	14	2	0.43
6-10	14	2	0.43
>10	19	8	0.10
Gender (Males)	35	7	0.50
Undernutrition	25	8	0.37
Overweight or obese	5	1	0.85
Co-morbidities	16	5	0.56
Malignancy	2	2	0.11
Neurological co-morbidity	8	4	0.19
Co-infections	15	10	0.0019
Tuberculosis	8	4	0.19
Culture positive bacterial sepsis	2	7	0.82
Disease severity (severe)	29	15	<0.001
Hypoxia <93% at admission	15	14	<0.001
Acute respiratory distress syndrome	5	9	<0.001
Acute Kidney Injury	3	3	0.05
Shock	4	11	<0.001
Congestive Heart Failure	2	2	0.44
Myocarditis	4	1	0.97
COVID-19 pneumonia	35	7	0.50
COVID-19 gastroenteritis	20	1	0.047
Neurological manifestations	20	10	0.016
Bleeding manifestations	6	4	0.08
Renal manifestations	10	5	0.13
Hemoglobin	9.6 (8-10.6)	9.5 (8.25-10.3)	0.62
Platelet count	2.1 (1.4-3.11)	1.24 (1-1.915)	0.021
Total leucocyte count	10260 (6500-15170)	5000 (4175-7800)	0.028
Absolute lymphocyte count	2898 (1924-5574)	1260 (571.5-2965)	0.021
Absolute neutrophil count	6640 (3613.5-9410)	3956 (2672-6310)	0.098
N:L ratio	1.54 (1.11-3.43)	4.82 (0.975-7.915)	0.32
P:L ratio	66.64 (43.67-96.3)	100.65 (35-225.08)	0.40
Azotemia	25 (21.5-34.5)	40 (25-52.5)	0.038
Raised creatinine	0.4 (0.3-0.6)	0.7 (0.5-0.8)	0.05
Hyperbilirubinemia	0.8 (0.5-1.325)	0.9 (0.65-1.2)	0.65
Raised SGOT	49.5 (29-92.25)	70 (26.5-88.5)	0.83
Raised SGPT	56 (25-87.75)	56 (24.5-81)	0.89
Raised SAP	248.5 (196.5-319)	276 (190-325)	0.82
Raised INR	1.15 (1.0-1.575)	1.575 (1.255-1.9)	0.22
Hypoalbuminemia	3.2 (2.6-3.575)	3.1 (2.9-3.4)	0.58
Raised D dimer	1331.5 (649-1821)	2028 (1108.75-4403)	0.39

COVID-19 and TB impede the host's immune responses and their synergism may contribute to more severe clinical evolution.²⁴ It is postulated that as TB lung infection predisposes to other airborne infections, similarly it enhances susceptibility to and severity of COVID-19 infection. Moreover, impairment of the immune mechanisms and cytokine overexpression in COVID-19 infection play a vital role in reactivation of latent TB and progression of existing TB infection. In our cohort, we identified being underweight as a risk factor for development of moderate to severe disease. Another study

from India showed 50% of their cohort with moderate to severe disease had malnutrition.⁷ This may be attributed to poor disease healing (due to hyperinflammation and immunosuppression) in such children and concomitant predisposition to other co-infections.²⁵ However, contrary to western literature, overweight and obese children in our cohort had significantly less symptomatic or severe disease.



The box on top of the bars denotes number of children tested for the given parameter and percentage of children having abnormality of the tested parameters.

Figure 4: Comparative chart of laboratory manifestations in pediatric COVID-19.

Previous literature correlates obesity with poorer outcomes, due to a hyper-inflammatory state and associated cardiovascular co-morbidities, diabetes and sleep apnoea. In our cohort, none of the overweight and obese children had these co-morbidities. Interestingly, as per the obesity-paradox-hypothesis, obesity in certain individuals (with specific characters) may counter-protective against certain infections due to their different physiological response. Studies have particularly shown that in tuberculosis, community-acquired pneumonia and sepsis, individuals with obesity had better outcomes than lean ones.²⁶ It is possible that the obesity paradox holds true for children in the LMICs especially with a large proportion of our cohort having tuberculosis, bacterial pneumonia and sepsis.

Laboratory abnormalities

Anemia was the commonest laboratory abnormality in our cohort and had significant correlation with disease severity. Correlation with severe disease is corroborated by published literature and is likely because anemia is a biomarker for more severe inflammation.²⁷ While anemia due to COVID-19 is postulated to be caused by altered iron metabolism, autoimmunity, altered RBC structure and ACE2 mediated destruction of EPO producing kidney cells. It is likely that a proportion of our cohort had nutritional anemia.²⁸ Leucopenia and neutrophilia were commoner findings in our older children akin to adults. However, in our younger children, leucocytosis and lymphocytosis predominated. This maybe because of age related immune system response and presence of co-infections and sepsis in a large proportion of our cohort.²⁷ Like in adults, we found a significant association between high N:L ratio >3.03 with disease severity.²⁹ In concordance with previous literature, anemia, neutrophilia,

hypoalbuminemia, azotemia and raised creatinine were associated with severe disease.^{8,30}

Radiologic findings of COVID-19 in our cohort were similar to those seen in adults, and range from normal to severe ARDS type appearance. Treatment-wise, requirements of oxygen by non-invasive modes was similar to that in the western data (2.1% to 9.6%).^{1,24} Higher proportion of our children required invasive ventilation compared to western cohorts, although correlating with available Indian data.⁸ This is likely due to greater proportion of severe COVID-19 children, higher co-infections and underlying undernutrition in Indian cohorts. A larger proportion of our children had moderate to severe disease (24%) and mortality (4.8%) compared to the western population (mortality: 0.1-1%).¹ This heterogeneity may be attributed to the variability in the cohort analysed, ethnic difference, referral bias with admissions of sicker children, higher transportation time due to limited means during lockdown, comorbidities, malnutrition and infections prevalent in the authors' setting.

Predictors of mortality

We found presence of co-infections, hypoxia <93% at admission, ARDS, AKI and shock at presentation as the clinical predictors of mortality in children with moderate to severe COVID-19. This is in corroboration with previous studies in children which identified hypoxia and AKI at admission as important risk factors for mortality.⁵ Additionally, we found that children with neurological manifestations of COVID-19 were at higher risk of death. Published data reports pooled prevalence of neurological manifestations and mortality rate of COVID-19 patients with neurological features in adults to be 23.0% and 29.1% respectively. However, pediatric data is limited.³¹ A few studies have reported higher mortality in children with neurological manifestations albeit this was in association with high prevalence of MISC in these children.²³ Children with COVID-19 gastroenteritis had significantly less mortality. Previous published literature is discordant regarding prognostic significance of gastrointestinal manifestations of COVID-19 on disease severity and mortality. Some studies report that association of gastrointestinal symptoms with severe COVID-19 in children.²² However, a meta analysis showed no increase in mortality in patients with gastrointestinal manifestations of COVID-19.³² Laboratory predictors of mortality in this group included thrombocytopenia, leucopenia, lymphopenia, neutrophil:lymphocyte ratio>3.03, azotemia and raised creatinine. These findings are similar to published systematic reviews on predictors of adult mortality in COVID-19 and risk factors for PICU admission among the paediatric population.^{33,34} Neutrophil: lymphocyte ratio as a predictor has been reported less in the pediatric population, while multiple studies in adults have corroborated its value in predicting mortality in COVID-19.³⁵

Limitations

The limitations of this study is that only COVID-19 positive admitted children were included with laboratory and radiological tests conducted in selected children as per clinical indication. Thus, the findings may be over-estimate the true prevalence of observations compared to community based studies or studies enrolling both hospitalized and non-hospitalized children.

CONCLUSION

COVID-19 in children most commonly presents as a mild flu-like illness with no age or gender predilection. Respiratory manifestations are the commonest followed by associated or isolated GI manifestations. Children with neurological co-morbidities are predisposed to neurological manifestations of COVID-19. Risk factors for development of Severe COVID-19 in children include underlying co-infection, associated tuberculosis, associated culture positive bacterial sepsis and being underweight. Overweight and obese children have less severe COVID-19. Clinical predictors of mortality in children with moderate to severe COVID-19 include co-infections, hypoxia at admission, neurological manifestations, acute respiratory distress syndrome, acute kidney injury and shock at presentation. Laboratory predictors of mortality include thrombocytopenia, leucopenia, lymphopenia, high Neutrophil:Lymphocyte ratio >3.03, coagulopathy, azotemia and raised creatinine. Children with identified risk factors for severe disease and mortality should receive prioritized treatment to prevent undesirable outcomes.

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