COVID-19-associated Multisystem Inflammatory Syndrome in Children: A Multicentric Retrospective Cohort Study

Bharat Mehra[1], Mukul Pandey[2], Dhiren Gupta[3], Tania Oberoi[4], Nameet Jerath[5], Rachna Sharma[6], Naresh Lal[7], Chandrasekhar Singha[8], Bhavana Malhotra[9], Vinamra Manocha[10], Ashish K Simalti[11], Yogesh Arya[12], Sandeep K Dugaya[13], Swati Kalra[14], Amar J Chitkara[15], Anil Sachdev[16], Neeraj Gupta[17]

Abstract

Background: Multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new entity affecting a small percentage of children during the COVID-19 pandemic.

Materials and methods: Demography, clinical, and laboratory variables of children admitted from April to September 2020 with MIS-C were studied retrospectively at eight hospitals in Delhi, India.

Results: We identified 120 patients [median age: 7 years (interquartile range (IQR): 4–10)] with male-to-female ratio of 2.3:1. Overall, 73 out of 120 children (60.8%) presented with shock, 63 (52.5%) required inopressor support, and 51 (43%) required respiratory support. We categorized the cohort into three observed clinical phenotypes: MIS-C with shock ($n = 63$), MIS-C with Kawasaki disease (KD) ($n = 23$), and MIS-C without shock and KD ($n = 34$). Atypical presentations were hypothermia, orchitis, meningoencephalitis, demyelination, polyneuropathy, pancreatitis, and appendicitis. Ninety-four percent had laboratory evidence of SARS-CoV-2 (78.3%, seropositive and 15.8%, RT-PCR positive). The median C-reactive protein (CRP) was 136 mg/L (IQR, 63.5–212.5) and ferritin was 543 ng/mL (IQR, 225–1,127). More than 90% received immunomodulatory therapy (intravenous immunoglobulins and/or steroids) with an excellent outcome (96% survived). CRP and absolute neutrophil count (ANC) were correlated statistically with severity.

Conclusion: MIS-C data from Delhi are presented. Rising CRP and ANC predict the severe MIS-C.

Keywords: Corticosteroids, Hyperinflammation, Intravenous Immunoglobulin—IVIG, Kawasaki disease, Multisystem inflammatory syndrome in children (MIS-C), SARS-CoV-2.

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Introduction

Multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel entity being reported in children with increasing frequency from countries where the coronavirus disease-2019 (COVID-19) pandemic has peaked or fading.[1,2] Children with this multisystem illness have been described to have overlapping features of Kawasaki disease (KD), toxic shock syndrome, and macrophage activation syndrome. The initial cases from India were reported in May 2020,[3,4] and as the number of COVID-19 cases grew exponentially across the country, clinicians identified this new entity more frequently. In view of the paucity of data from the Asian countries, we conducted this retrospective study with the objective to study the patient characteristics, clinical and laboratory variables, and their analysis for severity prediction.

Study Design and Data Collection

We conducted a retrospective multicenter cohort study at eight pediatric centers in Delhi, an early epicenter of the COVID-19 pandemic in India. After getting institutional ethical clearance, MIS-C cases were identified retrospectively at each participating site, for the study period from April 1 to September 30, 2020, using Centers for Disease Control and Prevention criteria for MIS-C.[2] Organ system involvement was defined as described by Feldstein et al. in their study on MIS-C in the United States.[5] Data were extracted for demographics, clinical presentation, radiological findings, underlying comorbidities, echocardiographic (ECHO) findings, laboratory investigations, treatment modalities, and outcome.

[1]Department of Pediatric Intensive Care, Max Super Speciality Hospital, New Delhi, India

[2]Department of Pediatrics, St Stephens Hospital, New Delhi, India

[3,9,16,17]Department of Pediatric Intensive Care, Sir Ganga Ram Hospital, New Delhi, India

[4,5]Department of PICU, Apollo Hospital, New Delhi, India

[6,7]Department of Pediatric Critical Care, BLK Super Speciality Hospital, New Delhi, India

[8,12]Department of PICU, Madhukar Rainbow Children's Hospital, New Delhi, India

[10]Department of Pediatrics, Mata Chanan Devi Hospital, New Delhi, India

[11]Department of Pediatric Critical Care, Military Hospital, Dehradun, Uttarakhand, India

[13,15]Department of Pediatrics, Max Super Speciality Hospital, New Delhi, India

[14]Department of Pediatrics, Baba Saheb Ambedkar Hospital, New Delhi, India

Corresponding Author: Bharat Mehra, Department of Pediatric Intensive Care, Max Super Speciality Hospital, New Delhi, India, Phone: +91 9999538720, e-mail: bharatmehra909@gmail.com

Statistics

We described the patient characteristics as numbers and percentages for categorical variables, and median with interquartile range (IQR) for quantitative ones. The Chi-square test was used for assessing the statistical significance of the difference in the percentage of cases with different characteristics between the groups. KruskalWallis test was used for the difference in medians of quantitative data in view of a highly skewed distribution of these measurements. For severity prediction, two models were used, viz. "Binary logistic regression" model and "Random-Forest" model. Receiver operating characteristic (ROC) curves were used to obtain the optimized cutoff value for the score maximizing sensitivity and specificity to distinguish severe and non-severe patients. SPSS 21 was used for calculations.

RESULTS

Initially, 141 cases were identified. Twenty-one cases were excluded (evidence of other tropical infections along with COVID-19, duplicate patients, detailed investigations not done, and those who expired within 24 hours of hospital stay). Finally, 120 cases were enrolled. The surge of MIS-C cases in our cohort was observed during July and August (Fig. 1), a month after the first surge of acute COVID-19 cases in Delhi, which was observed during the end of May and early June.[6]

Clinical Characteristics, Organ System Involvement, Treatment, and Outcome

In our cohort, there was a male preponderance (70%), and the majority ($n = 73$; 61%) were from 5 to 12 years of age-group (Table 1). Twelve children were <1 year old, 20 were between 1 and 4 years, and the rest 15 were >13 years old. The youngest case of MIS-C was a child of 6 weeks of age. Figure 2 describes the organ system involvement.

The most common symptom was fever (99%), although one infant presented with severe hypothermia (31°C) with multi-organ dysfunction. Mucocutaneous involvement was noted in the form of rash (maculopapular, morbilliform, urticarial, and erythroderma), non-purulent conjunctivitis, oral mucositis, and non-pitting edema in hands and feet. We categorized the cohort based on the major clinical phenotype. The first group ($n = 63$; 52.5%) had features of shock during the stay. The second group fulfilled the criteria for KD with or without shock ($n = 23$; 19.2%), and the last group had features of multisystem involvement but did not have shock or KD
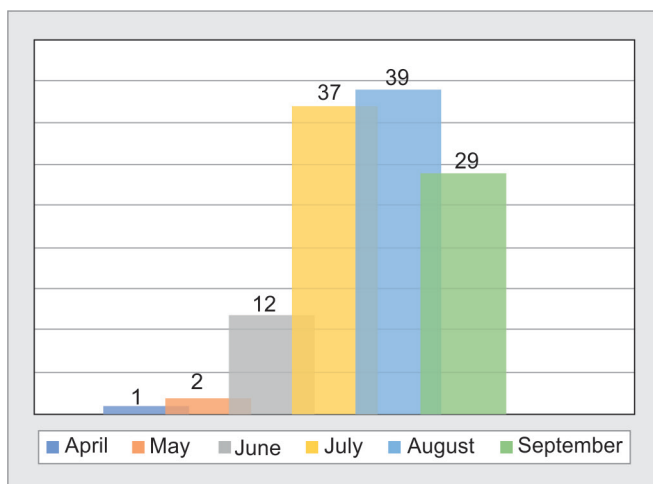
($n = 34$; 28.3%). Abnormal ECHO findings [such as left ventricular (LV) dysfunction, pericardial effusion, and abnormal coronaries] were observed in 63 patients (58.3%) out of 108 ECHOs performed. Coronary artery dilatation (defined as coronary artery diameter z score >2)[7] was found in 11 patients. In five patients, it was reported as prominent and echogenic. Acute respiratory distress syndrome (ARDS) was observed in 23 patients (10, RT-PCR positive; 13, antibody positive).

Regarding nervous system involvement, 32 patients had encephalopathy (defined as confusion, irritability, or GCS <14 despite correction of shock or hypoxemia). Significant neurological involvement was observed in four patients [one case each of acute disseminated encephalomyelitis, Guillain–Barré syndrome, polyneuropathy, and meningoencephalitis (cerebrospinal fluid and nasopharyngeal swab positive for SARS-CoV-2)]. Ultrasonography of the abdomen was performed in 58 cases, and gall bladder edema with or without sludge was observed in 39 cases. Unusual findings noted were orchitis ($n = 1$), pancreatitis ($n = 2$), and inflamed appendix ($n = 2$).

More than 90% of cohorts (110/120) received some form of immunomodulatory therapy [intravenous immunoglobulins (IV-IG) and/or steroids]. None of the patients in our cohort received biologic agents, such as tocilizumab or anakinra.

The overall outcome was excellent with 96.6% of survival rate. Among four deaths, two cases were RT-PCR positive, one was antibody positive, and one had the epidemiological link in family. One was an adolescent with acute COVID-19 (positive for RT-PCR)-related cytokine release syndrome with severe cardiogenic shock and ARDS, who later succumbed to pancreatitis and peritonitis. Others were: 10-year-old girl from a COVID-19 hotspot (but RT-PCR-negative), who presented with vasoplegic shock, ARDS, and renal failure; a 3-month-old infant with acute COVID-19 related severe ARDS and shock, and last one was a 3-year-old with seizures and acute renal shutdown followed by multi-organ failure.

Laboratory Parameters

Table 2 describes the values of various laboratory parameters done within first 48 hours of admission. One-hundred and thirteen out of 120 patients had laboratory evidence of exposure to SARS-CoV-2 (94 cases seropositive, 16 cases RT-PCR positive, and 3 patients with both RT-PCR- and antibody positive). Rest seven patients were included based on the epidemiological link (out of these, five could not be tested for antibody as it was not available during that time). All patients had one or more elevated biomarkers of inflammation [C-reactive protein (CRP) and ferritin]. When compared across the three clinical phenotypes, median platelet count and absolute lymphocyte count (ALC) were lower, and the incidence of thrombocytopenia (defined as platelet count <120 x 10^9/L) was significantly higher in MIS-C with shock. Similarly, the values of CRP, D-dimer, ferritin, neutrophil-to-lymphocyte ratio (NLR), and absolute neutrophil count (ANC) were significantly higher ingroup 1 (MIS-C with shock).

Predictors of Severity

Among 120 cases, severe MIS-C cases ($n = 71$, 59%) were identified as (presence of any of the following):

- Use of inotropes
- Use of invasive or noninvasive ventilation
- ARDS
- Use of renal replacement therapy

Logistic regression analysis of the whole cohort for severity versus age and obesity did not show a statistically significant

Fig. 1: Month-wise trend of MIS-C cases during COVID-19 pandemic

Table 1: Demographic, clinical features, treatment, and outcome of MIS-C cohort

Clinical variables		TOTAL (n = 120)		Group 1 Shock (n = 63)		Group 2 KD complete (n = 23)		Group 3 No Shock/KD (n = 34)		p value
Demographics										
Median age, y (IQ-R)		7	(4–10)	8	(5–10)	4	(8 months–6 years)	7	(4–11)	**0.002**
Males		84	(70%)	42	(66.7%)	19	(82.6%)	23	(67.6%)	0.339
BMI >95th centile		34	(28.3%)	17	(27%)	4	(17.4%)	13	(38.2%)	0.217
Comorbidity		8	(6.7%)	5	(7.9%)	0		3	(8.8%)	
Clinical features at admission										
Fever duration	<5 days	37	(30.8%)	21	(33%)	0		13	(38.2%)	
	≥5 days	82	(68.3%)	41	(65%)	23	(100%)	21	(61.8%)	
GI symptoms		86	(71.7%)	48	(76.2%)	16	(69.6%)	22	(64.7%)	0.26
Rash		79	(65.8%)	39	(61.9%)	20	(87%)	20	(58.8%)	0.126
Conjunctivitis		68	(56.6%)	31	(49.2%)	22	(95.7%)	15	(44%)	0.326
Shock*		73	(60.8%)	63	(100%)	10	(43.5%)	0		**<0.001**
Respiratory distress		52	(43.3%)	40	(63.5%)	3	(13%)	9	(26.5%)	**<0.001**
ARDS@		23	(18.3%)	16	(25.4%)	1	(4.3%)	6	(17.6%)	0.078
Abnormal ECHO		63/108	(58.3%)	48/63	(76.1%)	12/23	(52.1%)	3/22	(13.6%)	
• LV dysfunction		37	(30.8%)	32	(50.8%)	4	(17.4%)	1	(2.9%)	**<0.001**
• CA abnormality		16	(13.3%)	5	(7.9%)	9	(39.1%)	2	(5.9%)	**0.001**
• Pericardial effusion		15	(12.5%)	13	(20.6%)	1	(4.3%)	1	(2.9%)	
Encephalopathy		32	(26.7%)	22	(34.9%)	5	(21.7%)	5	(14.7%)	0.454
Seizures		7	(5.8%)	5	(7.9%)	0		2	(5.9%)	0.072
Acute kidney injury#		27	(22.5%)	23	(36.5%)	0		4	(11.8%)	**<0.001**
Abnormal CXR		45	(37.5%)	32	(50.8%)	2	(8.7%)	11	(32.4%)	**0.001**
• Infiltrate/opacity		37	(30.8%)	26	(41.3%)	2	(8.7%)	9	(26.5%)	
• Pleural effusion		25	(20.8%)	19	(30.2%)	1	(4.3%)	5	(14.7%)	
• Pneumothorax		1		1		0		0		
≥4 Organ system involved		70	(58.3%)	51	(81%)	10	(43.5%)	9	(26.5%)	**0.001**
Treatment										
PICU care >48 hours		108	(90%)	53	(84.1%)	20	(86.9%)	25	(73.5%)	**0.047**
HHFNC/NIV		25	(20.8%)	16	(25.4%)	2	(8.7%)	7	(20.6%)	0.245
Invasive ventilation		26	(22.5%)	25	(39.7%)	0		1	(2.9%)	**<0.001**
Vasoactive infusion		63	(52.5%)	56	(88.9%)	7	(30.4%)	0		**<0.001**
RRT		12	(8.3%)	9	(14.3%)	0		3	(8.4%)	0.814
ECMO		1		1		0		0		
Pharmacotherapy										
Steroids >3 days		95	(79.1%)	55	(87.3%)	19	(82.6%)	21	(61.7%)	
IV-IG		82	(68.3%)	44	(69.8%)	22	(95.7%)	16	(47.1%)	
No IV-IG/steroids		10	(8.3%)	4	(6.3%)	0	0	6	(17.6%)	
Aspirin		36	(30%)	17	(27%)	16	(69.6%)	3	(8.8%)	
Enoxaparin/heparin		59	(49.2%)	37	(58.7%)	19	(82.6%)	21	(61.7%)	
Remdesivir		4	(3.3%)	4	(6.3%)	0		0		
Outcome										
Survived todischarge		116	(96.7%)	60	(95.2%)	23	(100%)	33	(97.1%)	
Death		4		3		0		1		

ARDS, acute respiratory distress syndrome; BMI, body mass index; CA, coronary artery; CXR, chest X-ray; ECMO, extracorporeal membrane oxygenation; ECHO, echocardiography; GI, gastrointestinal; HHFNC, humidified high-flow nasal cannula; IQR, interquartile range; IV-IG, intravenous immunoglobulin; KD, Kawasaki disease; LV, left ventricle; PICU, pediatric intensive care unit; NIV, noninvasive ventilation; RRT, renal replacement therapy. *Shock was defined as requirement of fluid bolus of ≥20 mL/kg or need for vasoactive medication. @ARDS was defined as per Pediatric Acute Lung Injury Consensus Conference Group (2015). #Acute kidney injury was defined as a creatinine level above the values for age as follows: 1 month – <1 year, 0.6 mg/dL; 1–10 years, 1.05 mg/dL; ≥11 years, >1.5 mg/dL
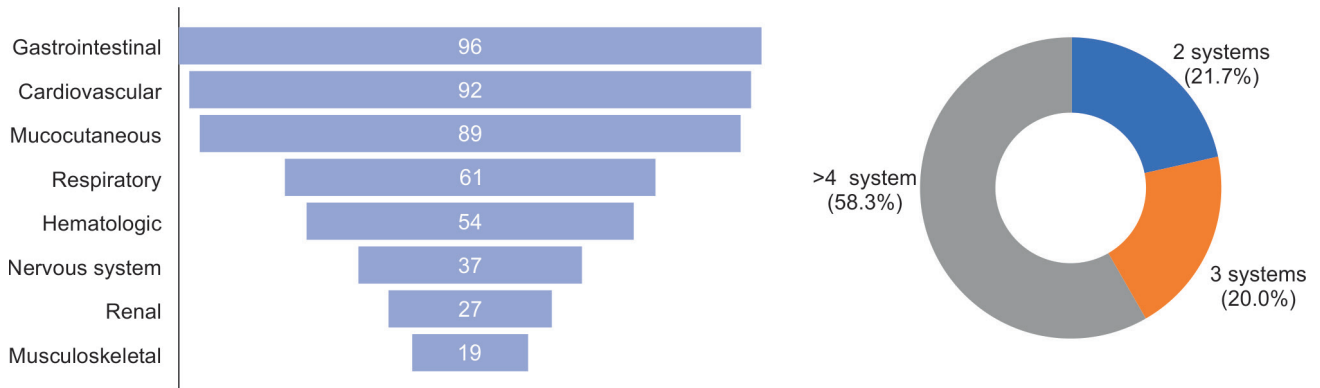
Fig. 2: Organ system involvement of the MIS-C cohort

Table 2: Laboratory parameters of MIS-C cohort

	TOTAL (n = 120)		Clinical phenotype of MIS-C						p value
			Group 1 Shock (n = 63)		Group 2 KD complete (n = 23)		Group 3 No Shock/KD (n = 34)		
Evidence of SARS-CoV-2									
Only antibodypositive[*]	94	(78.3%)	51	(81%)	20	(87%)	23	(67.6%)	
RT-PCR positive[$]	19	(15.8%)	9	(14.3%)	3	(13%)	7	(20.6%)	
Epidemiological link	25	(20.8%)	12	(19%)	4	(17.4%)	9	(26.5%)	
Laboratory values in the first 24 hours, median (IQR)									
Total leukocyte count, x10^9/L	12.5 (7.5–19.6)		13,100 (7,030–20,500)		11.7 (9.0–18.3)		9.0 (7–17.8)		0.397
ANC,x10^9/L	9.5 (5.5–15.6)		11.0 (5.7–16.8)		9.4 (6.2–12.1)		6.8 (3.9–12.3)		0.077
ALC,/µL	1,912 (892–3,515)		1,500 (862–3,110)		2,600 (1,120–4,860)		2,200 (820–3,636)		0.166
NL ratio (NLR)	4.6 (2.2–10.1)		6.9 (2.9–11.0)		2.8 (1.5–10.4)		3.4 (1.9–5.7)		**0.014**
Platelet count, x10^9/L	170 (106–265)		120 (52–206)		247 (162–480)		195 (158–322)		**<0.001**
CRP, mg/L	136 (63.5–212.5)		160 (78–225)		113.5 (46.6–196)		106 (33.5–161)		**0.028**
Ferritin, ng/mL	543 (225–1,127)		559 (283–977)		319.5 (139–651)		250 (122–1,204)		0.289
D-dimer, ng/mL	2,075 (1,120–5972)		3,230 (1,400–7,034)		710 (460–1,900)		1,660 (857–6,000)		**0.002**
Thrombocytopenia[**]	43 (35.8%)		34 (54%)		3 (13%)		6 (17.6 %)		**<0.001**
Lymphopenia[#]	51 (42.5%)		26 (41.3%)		11 (47.8%)		14 (41.1%)		0.516
Cardiac marker elevated[@]	59/104 (56.7%)		38/55 (67.2%)		8/21 (38.1%)		13/28 (46.4%)		**0.036**
ALT>40 IU/L	64 (53.3%)		35 (55.6%)		7 (30.4%)		22 (64.7%)		**0.034**
INR>1.1	38 (31.7%)		25 (39.7%)		4 (17.4%)		9 (26.5%)		0.068

ALT, alanine aminotransferase; INR, international normalized ratio; NL ratio, neutrophil-to-lymphocyte ratio; RT-PCR, real-time polymerase chain reaction. [*]Tested for either total antibody or anti-S1- and anti-S2-specific IgG antibody by chemiluminescent immunoassay (CLIA). [$]Out of total 19 positive for RT-PCR, 3 were also positive for antibody. [**]Thrombocytopenia: Platelet count less than 120 x 10^9/L; [#]Lymphopenia: Absolute lymphocyte count of less than 1,500/µL in patients 8 months of age or older and of less than 4,500/µL in patients younger than 8 months of age. [@]Increased cardiac markers (troponin-I, CPKMB, NT-ProBNP) were defined on the basis of the hospital cutoff for the upper limit of the normal range

association. Laboratory parameters (TLC, ANC, ALC, platelet count, CRP, D-dimer and ferritin) were analyzed for severity prediction for 100 patients (20 cases got excluded as they were not tested for either ferritin or D-dimer). Two models were used for severity prediction. In the first model (logistic regression), statistically significant (*p* <0.05) predictors of severity were rising CRP and rising neutrophil count

(Table 3). In the second model (random forest), CRP was considered as the first split attribute 204 times(out of 322 times = 63%) and the second split attribute 308 times and thus was found to be the most significant predictor of severity. The best cutoff for various laboratory parameters was identified using ROC curves (Table 4). Using the results from logistic regression and random forest method, five-node "Classification And Regression Tree" (CART) model was developed to identify the early predictors of severity (Fig. 3).

Discussion

This study describes the characteristics and outcomes of 120 children with MIS-C admitted to hospitals that serve diverse geographical regions of Delhi. This is so far the largest cohort of MIS-C described from India. Similar to the trends observed in the United States, United Kingdom, and European cohorts of MIS-C, we witnessed the surge of MIS-C a month later to the peak observed in adults.[5,8–10] This trend further reaffirms the temporal association of this syndrome to SARS-CoV-2.

Whereas in adults, severe COVID-19 is usually observed in second week of illness, MIS-C can occur both during the acute COVID-19 (when RT-PCR comes positive) and 2 to 6 weeks later when the antibodies have been formed.[11] The latter scenario was

much more common in our cohort (78.3%), and similar findings have been reported across all case series described so far.[5,8–10] Many of our children who were seropositive did not report any prior COVID-19-like illness in the family or the child. This shows that even asymptomatic COVID-19 infection in children can trigger an immune dysregulation weeks later, resulting in multi-organ dysfunction.

Though the febrile phase precedes the presentation, one infant presented with severe hypothermia and was included in the study because all other clinical and laboratory findings were consistent with MIS-C. Hypothermia at presentation has not been described in any of the previous studies of MIS-C. There is a reported case of a 62-year-old man with COVID-19 who presented with hypothermia and lethargy.[12] The underlying mechanism could be similar to rare presentation of systemic inflammatory response with hypothermia (instead of fever) in small children.

We observed three clinical phenotypes, although some degree of overlap between the groups can always be argued. The first group (MIS-C shock, 52%) with hemodynamic instability at presentation was relatively sicker, with a higher incidence of multi-organ dysfunction, with higher use of respiratory and cardiac support. In the UK cohort, the overall shock was observed in 50% of children, and complete KD was observed in 22.4%.[9] Italy reported 30-fold increase in the incidence of "KD like illness" in children during

Table 3: Logistic regression model for severity prediction

	aOR	(95% C.I. for aOR)	p value
Age (per 1-year increase)	1.094	(0.983–1.218)	0.099
Male gender (reference = female)	0.300	(0.034–2.671)	0.280
Obesity (reference = no obesity)	2.255	(0.862–5.898)	0.097
TLC (per unit increase in 10^9/L)	1.000	(0.999–1.001)	0.787
Neutrophil count (per unit increase in 10^9/L)	1.000	(1.000–1.001)	**0.036**
Lymphocyte count (per unit decrease in 10^9/L)	1.000	(0.999–1.001)	0.167
NL RATIO (per unit increase)	0.987	(0.867–1.123)	0.838
CRP (per unit increase in mg/L)	1.007	(1.002–1.018)	**0.010**
Ferritin (per unit increase in ng/mL)	1.000	(0.999–1.000)	0.450
Platelet count (per unit decrease in 10^9/L)	0.997	(0.994–1.001)	0.096
D-dimer (per unit increase in ng/mL)	1.000	(1.000–1.001)	0.554

Table 4: "Best cutoffs coordinates of the Curve" for severity prediction

| Variable (s)	Value	Sensitivity	1-specificity	AUC
Logistic regression model (n = 100)				
CRP (mg/L)	>138.50	0.710	0.237	0.742
Ferritin (ng/mL)	>217.50	0.903	0.658	0.597
D-dimer (ng/mL)	>2170.00	0.581	0.342	0.622
TLC ($\times 10^6$/L)	>10085.00	0.710	0.395	0.635
Neutrophil count ($\times 10^6$/L)	>8387.00	0.710	0.342	0.684
NL ratio	>4.150	0.661	0.368	0.677
Random forest model (n = 100)				
CRP (mg/L)	>115	0.611	0.500	0.766
Ferritin (ng/mL)	>435	0.522	0.367	0.82
D-dimer (ng/mL)	>1,815	0.551	0.467	0.58
Neutrophil count ($\times 10^6$/L)	>9,500	0.680	0.411	0.70
Lymphocyte count ($\times 10^6$/L)	<1,965	0.389	0.767	0.935
NL ratio	>2.25	0.811	0.600	0.727
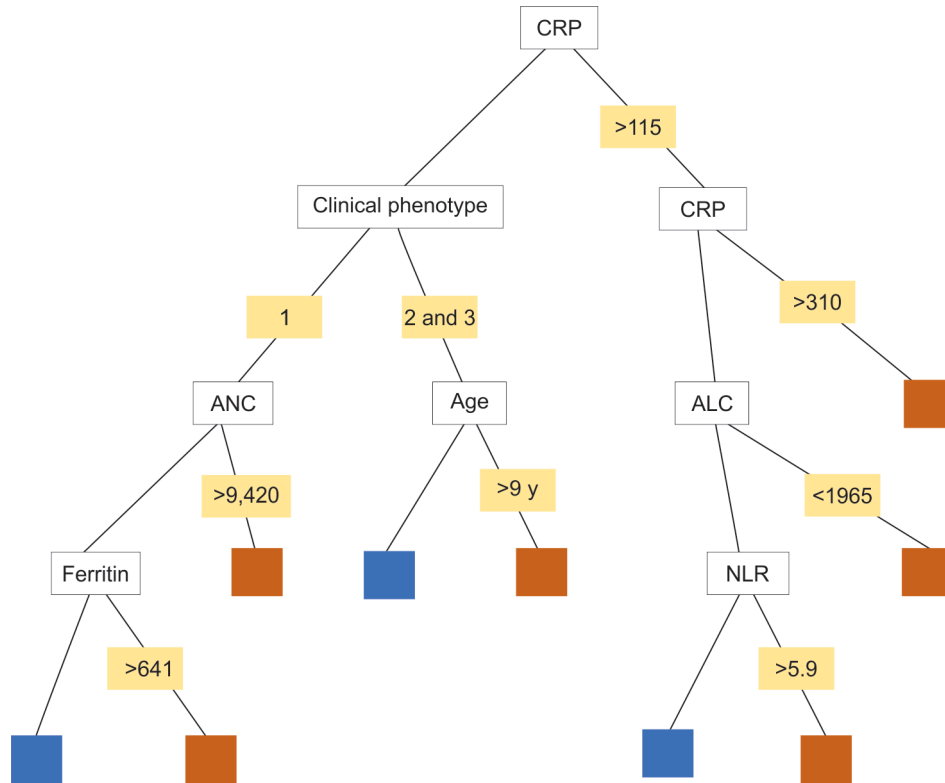
Fig. 3: Five-node CART classification model for severity prediction with splits. Orange squares—severe case; blue squares—non-severe cases

the peak of the COVID-19 pandemic, with 50% of cases fulfilling complete KD criteria, and shock was present in 50% of children.[8] Contrary to the findings in European countries where coronary artery abnormalities were found in around 30% of children, our study showed lesser involvement of coronaries (13%), with more of LV dysfunction (31%).[10] Small cohorts of pediatric multisystem inflammatory syndrome temporally related to SARS-CoV-2 from Chennai and Mumbai, India, reported coronary involvement in 16 and 26% of patients, respectively, whereas LV dysfunction was observed in one-third of children in the Mumbai cohort.[13,14] None of the patients in our cohort had arrhythmia, as compared to 12% reported in the US cohort.[5]

Unlike adults, only 18% of our cohort had ARDS. The incidence of ARDS in the spectrum of MIS-C has not been previously reported. The need to highlight this finding is because the chest X-ray (CXR) or computerized tomography findings in MIS-C resemble the late-stage adult COVID-19, with negative results for respiratory pathogens, and they respond very well to the immunomodulatory therapy, particularly steroids.[15] Serious neurological insult to the nervous system as spectrum of MIS-C, though rare, needs to be highlighted. Abdel-Mannan et al. reported four children with severe MIS-C having encephalopathy with myopathic changes. Neuroimaging revealed lesions in the splenium of the corpus callosum in all patients and T2-hyperintense lesions with restricted diffusion in three children.[16] Our cohort had four cases of serious neurological involvement, with two cases already published.[17,18]

Literature on severity predictors in MIS-C is scarce till the time of writing this article. Fernandes et al. studied the predictors of severity on 281 children with COVID-19 related respiratory illness and MIS-C.[19] Their criteria for the severe disease was ICU care

>48 hours. In their MIS-C group, lower ALC and increasing CRP were the predictors of severity. Pouletty et al. compared 16 children with KD-like illness following SARS-CoV-2 infection with a historical cohort of "classical" KD and found higher age and high ferritin associated with severe disease.[20] In our cohort, age and obesity were not associated with severe disease. CRP and neutrophil count served as predictors of severity. The difference in findings could be due to the different criteria used for defining the severity.

Limitations

Clinical management, laboratory testing protocols, laboratory techniques, and units for reporting of various parameters differed among different centers. Therefore, we may not have captured certain variables uniformly and accurately. For severity prediction, only values taken at admission were measured; however, their values may have changed during the course of illness as the disease progressed.

CONCLUSION

The young population is not universally spared from the morbidity of COVID-19 and that even previously healthy children can develop severe disease requiring supportive therapy. The major gain of this study was identifying severity predictors. CRP and ANC are simple laboratory tests that predict the severity.

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ORCID

Bharat Mehra ● https://orcid.org/0000-0001-8194-7623
Mukul Pandey ● https://orcid.org/0000-0003-4544-7423
Dhiren Gupta ● https://orcid.org/0000-0002-8244-0768
Tania Oberoi ● https://orcid.org/0000-0001-5868-268X
Nameet Jerath ● https://orcid.org/0000-0002-1688-3317
Rachna Sharma ● https://orcid.org/0000-0003-2282-3801
Naresh Lal ● https://orcid.org/0000-0003-1806-3803
Chandrasekhar Singha ● https://orcid.org/0000-0002-1620-9963
Bhavana Malhotra ● https://orcid.org/0000-0002-6169-6887
Vinamra Manocha ● https://orcid.org/0000-0002-4844-2524
Ashish K Simalti ● https://orcid.org/0000-0002-8227-9038
Yogesh Arya ● https://orcid.org/0000-0002-4918-7385
Sandeep K Dugaya ● https://orcid.org/0000-0003-2154-6144
Swati Kalra ● https://orcid.org/0000-0002-9714-5710
Amar J Chitkara ● https://orcid.org/0000-0002-7066-8407
Anil Sachdev ● https://orcid.org/0000-0002-7624-6985
Neeraj Gupta ● https://orcid.org/0000-0002-7131-4985

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