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Research Article

Profile of Critical COVID-19 Illness in Children During the Second and Third Wave of the Pandemic: A Single Center Study from South India

Sangeeta V Budur, Sujatha Thyagarajan*

Department of Pediatrics and Pediatric Intensive Care Unit, Aster RV Hospital, JP Nagar, Bangalore, India

***Corresponding author:** Dr. Sujatha Thyagarajan, Department of Pediatrics and PICU, Aster RV Hospital, CA 37, 24th Main Rd, ITI Layout, 1st Phase, J. P. Nagar, Bengaluru, Karnataka 560078. India.

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Abstract

Aims: To describe the clinical characteristics of children with critical COVID-19 illness from a single tertiary referral center during the second and third waves to understand the burden of critical COVID-19 illness in children which may guide preparedness in terms of resources, training, and services. **Methods:** A prospective observational study of critical COVID-19 children under the age of 18 years admitted to a ten-bedded PICU during the second wave (April-July 2021) and third wave (December-February 2022) of the COVID-19 pandemic. We categorized the children into 1) Acute COVID-19 infection and 2) Multi-inflammatory Syndrome in Children - MISC (post COVID-19/MISC secondary to acute COVID-19 infection). Demographic data, clinical data, investigations, treatment given, and outcome measures were studied. **Results:** Seventy-six critical COVID-19 illness admissions occurred with male preponderance. Sixty-two (81%) children presented with acute COVID-19 illness, 20 in the second wave and 42 in the third wave. Respiratory symptoms (85% vs 30%) predominated during the second wave and neurological symptoms (35% vs 20%) during the third wave. Critical care interventions were higher in the second wave. Neurological comorbidity led to mortality (5% vs 2%). MISC was seen in fourteen (19%) children. Intravenous immunoglobulin and methylprednisolone were given more during the third wave (80% vs 11%). One child in each wave died (11 % vs 20%). **Conclusions:** The clinical profile of children with critical COVID-19 illness has been changing and becoming progressively complex and atypical during each wave with significant morbidity but with good clinical outcomes/recovery rate.

Keywords: Children; Critical COVID-19; Second wave; Third wave

Introduction

The COVID-19 illness due to the novel Coronavirus SARS-CoV-2 over the last 3 years led to a major global health crisis affecting all age groups [1]. Children comprised less than 5% of cases of COVID-19 worldwide [2], and presented with a myriad of clinical manifestations with varying disease spectrum and severity (especially children with co-morbidities), atypical disease phenotypes, unique hyperinflammatory immune syndrome - known as MISC which was presumed to be due to dysregulated innate and adaptive immune response [3].

To date, India has reported a high number of COVID-19 cases second only to the United States, and third highest number of COVID-19 deaths after the United States and Brazil [4]. India reported a slightly higher percentage (8%) among the under-17-year age group [5]. In a meta-analysis comprising 27 studies, the incidence of critical COVID-19 illness was reported to be 1- 3%, and mortality due to critical COVID-19 illness in children was less than 1% with the youngest age groups tending to be the least vulnerable [6].

The majority of infections reported in children were mild or asymptomatic, and very few with severe illness, especially in the first wave [7,8]. However, there is a paucity of literature on critical COVID-19 illness in children, especially the second and third waves in the Indian context. India has fewer Pediatric intensive care unit (PICU) beds compared to the demand and they are predominantly located in urban areas [9]. The Ministry of Health and family welfare, India provided the national guidelines for the management of COVID-19 illness especially in upgrading and upskilling the existing infrastructure and human resources to meet the sudden rise in demand during the pandemic. Adult services could be provided with this protocolized approach [10]. However, the pattern of children presenting in the second and third waves gave the clinicians better insight and understanding of the disease process. Understanding the changing profile of critical COVID-19 illness in children specifically may help us plan the services for the future.

The objective of this study is to describe the clinical characteristics of children with critical COVID-19 illness from a single tertiary referral center during the second and third waves to understand the burden of critical COVID-19 illness in children which will help preparedness in terms of resources, training, and services.

Materials and Methods

A prospective observational study of critical COVID-19 children admitted to a ten-bedded PICU in a single center in South India during the second wave (April to July 2021) and third wave (December to February 2022) of the COVID-19 pandemic. All children under 18 years of age admitted with symptomatic acute COVID-19 infection and nasopharyngeal swab specimens positive by one of the following tests - rapid antigen test, real-time polymerase chain reaction (RT-PCR), were included. Diagnosis of Multisystem Inflammatory Syndrome in Children (MISC) was done as per the Centers for Disease Control and Prevention (CDC) criteria [11].

The parameters to define critical COVID-19 illness were 1) children needing critical care admission 2) cardiopulmonary/ renal/ organ support 3) death attributed to either acute COVID-19 infection /MISC (post COVID/MISC secondary to acute COVID-19 infection). We categorized the children into 1) Acute COVID-19 infection 2) MISC (post COVID-19/MISC secondary to acute COVID-19 infection).

Demographic data, clinical signs and symptoms at presentation, and associated co-morbidities were obtained from the electronic medical records. Treatment given in the form of respiratory support, inotropes, intravenous immunoglobulin, steroids, aspirin, and low molecular weight heparin were studied. The laboratory parameters studied were Complete Blood Counts (CBC), C-reactive protein (CRP), and relevant microbiological cultures done for all the children. Other tests studied were serum procalcitonin, ferritin, D-dimer, BNP (natriuretic peptide), chest x-ray, neuroimaging, and echocardiography in selected patients. A z score of coronary artery diameter with a value of more than 2 was considered to have coronary artery dilatation/aneurysm [12]. acute respiratory distress syndrome (ARDS) was diagnosed based on PALIC guidelines [13]. Acute kidney injury (AKI) was defined by KDIGO staging [14]. SARS-CoV-2 IGG titers were considered to diagnose post-COVID MISC.

The outcome measures studied were in-hospital mortality, need for intensive care, invasive mechanical ventilation, and length of hospital stay.

Statistical Analysis: Descriptive statistics have been applied. Continuous variables are shown as median and Categorical variables are presented as a percentage.

Results

We describe the profile of critical COVID-19 children in two categories: 1) Acute COVID-19 infection and 2) MISC (either post-COVID or associated with acute COVID-19 infection) (Table 1).

Table 1: Demographic profile of critical acute COVID-19 illness in children.

	2nd wave	3rd wave	2nd wave	3rd wave
Category	**Acute COVID-19 infection (RTPCR+)**	**Acute COVID-19 infection (RTPCR+)**	**MISC**	**MISC**
n=number of patients (%)	20(68.9%)	42(89.3%)	3(10.3%) (Acute COVID -19 RTPCR +) 6(20.6%) (Post-COVID-19) infection antibody IGG+VE)	3(6.3%) (Acute COVID-19 RTPCR +) 2(4.2%) (Post-COVID-19) infection antibody IGG+VE)
Age (in years)	*(Median -10.5y)*	*(Median-1.6y)*	*(Median -7y)*	*(Median -6y)*
<2y	6	24	1	2
2-5 y	4	7	4	0
5-10 y	2	6	2	2
10-15y	5	3	2	1
15-18 y	3	2		
Gender				
Female	6	17	4	1
Male	14	25	5	4

Demographic profile

During the study period, there was a total of 76 admissions with critical COVID-19 illness. During the second wave, there were 29 admissions, of which 20 had acute COVID-19 infection, 9 had MISC (6 - post-COVID MISC and 3 with acute COVID-19 infection). During the third wave, there were a total of 47 admissions, of which 42 had acute COVID-19 infection, and 5 had MISC (2 with post-COVID MISC and 3 with acute COVID-19 infection). The male-to-female ratio was 2.3:1 and 1.4:1, the median age group was 10.5 years and 1.6 years, among acute COVID-19 infection, whereas the male-to-female ratio was 1.2:1 and 4:1 and the median age group was 7 years and 6 years among MISC group during the second wave and third wave respectively.

Acute COVID-19 infection

Sixty-two children presented with acute COVID-19 illness, of which 20 were in the second wave and 42 were in the third wave.

Clinical Profile

Fever was the presenting complaint among all the children (100%). Respiratory symptoms (85%) were predominant followed by Gastrointestinal (GI) (60%) and neurological (20%) during the second wave versus predominant neurological symptoms (35%), respiratory (30%), and GI (14%) symptoms during the third wave.

Of these, 5/62 (8%) children developed acute respiratory distress syndrome - ARDS (requiring invasive ventilation) with Multi Organ Dysfunction Syndrome (MODS), and 2/62 (3%) children developed acute kidney injury - AKI (requiring continuous renal replacement therapy - CRRT), during the second and third waves together. Atypical presentations included 2 children with acute pancreatitis, 1 child with new onset Diabetic Keto-Acidosis (DKA), and 3 children with GI bleeding. About 50 % of the children during the second wave had comorbidities (developmental delay-3, SMA-1, Neurodegenerative disorder-1, cyanotic congenital heart disease (CCHD)-1, Acute Lymphoblastic Leukemia (ALL)-1, Thalassemia major-1, obesity-2) compared to 33% of the children during the third wave (Duchenne's muscular dystrophy-1, seizure disorder/developmental delay-3, Spinal Muscular Atrophy (SMA)-1, asthma-2, Acute lymphoblastic leukemia- 1, Prader-Willi Syndrome-1, obesity-1). Co-infections were found in 8 % of children in both waves (nosocomial- 3, 1 child with associated E. Coli urinary tract infection, 1 child with Candida tropicalis Ventilator-associated Pneumonia).

Inotrope requirement was 15% versus 9.5%, HFNC 25% versus 7.1%, NIV 15% versus 4.7%, mechanical ventilation, 25% versus 4.7%, duration of the mechanical ventilation 2 to7 days versus 6 to 7 days respectively for children admitted during the second and third waves. Tracheostomy, CRRT, and plasmapheresis were required in one each during the third wave. Second-line

antibiotics such as meropenem, colistin, ceftazidime, linezolid, and vancomycin (based on culture sensitivity reports) were required in 60% versus 4.7%, anticoagulation in 10% vs 11.1%, low dose methylprednisolone was required in 45% versus 2.3% respectively during the second and third waves. High-dose methylprednisolone was used in 7.1% and intravenous immunoglobulin (IVIG) alone was used in 2.3% during the third wave. (Table 2, 4).

Table 2: Clinical profile of Critical Acute COVID-19 illness in children.

	2nd wave	3rd wave	2nd wave	3rd wave
Clinical features	**ACUTE COVID-19**	**ACUTE COVID-19**	**MISC**	**MISC**
Fever	20(100%)	42(100%)	9(100%)	5(100%)
Rash	2(10%)	2(4.7%)	5(55.5%)	2(40%)
Lymphadenopathy	0	0	3(33.3%)	2(40%)
Gastrointestinal symptoms	12(60%)	6(14.2%)	1(11.1%)	2(40%)
Respiratory symptoms	17(85%)	13(30.9%)	5(55.5%)	1(20%)
Neurological symptoms	4(20%)	15((35.7%)	3(33.3%)	2(40%)
Bleeding	3(15%)	0	0	3(60%)
Comorbidities	10(50%)	14(33.3%)	2(22.2%)	2(40%)
Pneumonia	10(50%)	5(11.9%)	3(33.3%)	1(20%)
ARDS	2(10%)	3(7.1%)	1(11.1%)	1(20%)
Left ventricle dysfunction with hypotension	2(10%)	0	5(55.5%)	2(40%)
KD-like illness	0	0	5(55.5%)	2(40%)
Seizures with encephalopathy	0	4(9.5%)	2(22.2%)	2(40%)
Acute Pancreatitis	1(5%)	1(2.3%)	0	0
New onset DKA	1(5%)	0	0	0
Gastrointestinal bleeding	2(10%)	1(2.3%)	0	0
Vocal cord palsy with aspiration pneumonia	0	0	1(11.1%)	1(20%)
MODS	2(10%)	3(7.1%)	1(11.1%)	3(60%)
AKI	1(5%)	1(2.3%)	1(11.1%)	3(60%)
Length of hospital stay (in days)	3-20(median-4)	1-14(median-3)	3-15(Median-4)	5-23(Median-9)
Coinfections/ nosocomial	2(10%)	3(7.1%)	2(22.2%)	3(60%)

Laboratory Parameters

Severe Anemia (Hb <6gm%) was observed in children presenting with significant GI bleeding (4.8%). Varying degrees of lymphopenia (neutrophil-lymphocyte ratio (NLR) 1.9 vs 1.85), borderline low platelet counts, marginally elevated inflammatory markers (CRP (12 vs 1.38 mg/dl), procalcitonin (1 vs 0.72 ng/ml), ferritin (249 vs 232 ng/ml), coronary dilation (without classical features of MISC) (2/20 (10%) vs 5/42 (11.9%)) were seen in children during second and third waves. The duration for normalization of inflammatory markers was similar during both waves (median of 3 days). (Table 3).

Table 3: Key parameters of critical Acute COVID-19 illness in children.

	2nd wave	3rd wave	2nd wave	3rd wave
Category (Median)	**ACUTE COVID-19**	**ACUTE COVID-19**	**MISC**	**MISC**
Hb%(g/dl)	5.9-15.6 (11)	5.5-13.1 (12)	9.1-12.6 (11.3)	8-13.5 (9.3)
Total count(cells/mm^3)	2710-17400(6000)	5800-17890 (8400)	2390-18000 (13700)	6000-18600 (8000)
NLR (neutrophil- lymphocyte ratio)	0.11-13.53(1.94)	0.07-15.1 (1.85)	0.24-28.18(6.31)	0.85-8.6(1.6)
Thrombocytopenia(cells/mm^3)	14000-122000(50%) (219000)	10-154 (19%) (122)	39000-128000(55%) (128000)	20-100 (80%) (38.5)
CRP (mg/dl)	0.6-344(12.58)	0.1-211 (1.38)	54-190(127)	2.59-264 (151.2)
Procalcitonin(ng/ml)	0.05-2.5(1.07)	0.23-3.2 (0.72)	0.12-165(37)	6.8-200 (100)
Serum Ferritin(ng/ml)	10.8-2000(249)	79-2200 (232)	111-2000(1224.5)	629-21000 (9500)
Coronary dilation (2D ECHO)	2(10%)	5(11.9%)	2(22.2%)	3(60%)
Mean duration of inflammatory markers to normalize (in days)	2-14(3)	2-13(3)	3-16(6)	3-14(6)

Outcomes

The length of the hospital stay was slightly prolonged (mean: 5.5 days, median 4 days) during the second wave compared to the third wave (mean 4 days, median 3 days). The mortality rate was 5 % (1 child with SMA) in the second wave and 2.3% in the third wave (2-year-old developmental delay, seizure disorder) (Table 4).

Table 4: Management of Critical Acute COVID-19 Illness in Children.

	2nd wave	3rd wave	2nd wave	3rd wave
Category (%)	**ACUTE COVID-19**	**ACUTE COVID-19**	**MISC**	**MISC**
Inotropes	3(15%)	4(9.5%)	8(88.8%)	4(80%)
Adrenaline+Noradrenaline+Vasopressin	0	0	2(22.2%)	1 (20%)

Fluid bolus>20ml/kg	3(15%)	2 (4.7%)	6(66.6%)	2 (40%)
HHHFNC	5(25%)	3 (7.1%)	0	0
NIV	3(15%)	2 (4.7%)	1(11.1%)	0
Mechanical ventilation	5(25%)	2 (4.7%)	3(33.3%)	2 (40%)
Duration of mechanical ventilation in days	2-7	6-7	3-9	6-18
Tracheostomy	0	1(2.3%)	0	0
CRRT	0	1(2.3%)	0	0
Plasmapheresis	0	1	0	0
Antibiotics				
Higher antibiotics	12(60%)	2 (4.7%)	8(88.8%)	3 (60%)
No antibiotics	3(15%)	25 (59.5%)	0	0
Anticoagulation	2(10%)	5 (11.9%)	2(22.2%)	3 (60%)
LMW Heparin+ Aspirin	2(10%)	0	2(22.2%)	0
Remdesivir	1(5%)	1 (2.3%)	0	0
DEFINITIVE TREATMENT				
Methylprednisolone (2mg/kg)	9(45%)	1 (2.3%)	1(11.1%)	0
Methylprednisolone (10-30mg/kg)	0	3 (7.1%)	1(11.1%)	4 (80%)
IVIG	0	1 (2.3%)	1(11.1%)	1 (20%)
IVIG+Methylprednisolone	0	0	5(55.5%)	4 (80%)
None	11(55%)	38 (90%)	1(11.1%)	0
Tocilizumab	0	0	1(11.1%)	0
Tocilizumab +Anakinra	0	0	1(11.1%)	1 (20%)
OUTCOMES				
Survival	19(95%)	41 (97.6%)	8(88.8%)	4 (80%)
Expired	1(5%)	1 (2.3%)	1(11.1%)	1 (20%)

MISC

Overall, 14/76 (5.4%) children, 9 from the second wave and 5 from the third wave presented with MISC.

Clinical Profile

The common clinical presentations observed include erythematous maculopapular rashes at presentation, (55% vs 40%), lymphadenopathy (33% vs 40%), respiratory symptoms (55.5% vs 20%), neurological (33.3% vs 40%), G.I. symptoms (11.1% vs 40%) during the second and third waves. Two children in each wave had asthma as a comorbidity. Co-infections were found in 35.7% of children in both waves. (1-Extended-spectrum beta-lactamase E. coli, 1-Pseudomonas, 1- Acinetobacter in blood cultures, 1-Candida tropicalis – in bronchioalveolar lavage, 1-Klebsiella - in urine culture).

One child developed ARDS, another one had vocal cord palsy with aspiration pneumonia. Left ventricular dysfunction with hypotension, Kawasaki Disease KD-like illness was present in 5/9 versus 2/5 during the second and third waves respectively. MODS, AKI was present in 1/9 vs 3/5, 2/9 (one child developed HHES - Hemi Convulsion-Hemiplegia-Epilepsy-Syndrome) versus 2/5 presented with seizures with encephalopathy during the second and third waves respectively. The length of the hospital stay was 3 to 15 days (mean – 5.7 days, median 3 days), and 5 to 23 days (mean – 11.2 days, median 9 days) during the second and third waves respectively.

Two children presented with vocal cord palsy with aspiration pneumonia at admission (post-infectious neuropathy), one child with HHES (presented with fever, right facial palsy, left-sided hemiparesis, refractory seizures, MRI suggestive of hemi cerebral atrophy, felt to be of multifactorial etiology in the setting of MISC/acute COVID-19 infection), one child with acute abdomen, perforated appendix, refractory septic shock, evidence of coronary dilatation on ECHO (likely related to Appendicular artery vasculitis with KD like illness in MISC).

The requirements of inotropes were 88.8% vs 80%, mechanical ventilation 33.3% vs 40%, second-line antibiotics 88.8% vs 60%, and anticoagulation 22.2% vs 60% during the second and third waves in the MISC group. 11.1% of Children required NIV, low-dose methylprednisolone, and Tocilizumab during the second wave. 11.1% vs 80% required high-dose methylprednisolone, 55.5% vs 80% required IVIG and methylprednisolone, 11.1% vs 20% required IVIG (alone), 11.1% vs 20% required Tocilizumab, and Anakinra during second and third waves respectively. (Table 2,4)

Laboratory Parameters

Lymphopenia (NLR-median: 6.31 vs 1.6), severe thrombocytopenia (128000 vs 38000 cells/ mm^3), markedly elevated inflammatory markers – CRP (median 127 vs 151 mg/dl), procalcitonin (37 vs 100 ng/ml), serum ferritin (1224 vs 9500 ng/ml), 2/9(22.2%) vs 3/5(60%) had coronaries dilated in 2D ECHO during the second wave and third waves respectively. The duration for normalization of inflammatory markers was similar during both waves (median 6 days). (Table 3).

Outcomes

The length of the hospital stay was 3-15 days, (median 4 days) vs 5-23 days (median 9 days) during the second and third waves respectively. The mortality rate was 11.1 % (1 child with MISC with Refractory septic shock, MODS, appendicular perforation) in the second wave and 20% in the third wave (Acute Necrotizing Encephalopathy, refractory intracranial hypertension, with MISC). (Table 4)

Discussion

Critical COVID-19 illness in children in this study showed a variable demographic and clinical presentation during the second and third waves.

The incidence of critical illness from COVID-19 and risk factors for severe disease in children are not yet well defined. The COVID-19 first wave in India started in early March 2020 followed by the second wave in February 2021 and the third wave in November 2021 [15]. The majority of the children were asymptomatic during the first wave [7], whereas a significant increase in the incidence of severe infections requiring PICU care was observed during the second and third waves. Overall, it was observed that the Delta strain was the leading cause of SARS-CoV-2 infection in children in India during the second wave [16] and the Omicron variant during the third wave [15].

There were more admissions due to acute COVID-19 infection during the third wave (55%) compared to the second wave (26%) with the younger population significantly affected during the third wave (median 1.6 years) compared to the 2nd wave (10.5 years) in our study. One of the largest studies from Brazil, comprising 7442 pre-teens reported a younger population (median age group 2.6 years, 44% under 2 years) during the third wave compared to the previous waves [17]. Pediatric data from South Africa during the Omicron surge revealed that young children (0-4 years) were the most affected (62%) [18]. One of the possibilities could be that the Omicron variant of SARS-CoV-2 infection was felt to be more infectious, adolescents (> 12 years) had received

at least one dose of vaccination prior to the onset of the third wave, and younger children were probably more vulnerable to infection due to additional exposure from asymptomatic adults. Though some meta-analyses and systemic reviews [19,20] did not reveal any gender predilection in children with acute COVID-19 infection there was a male predominance (62%) in our study.

Children with MISC (either post-COVID/ MISC with acute COVID-19 infection) were relatively older (median age 7yrs and 6yrs in second and third waves respectively) in our study in comparison to the median age 10.7 years in one meta-analysis [19]. The male preponderance of 64% observed in our study was similar to other studies [21,22].

Acute COVID-19 Infection

Clinical profile

The most common indications for admission were acute respiratory illness with hypoxia (85%) and GI causes (60%) (-gastrointestinal bleeding/ acute pancreatitis) during the second wave compared to predominantly neurological (35%) (-seizures with encephalopathy) and respiratory indication (30%) during the third wave. Unlike in our study, a significant surge in CNS involvement was reported in the second wave in a few studies compared to the third wave [23]. Cytokine storm, endothelitis, coagulopathy, and neurotropism of spike protein in SARS-CoV-2 are attributed to the neurological manifestations associated with COVID-19 infection [24]. We noticed a few cases with atypical disease phenotypes, e.g. 2 children with acute pancreatitis, one child with new onset DKA, and 3 children with GI bleeding, including one with bleeding duodenal ulcer likely related to the affinity of COVID-19 virus towards ACE2 receptors present in pancreas and intestines [25].

Comorbidity

Severe COVID-19 illness is observed in children with significant comorbidities in 33% of admissions in our study similar to 19.6 - 42% reported in various studies [26,27].

We report a mortality rate of 38.7% in this subgroup which is similar to other studies which reported rates of 20 -50% [28]. Children with neurological comorbidity had a higher mortality rate of 75% in our study as observed in other studies [28]. All children with hematological malignancies survived similarly to the study by Qatawneh et al. [29]. Although asthma and childhood obesity are risk factors, all children had good clinical outcomes in our study.

Key Laboratory results

In contrast to MISC, inflammatory markers were not elevated in acute COVID-19 infections unless they had co-infections. We note that the clinical and laboratory findings in critically ill children with acute COVID-19 do not identify any specific clinical findings or biomarkers that might distinguish critical COVID-19 from sepsis. Also, in critically unwell children with raised inflammatory markers and a septic clinical profile, no pathological organism was identified in the majority (81%). In our study, the co-infections rate was 8% similar to other studies [30] which is quite less compared to the coinfection rates of 25% noted during the Influenza pandemic [31]. Hence, we discourage the empirical use of antibiotics in patients with acute COVID-19 infection.

We noticed 7/62 (11.2%) had asymptomatic incidentally detected coronary artery dilatation in the absence of classical features of MISC which normalized with Aspirin during subsequent follow-up within 6-10 weeks. This was an important and peculiar finding raising a red flag for subclinical cardiac involvement with an unknown risk for cardiac morbidity if not addressed and followed up [32].

Management Aspects

Our empirical antibiotic usage markedly reduced during the third wave (40%) compared to the second wave (85%) probably due to a better understanding of the disease manifestations with experience. We used Remdesivir in two patients as it was started by the referring center. A randomized control trial revealed that anti-viral regimens had little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay [33]. None of our children received hydroxychloroquine/azithromycin/zinc. Plasmapheresis was done for one child with Thrombotic thrombocytopenic purpura with acute COVID-19 infection. (ADAMTS13 activity - zero, antibodies positive for ADAMTS/ multifactorial etiology in the setting of acute COVID-19 infection). We used aspirin, low-dose steroids, and IVIG in various combinations in a few cases that presented mixed findings of acute COVID-19 infection and were not completely fulfilling the definition of MISC (e.g., isolated coronary dilatation).

Outcomes

Studies have quoted the Delta variant to be less infective and more severe during the second wave compared to the omicron variant which was less severe and more infective during the third wave [34]. However, children during the third wave in our study were equally sick with prolonged hospital stays and associated morbidity [17].

In our study, age < 2 years, delayed referral, wrong diagnosis, associated comorbidities especially neurological, and requirements of invasive procedures (mechanical ventilation, CRRT, plasmapheresis) led to prolonged length of stays. We observed neurological comorbidity accounted for higher death rates among the acute COVID-19-infected children.

MISC

Clinical profile

In our study, MISC was seen both in children with acute SARS-CoV-2 infection and in the post-acute or convalescent phase of infection. The most common indications for PICU admission were hypoxia and hemodynamic instability, shock during the second wave compared to multi-organ involvement (Neurological with seizures and encephalopathy along with variable cardiac and respiratory illness) during the third wave.

Comorbidity

Our findings reveal that having comorbidities is not a risk factor for having more severe MISC (2/14 in our study with a prior history suggestive of asthma) compared to having no comorbidities. This is in accordance with previous findings that pre-existing comorbidities among MISC patients are rare [35].

Key Laboratory results

Significant Lymphopenia, thrombocytopenia, and elevated NLR were seen in MISC children compared to children with acute COVID-19 infection. We found that all MISC patients had evidence of a marked inflammatory state suggestive of the cytokine storm. CRP, procalcitonin, and BNP were significantly elevated in MISC children and correlated with disease severity compared to children with acute COVID-19 infection, which is in line with one of the multicentric studies from Eastern India [22]. Most of the co-infections in the MISC group were due to nosocomial/ hospital acquired related to prolonged length of stay/ immunosuppressive drugs.

About 5/14(35%) children in the MISC group had coronary artery dilatation which normalized during subsequent follow-up. (6-10 weeks). A systematic review reported coronary artery abnormalities (CAAs) in 8-24% of the cases [36].

Management Aspects

Inotrope Requirement was quite high among the MISC (85%) group compared to the acute COVID-19 infection group (11.2%) during the second and third waves together indicating significant hemodynamic instability in children with MISC. About 5/14(35%) vs 7/62(11.2 %) required invasive mechanical ventilation in the MISC group and acute COVID-19 infection group respectively in our study similar to the reported literature [37]. One child with Hemorrhagic ADEM and AKI required tracheostomy and CRRT. 64.2% of children required IVIG in combination with high-dose steroids in our study which was the standard treatment recommendation by various guidelines and multi-centric study results [38]. Cytokine-directed therapies-anakinra, and tocilizumab (3/14 (21.4%) in our study) were used on an individual case basis with expert opinion.

Outcomes

The length of the hospital stay was quite prolonged among the MISC group in the third wave (median 9 days) likely related to co-infection and multi-organ involvement (predominantly CNS and variable respiratory and cardiac involvement) unlike the second wave (median 4 days) during which most children presented with hemodynamic instability and responded quickly to immunomodulators. We observed the highest mortality among the MISC group (14.2%) despite no comorbidities unlike the reported rate of 1.8%- 9% from the reported literature [21,39]. The delay in presentation, presence of co-infections, high CRP and NLR, severe thrombocytopenia at presentation, and not considering immunomodulators earlier due to atypical presentations contributed to the prolonged length of stay and associated morbidity and mortality in our study. The immunological events that lead to the development, clinical course, and resolution of MISC are not known, nor is it understood why children are uniquely vulnerable [34].

We noticed an overall 5.2% (4/76) mortality and survival was 94.7%, compared to the report from the government of India (<2% mortality under 20 years of age) [40] and Olivia et al [23]. Although the incidence of severe COVID-19 illness was higher among males, the mortality was highest in female children 3/ 4 (75%).

Our study demonstrates the changing and progressively more complex patterns of the clinical profile of the critical COVID-19 illness in children during each wave. We also observe that the mortality was higher in our Indian setup. This may be due to atypical presentation, delayed referral, and variable access to tertiary care PICU services. This underlines the need to constantly evaluate and share lessons on a continuous basis, especially amongst the general public as well as the referring pediatricians. We may need to anticipate newer clinical presentations in the future and adapt clinical strategies accordingly. This poses a challenge to the preparedness of the healthcare systems to handle the pandemic burden of the illness considering this varying complex pattern and the extent of resources required to provide good outcomes. Hence, there is a need to focus on improving the basic infrastructure, resources, and training for managing critically ill children in general and empowering the healthcare system to adapt to challenges during epidemics or pandemics.

Limitations

This is a single-center hospital-based prospective study data of small numbers, especially in a tertiary referral center catering to the sickest children in the region, and the services are self-funded by the patients. Further multicentric and population-based

studies are required to make the results more generalized. This study has reported short-term in-hospital outcomes only. We did not carry out genome sequencing to confirm the presence of the Omicron variant in the patients. However, this study manages to give an overview of the changing complex clinical burden of critical COVID-19 illness in children and gives an insight into the resources required for planning for future pediatric services.

Conclusions

The clinical profile of children with critical COVID-19 illness has been changing and becoming progressively complex and atypical during each wave with significant morbidity but with good clinical outcomes/recovery rate. Children with acute COVID-19 infection and neurological co-morbidities had a longer length of stay. NLR, CRP, and procalcitonin were significantly elevated in children with MISC in comparison to acute COVID-19 infection and associated with disease severity. Children with MISC requiring invasive mechanical ventilation needed drugs such as Tocilizumab/ anakinra in addition to IVIG and steroids. Larger studies are needed to examine associations with severe COVID-19 infection in pediatrics. There is a need to develop a rapid and collaborative approach to understand the variations and share lessons amongst all healthcare professionals caring for children to ensure good outcomes. In the Indian setup, there is a need to focus on improving the basic infrastructure, resources, and training of healthcare professionals so that there is accessibility to critical care for children beyond epidemics and pandemics.

Disclosure

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Data Availability Statement: Data supporting the study results can be provided followed by a request sent to the corresponding author's e-mail.

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