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Covid-19 in pediatric hematology-oncology and stem cell transplant patients –The spectrum of illness, complications and comparison of first two waves

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ABSTRACT

Introduction: Indian subcontinent witnessed first wave of COVID-19 around March 2020 and second wave in April 2021. The mutant delta variant was ≈ 2.5 times more transmissible and led to the severe second wave. We compared the impact of two waves on pediatric hematology and oncology patients at our tertiary care centre that was at heart of managing COVID-19.

Methods: Children between 0 and 18 years, who were treated for a haematological illness, malignancy or stem cell transplant with confirmed COVID-19 infection or who developed multisystem inflammatory syndrome in children were included.

Results: A total of 48 (22-first, 26-second wave) children were evaluated. Despite better understanding of disease and standardised management algorithms, we found a trend towards younger age, increased requirements of oxygen, severe pneumonia and other post-covid complications in admitted patients during the second wave. We observed early RTPCR negativity in second wave. Invasive aspergillosis, disseminated candidiasis, reactivation of tuberculosis, HLH and MISC were the main complications. No child died of COVID-19.

Conclusion: The second wave hit pediatric hematology and oncology patients harder than the first wave. COVID-19 infection in these patients may lead to significant morbidity and complications that interfere with treatment of their primary illnesses. They need close monitoring for development of life threatening infections. Early recognition and prompt therapy can optimise outcomes.

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1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a devastating effect on the world's population resulting in more than 281 million cases and 5.4 million deaths worldwide and emerged as the most significant global health crisis since the influenza pandemic of 1918 as of February 2022 [1]. COVID-19 was first reported in Wuhan, China at the end of January 2020 and declared a

pandemic by World Health Organization (WHO) in March 2020 [2]. Like the Spanish flu, COVID-19 has also affected the globe in tsunami like waves. Despite the phenomenal pace at which mass vaccination efforts have been carried out across the world, the emergence of new variant strains of SARS-CoV-2 threaten to overturn the progress made so far and the concern of future waves still looms around.

Patients affected by cancers are at higher risk of SARS-CoV-2 infection owing to the immunocompromised status [3]. Adult cancer patients with COVID-19 have had worse outcomes and higher fatality [4,5] as compared to the normal population [6,7]. Children with cancer are a vulnerable population for severe COVID-19 owing to the primary illness, chemotherapy related immunosuppression, frequent exposure and repeated visits to the hospital.

Indian subcontinent witnessed 2 peaks, first wave hit around March 2020 and peaked until September 2020 and second wave hit by April 2021. The rise in case load during the second wave was

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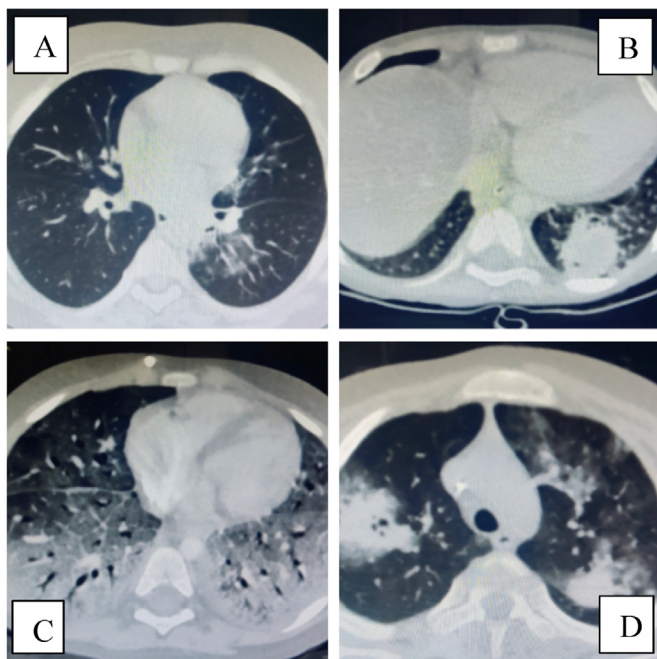


Image 1. Imaging characteristics in two waves Image A .15 year/male with Pre B ALL CT suggestive of ill-defined nodular and ground glass densities in peribronchial and centrilobular distribution in the left lung and right middle lobes. CT severity score is 8/25. Child had mild respiratory distress and was given oxygen by mask. Image B. 3year/ female with Pre B ALL. CT chest suggestive of enlarged necrotic, mediastinal and left hilar nodes, cavitary lesion in the left lower lobe and multiple nodular lesions in bilateral lung field. Likely tubercular aetiology. Image C. 4 year/male with medulloblastoma. CT suggestive of ground glass opacities in both lungs consistent with ARDS with organized consolidation in bilateral lower lobes. CT findings corroborated with clinically and child needed HFO. Image D. 13 year/male with Pre B acute lymphoblastic leukemia (ALL). CT showing large irregular areas of consolidation with ground glass in apical segment right upper lobe. CT severity score (CTSS) is 16/25. Child was extremely sick and needed hospitalization in the ICU unit.

astronomical and saturated the health care facilities within no time [8]. The culprit of the second wave was a delta strain (B.1.617.2) that was ≈ 2.5 times more transmissible than the strain of the first wave [9,10]. Since the emergence of variants, their spread across the globe has been fast and studies highlight that they are more severe with higher risk of mortality, hospitalizations and Intensive care unit (ICU) admissions [11]. Other reasons contributing to the further outbreak are lack of covid appropriate behaviour by the public and vaccination coverage that still doesn't cover the majority of pediatric population and adults completely. Data suggests that higher age, requirements of oxygen and ventilation, ICU admission, and organ impairment were more prevalent in the admitted COVID-19 cases during the second wave [12].

We have previously reported data of our patients with COVID-19 infection during the first wave [13]. We further studied the clinical profile and outcomes of the children with haematological illnesses, cancer and recipients of hematopoietic stem cell transplant (HSCT) who developed COVID-19 infection during the second wave in 2021. The study intends to compare the two waves, describe the complications of COVID-19, help formulate the baseline data to compare with future waves of SARS-CoV2 and aid in policy/strategy making.

2. Materials and methods

Study design, duration –This is a retrospective study from a tertiary care centre in North India conducted during the first and

second wave of the SARS-CoV-2 pandemic. The first wave included cases between March and December 2020 and the second wave included cases between March 2021 and June 2021 with a follow up till mid-October 2021.

2.1. Participants

- Children between 0 and 18 years, who were treated for a hematological illness, malignancy or those who underwent HSCT regardless of the current treatment status with confirmed COVID-19 positivity (SARS-CoV2 antigen/COVID Real-time reverse transcriptase-polymerase chain reaction (RT-PCR)/rapid realtime PCR (GeneXpert/biofire).
- Patient with above mentioned underlying illnesses who developed MIS-C (Multisystem inflammatory syndrome of children) as per WHO criteria.

The institutional protocol and the Delhi government policy suggested COVID-19 testing for patients with malignancies prior to administering chemotherapy, regardless of their symptoms. We therefore tested asymptomatic patients on fortnightly basis and symptomatic patients at presentation. The patients underwent antigen testing (Antigen standard Q COVID-19 antigen kit) or RT-PCR testing (Argene kit) or rapid real-time PCR test (GeneXpert/BioFire- Xpert kit) based on urgency of admissions, kit availability in the hospital. Repeat testing was performed every 5 days for the hospitalized patients during the first wave and every 7 days during the second wave and after 2 weeks for patients in home quarantine. Baseline blood investigations for all admitted patients included complete blood counts, liver and kidney functions, IL-6, serum ferritin and N-terminal pro b-type natriuretic peptide (NT-pro BNP). Children with mild symptomatology and normal oxygen saturation were managed at home and tele-consultation service was provided twice a day. A 24-h helpline service was provided to all patients on home quarantine. Patients received treatment for COVID-19 as per the institutional protocol and in accordance with the national guidelines for the management of COVID-19, issued by the government from time to time. Patients presenting with clinical features suggestive of MISC and fulfilling the WHO criteria were included. Patient underwent antibody testing as per VITROS Immunodiagnostic Anti SARS-CoV-2-IgG.

Exclusion criteria – Patient suspected to have COVID-19 infection without definitive evidence of positive antigen/PCR test report.

2.2. Statistical analysis

Data was described in percentages for categorical variables and as the mean \pm standard deviation and median for continuous variables. No sample size calculations were performed as all cases with COVID-19 positivity were enrolled. Percentage of children were compared using chi square tests. Demographic and clinical profile in the two groups were compared using chi-square for qualitative data and *t*-test for quantitative data.

3. Primary objectives

To compare the prevalence, clinical, laboratory parameters and outcomes of COVID-19 infection during the two waves of the pandemic in pediatric hematology oncology and HSCT patients during the first and second wave of SARS-CoV2 pandemic.

4. Results

A total of 181 children were tested during the first wave during 10 months with 650 tests performed (COVID RT-PCR, Covid antigen,

Biofire, COVID antibody) and total of 149 children were tested during the second wave with 280 testes performed(COVID RTPCR, Covid antigen, Biofire, COVID antibody). A total of 48 (22 during first wave, 26 during the second wave) COVID-19 positive patients with primary infection or MISC(Multisystem inflammatory syndrome in children) were identified based on WHO criteria during the two waves in our unit. The positivity rate was 12.1% during the first wave and 17.4% during the second wave.

4.1. Demography

Table 1 shows Demographic and symptomatology profile of COVID-19 positive patients.

Diagnosis - Majority of the patients in both waves had haematolymphoid malignancy (First wave - n = 17/22, 77.2%, second wave - n = 19/26,65.3%). Other cases included Ewing's sarcoma (First wave - n = 1), aplastic anaemia(First wave - n = 1), post-transplant patients (First wave - n = 3), refractory neuroblastoma (second wave - n = 1), metastatic rhabdomyosarcoma (second wave - n = 1), metastatic medulloblastoma post radiotherapy (second wave - n = 1) and haematological illness as ITP and iron deficiency anaemia (second wave - n = 1 each). Majority of the patients were receiving active chemotherapy/immunosuppression(First wave - n = 21/22, 95.4%, second wave - n = 21/26,80%).

Clinical Features - Majority of the patients in both waves were asymptomatic (First wave - n = 12/22, 54.5%, second wave - n = 19/26,65.3%) and most of them were diagnosed to have COVID-19 based on screening test before in-patient admission for chemotherapy. Amongst the symptomatic cases, most common symptom

was fever (first wave, n = 7/22; second wave n = 5/26) and cough (first wave, n = 7/22; second wave n = 4/26).

Table 2 shows details of symptomatic patients in two waves (First wave, n = 10/22; second wave n = 7/26).

4.2. Laboratory parameters

Table 3 shows laboratory parameters (mean/median) during the first and second wave.

Hospitalization and Treatment- Majority of patients were managed at home during both waves (First wave, n = 13/22, 59%, Second wave n = 22/26, 84.6%) using teleconsultation services. More patients were hospitalized in the first wave probably due to the fear of unknown outcomes (first wave -9/22, second wave- 4/26). ICU admissions (first wave -3/22, second wave- 3/26) and patients requiring oxygen support (First wave -3/22, second wave-4/26) were similar in both the waves. Median duration of hospital stay was prolonged during the second wave (first wave -6 days (n = 9, range = 3 days-49 days), second wave- 9 days (n = 4, range = 8 days-17 days). The course of illness was more complicated during the second wave.

All patients received oral Vitamin C and zinc. A total of 6 patients received steroids during active COVID-19 disease, 3 for the treatment of the underlying leukemia, 1 for treatment of chronic graft versus host disease (GVHD), 1 for the treatment of autoimmune hemolytic anemia associated with Hodgkin's lymphoma, and 1 for the treatment of MIS-C. The steroid usage was thus guided by clinical judgement. Contrary to the first wave, all the patients admitted during the second wave received early glucocorticoids.

Table 1
Demographic and symptomatology profile of COVID-19 positive patients.

Patient characteristic	First wave	Second wave
Median age (inter quartile range)	n = 22,Total = 181 7.6 years (3-13.25)	n = 26,Total = 149 6 years (4-12)
Gender		
Male	17 (77.2%)	16 (61.5%)
Female	5 (22.7%)	10 (38.4%)
Diagnosis		
Pre-B Acute lymphoblastic leukemia	11	15
T-lymphoblastic lymphoma	1	1
B lymphoblastic lymphoma	0	1
Mixed phenotype Acute leukemia	1	0
Chronic myeloid leukemia	0	1
Relapse T lymphoblastic leukemia/lymphoma	1	1
NHL (Burkitt leukemia)	2	1
Hodgkin's lymphoma	1	0
Ewing's sarcoma	1	0
Aplastic anemia	1	0
JMML	1(Post HSCT)	0
Metastatic rhabdomyosarcoma	0	1
Medulloblastoma	0	1
Refractory neuroblastoma	1(Post HSCT)	1
HLH	1(Post HSCT)	1
Iron deficiency anemia	0	1
Chronic ITP	0	1
Symptomatology profile		
Fever	7	5
Cough	7	4
Coryza	7	3
Breathlessness	3	2
Chest pain	1	0
Gastrointestinal	1#	0
CNS symptoms	2*	0
Rash	1	0

n = number of positive patients in each wave,Total = total number of patients tested in each wave,HSCT-hematopoietic stem cell transplantation, JMML-juvenile myelomonocytic leukemia, HLH- hemophagocytic lymphohistiocytosis, NHL- Non-Hodgkin lymphoma, ITP-Immune thrombocytopenic purpura.

#- bloody diarrhoea,vomiting, *- seizures (?cause),irritability.

Table 2
–Details of symptomatic patients in two waves (First wave, n = 10/22; second wave n = 7/26)–.

S. no	Age	Gender	Wave concerned	Diagnosis	Symptoms	Managed at	Comorbidities/Complications	Status
1	2yr	male	First	Pre B ALL	Fever, cough, coryza Difficulty breathing, vomiting, Diarrhoea, seizures, irritability rash	ICU	Invasive candidiasis Pulmonary Aspergillosis Encephalopathy Febrile neutropenia Dyselectrolytemia Gastroenteritis	Recovered
2	6 yr	male	First	Pre B ALL	Fever, Cough coryza	COVID ward	None	Recovered
3	2 yr	male	First	Burkitt leukemia	Fever, cough	home	None	Recovered
4	15 yr	male	First	Refractory HLH post haploidentical transplant	Breathing difficulty, vomitings	ICU	Adenovirus BKvirus reactivation	Recovered
5	13 yr	Male	First	Pre B ALL	Fever coryza	Home	None	Recovered
6	14 yr	Male	First	Relapse T LL	Breathing difficulty Chest pain	COVID ward	COVID pneumonia	Recovered
7	14 yr	Male	First	Pre B ALL	Fever, Cough, coryza Sore throat	Home	None	Recovered
8	5 yr	Male	First	Burkitt Leukemia	Fever, cough, coryza	Home	None	Recovered
9	3 yr	female	First	Pre B ALL with hyperdiploidy	Fever, coryza cough, seizures	ICU	MISC Pulmonary TB Cardiogenic shock PRES Febrile neutropenia	Recovered
10	6 yr	male	First	Pre B ALL	Cough, coryza	Home	None	Recovered
11	8 yr	Male	Second	B LL	Cough, Coryza Sore throat	Home	None	Recovered
12	3 yr	female	Second	Pre B ALL	Fever, Cough Coryza, Sore throat	Home	None	Recovered
13	15 yr	male	Second	Pre B ALL	Fever cough	COVID ward	COVID pneumonia (8/25)	Recovered
14	3 yr	male	Second	Pre B ALL	Fever, Cough coryza	Home	None	Recovered
15	13 yr	male	Second	Pre B ALL	Fever	ICU	COVID pneumonia (16/25), Pulmonary and CNS Aspergillosis, E coli pneumonia Pseudomonas sepsis Pneumothorax	Recovered
16	3 yr	female	Second	Primary HLH COVID triggered	Fever Difficulty breathing	ICU	Cytokine storm Coronary dilatation Hyperbilirubinemia	Recovered
17	4 yr	male	Second	Metastatic medulloblastoma post radiotherapy	Difficulty breathing	ICU	MISC Coronary involvement CMV pneumonia	Recovered

ALL_ acute lymphoblastic leukemia, LL-lymphoblastic lymphoma, HLH-hemophagocytic lymphohistiocytosis, HFNC- High flow nasal cannula, NIV-Non-invasive ventilation, ATT-anti-tubercular treatment, IVIg-Intravenous immune globulin, CMV-Cytomegalovirus.

Table 3
Laboratory parameters (mean/median) during the first and second wave.

Laboratory parameter	First wave n = 22	Second wave n = 26	Normal laboratory range
Mean hemoglobin (g/dl)	10.3 g/dl n = 22	9.5 g/dl n = 26	11.1–14.1 g/dl
Mean total leucocyte count (/cumm)	4.1 × 10 ⁹ /cumm n = 22	4.3 × 10 ⁹ /cumm n = 26	6–16 × 10 ⁹ cells/L
Mean platelet count	18.36 × 10 ⁹ n = 22	78.24 × 10 ⁹ n = 26	200–400 × 10 ⁹ /L
Median SGOT (IQR)	68 IU/L (43.5–221) n = 8	33 IU/L (19–146) n = 5	0–55 IU/L
Median SGPT (IQR)	37 IU/L (16–145) n = 11	28 IU/L (18–79) n = 7	0–55 IU/L
Median IL6 (IQR)	22.53 pg/ml (5.9–504) n = 7	61 pg/ml (6.5–783) n = 5	<6.40 pg/ml
Median Ferritin (IQR)	1123 ng/ml (376–3245) n = 7	1377 ng/ml (978–3311) n = 6	21–274 ng/ml
Median D Dimer (IQR)	0.67 µg/ml (0.25–2.265) n = 7	0.4 µg/ml (0.275–2.7) n = 5	<0.25 µg/ml
Median LDH (IQR)	262 IU/L (206–421) n = 7	279 IU/L (206.5–584) n = 5	210–340 IU/L

IQR – inter quartile range, IL6-Interleukin 6, LDH-Lactate dehydrogenase.

Azithromycin (First wave, n = 20/22, second wave, n = 6/26) and Ivermectin (First wave, n = 10/22, second wave, n = 00/26) usage declined during the second wave and antiviral therapy (Remdesvir) (First wave, n = 2/22, second wave, n = 4/26) became the frontline for all admitted patients. Steroid nebulisations were increasingly

used during the second wave. None of the patients during both waves received prophylactic anticoagulation, convalescent plasma therapy or tocilizumab.

4.3. Life threatening complications noticed during the 2 waves

4.3.1. First wave-

Invasive candidiasis and encephalopathy- A 3 year old newly diagnosed child with ALL presented with severe encephalopathy and COVID-19 infection. Within a week of diagnosis, he developed invasive candidiasis (blood culture positive for *Candida tropicalis*) with pulmonary aspergillosis.

Tubercular reactivation and MISC- A 3 year old girl with ALL developed severe MISC and coronary artery dilatation. She was managed with IVIg and steroids. She developed persistent fever during ALL induction when she was severely neutropenic and after extensive work up was found to have extensive tubercular activation in lungs and mediastinal lymph nodes.

4.3.2. Second wave

Cerebral/pulmonary aspergillosis, polymicrobial sepsis and pneumothorax- Thirteen year old boy developed severe COVID-19 pneumonia with CT severity score of 16/25 on CT chest (Figure Image 1). He required non-invasive ventilation with high frequency nasal canula. After recovery from COVID pneumonia, he developed sepsis with pseudomonas, E coli and invasive pulmonary aspergillosis complicated with pneumothorax. He was managed with IV amphotericin B and voriconazole. He responded well but later developed generalised seizures. MRI evaluation showed presence of multiple aspergillomas. He is on decongestive therapy and is stable on oral voriconazole for the last 6 months with improvement in Magnetic resonance imaging (MRI) findings.

Hemophagocytic lymphohistiocytosis- A 3 year old girl presented with severe pancytopenia and features of florid HLH in bone marrow. She had strong COVID-19 antibody (total antibody –1140 IU/ml, ref range >1 – positive for anti-SARS-CoV-2), Serum ferritin was 39113 ng/ml and sIL2 receptor level was 2918 U/ml (upper limit for age is 2000U/ml). She was managed in the intensive care unit for 13 days and required inotropes. Steroids, intrathecal methotrexate, cyclosporine and intravenous chemotherapy including etoposide was given as per HLH 2004 protocol. She was later found to have heterozygous PRF1 mutation. She underwent haploidentical transplant from her mother with TCR alpha beta depletion and is day 40 post-transplant with full donor chimerism.

Florid MISC with CMV infection- A child with medulloblastoma developed MISC and decompensated during the inflammatory cytokine storm. He was hemodynamically unstable and needed high frequency oscillatory ventilation along with three inotropes. He improved with IVIg and steroid therapy. He developed coronary artery dilatation with Z score of +2.70 in LAD (Z score +1.85 in LMCA, +1.88 in RCA) which completely recovered after 15 days. He continued to have oxygen requirement and showed features of interstitial lung disease. BAL was positive for CMV infection and he was managed with valganciclovir for 6 weeks.

MISC - We encountered 3 children with MISC based on WHO criteria during the two waves, one during the first wave and two during the second wave. The patient during the first wave was a 3 year old girl with ALL with severe MISC, coronary artery dilatation and tubercular activation in lungs and mediastinal lymph nodes. During the second wave, MISC cases were a child with medulloblastoma requiring high frequency oscillatory ventilation along with three inotropes with late CMV infection and another case with Pre-B ALL managed with short course oral steroids at home (Figure Image 1).

Time to COVID-19 negativity - The mean time to RT-PCR COVID-19 negativity was 21.3 days (7–63 days) (n = 22) during the first wave and 11.5 days (7–17 days) (n = 13) during the second wave. Six patients during the first wave had persistent COVID positivity,

maximum being up to 63 days. None of the patients were repeat positive when repeated after 14 days during the second wave.

Delay in chemotherapy- Cancer treatment was altered in 15 patients during the first wave and 10 patients during the second wave. The next scheduled cycle of chemotherapy was delayed (First wave –7/15, second wave- 8/10), maintenance chemotherapy was withheld (First wave –3/15, second wave- 1/10), surgery after neoadjuvant chemotherapy was deferred (First wave –1/15), and the use of drugs such as daunorubicin and rituximab was omitted (First wave –4/15, second wave- 1/10).

Chemotherapy interruptions declined during the second wave. The absolute number of patients with chemotherapy delay for the next cycle increased during the second wave. However, the median time to delay (First wave –14 days, second wave –9 days) reduced and the maximum delay period was kept as minimal as possible. We did not routinely add metronomic/oral chemotherapy to our patients facing delay in receiving the next cycle as the delay was minimal. The maintenance chemotherapy was withheld for a maximum of 7 days and restarted once the child was afebrile, free from symptoms and stable at home. We did modify administration of some myelosuppressive agents for example-skipped daunorubicin for ALL patients on induction chemotherapy if they developed COVID-19 infection and delayed rituximab for Burkitt leukemia patients till complete recovery from active COVID-19 infection.

Outcome - All patients had favourable clinical outcome from COVID-19 infection. All-cause mortality rate was 6.2% (n = 3) due to refractory neuroblastoma, early relapse T Lymphoblastic Lymphoma and a relapsed T cell leukemia. No COVID related mortality was documented in our cohort.

Delayed Sequelae - Two patients with MISC who developed coronary artery dilatations completed recovered and have normal fractional shortening on follow up scans. The child with cerebral and pulmonary aspergillosis continues on oral antifungals for the last 6 months with stable CNS aspergillomas. The child with pulmonary TB completed her course of ATT along with chemotherapy.

4.3.3. COVID antibody on follow up

COVID antibody testing was done in 10 patients during the first wave and 14 patients during the second wave. There was a trend of increased antibody titre during the second wave. Mean antibody titers were 182.4 IU/ml (n = 10, Range 0.1–638 IU/ml) during the first wave and 367.1 IU/ml (n = 14, Range 0.03–1140 IU/ml) during the second wave.

Two (9%) patients had negative antibody titer during the first wave, one being familial burkitt leukemia with underlying immunodeficiency. Three patients had negative antibody during the second wave, one being Burkitt leukemia and one being negative antibody MISC patients with medulloblastoma.

5. Discussion

Not only children with haemato-oncological illnesses had to face significant interruptions in treatment and logistic challenges that COVID-19 bestowed, it also led to increased morbidity and financial burden. The first wave witnessed usage of many therapeutic strategies, mostly out of desperation without adequate scientific proof of the benefit. Emergence of new mutations and rapidity of its spread exhausted the health care facilities and personnel. We looked at the extent of damage the virus did to pediatric hematology, oncology and HSCT patients on regular follow up with our unit.

Mean positivity rate during the first wave was 12.1% and during the second wave was 17.4%. The absolute incidence of COVID-19 amongst pediatric cancer patients continues to be low in first wave as well as second wave.

Median age at diagnosis showed a decreasing trend in our study from first wave to second wave. The trend to younger population involved is seen among children as well as adults during the second wave [14–17].

Similar to general population who were affected with COVID-19, majority of our patients during the second wave were asymptomatic [16,18]. There is also decreasing trend of fever and cough as the presenting symptom as observed in our study. Though studies showed more gastrointestinal symptoms during the second wave in general population, our cohort had lesser such symptoms when compared to the first wave [19]. Two of our patients during the first wave had neurological symptoms. One was encephalopathy of unknown origin and other child presented with PRES. The causal relationship with COVID-19 could not be established. However, literature does support that COVID-19 may precipitate neurological events in children [20,21].

We observed a higher median ferritin and median Interleukin 6 (IL6) levels during the second wave similar to other studies thereby explaining severity of cytokine storm and indirectly the cellular damage and organ dysfunction [22].

CT chest was extensively used during the second wave in diagnosing and prognosticating COVID-19 cases. CT severity score is used as a semiquantitative imaging tool and studies show the cut-off of 6.5/20 (with about 32.5% lung involvement) had 90.9% sensitivity and 69% specificity for identification of severe cases [23]. The most widely used method is based on scoring of percentage of involvement of each lobe and total score of 0–25 [24]. The CT findings of COVID-19 ranged from consolidation patches with air bronchogram, pulmonary nodules and atelectatic fibrous bands to extrapulmonary findings in the form of pleural effusion and pericardial effusion. Two of our patients from second wave had CTSS >7 and bilateral lung involvement. Both of these required oxygen support. Follow up scans in one patient with Pre B ALL showed invasive pulmonary aspergillosis.

Duration to negative RTPCR is variably found in studies from 10 days to 5 weeks. Studies have reported unfavourable outcome in persistent positive cases [25]. We observed that the time to negativity decreased during the second wave. The maximum persistent positivity during the first wave was 63 days in a child with HLH post haploidentical transplant who required intensive care whereas the maximum duration during the second wave was 14 days.

Although scarce, some studies have supported that patients with haematological malignancy mount a good antibody response and high rate of seroconversion [26,27]. Eight out of 10 (80%) and 11 out of 14 patients (73.5%) had positive antibody titres during the first and second wave respectively. Prospective studies are needed to analyse if these antibodies are sustained in the system and rise in titres once again if exposed to the virus. These patients should also be considered for clinical trials on safety and efficacy of vaccination [28].

The unique syndrome of MIS-C can also bring additional challenges in managing children with compromised immunity. We encountered 3 children with MIS-C based on WHO criteria [29]. Two children needed intensive care therapy including one child with medulloblastoma requiring high frequency oscillatory ventilation. Two of these patients developed coronary artery dilatation. These dilatations resolved on follow up and none had residual cardiac sequelae.

Some of our patients who developed COVID-19 illness were later found to have secondary complications, mainly in form of infections. One of the our patients had CMV infection one month post recovery from MIS-C. There has been case reports of COVID-19 and CMV co-infection in critically ill patients caused by the increasingly widespread use of *anti-IL-6* and *anti-IL-1* biological therapies in COVID-19 [30]. However, underlying immunocompromised status,

primary illness and prolonged steroids for MIS-C may explain CMV reactivation in our patient even though *anti-IL* therapies were not used.

Another child with Pre B ALL had pulmonary tuberculosis during the induction chemotherapy with MIS-C. Studies have postulated that COVID-19 infection may boost the development of active TB [31]. Prolonged T cell depletion post COVID infection, excessive usage of steroids, malnutrition and general debility may cause reactivation of latent TB in our patients [32].

Viruses have been traditionally associated with precipitation of HLH. COVID-19 triggered severe hemophagocytosis in a child with primary HLH has not been reported. During the second wave, a patient presented with life threatening hemophagocytosis triggered by COVID-19 and she was found to have compound heterozygous PRF1 mutation. This child needed extensive supportive therapy in ICU. She was given etoposide, steroids and cyclosporine based chemotherapy. After 10 weeks of treatment and control of inflammatory state, she successfully underwent haploidentical transplant with TCR alpha beta depletion.

Reinfection by SARS-CoV-2 is rare but has been documented. Surveys have identified a re-infection proportion of 4.5% from a pool of 1,300 participants infected between January 2020 and October 2020 [8]. Case report from pediatric oncology pool have reported reinfection as well [33]. In our study we found reinfection in one patient. This was a case of Burkitt leukemia who received 3 rituximab doses prior to his infection during the first wave. We withheld rituximab doses in the immediate post recovery chemotherapy due to poor outcomes of COVID-19 in patients with cancer and connective tissue disorders who have been treated with rituximab, [34]. The child had low titre antibody positivity (3.41 IU/ml) during the first wave but negative antibody response during the second wave. This could be explained by rituximab mediated humoral depletion which could compromise antiviral immunity, including development of SARS-CoV-2 antibodies, increase the risk of reinfection, and impair vaccine efficacy [35]. His clinical course was uneventful both times and recovered without any hospitalization.

The absolute number of patients with alteration in chemotherapy was less during the second wave. The median delay time was less and the maximum delay time was also kept as minimum as possible. This is because of the building evidence and confidence in continuing therapy in patients who are not unwell, and monitoring lessons learnt from first covid wave. The threat of cancer and relapse in these children is more than what a mild covid-19 disease could do. Most of pediatric guidelines have supported continuation of chemotherapy as comparison to adult guidelines who often need interruption due to co morbidities and complications of the viral infection [36].

We understand that the research was limited to patients from a single centre in North India. However, in the face of low incidence of COVID-19 in hematology and oncology children, our analysis is an aid to clarify the epidemiological and clinical data on pediatric COVID-19 in this vulnerable population.

Although, our analysis does not show mortality during the two waves, our patients did suffer from multiple significant complications and sequelae of SARS-CoV-2 infection.

6. Conclusion

COVID-19 infection in pediatric hematology and oncology patients may lead to significant morbidity and complications that interfere with treatment of their primary illnesses. These patients need close monitoring for development of life threatening infections. Early recognition and prompt therapy can optimise outcomes.

Consent

As it was a retrospective study, waiver of consent was taken from Institutional Ethics committee.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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