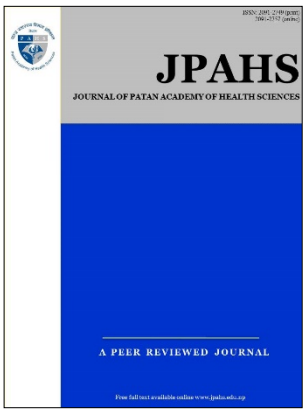

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Clinical profile and outcome of COVID-19 in pediatric hematology-oncology patients

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Abstract

Introduction: Pediatric hematology-oncology patients are assumed to be predisposed to severe COVID-19 disease and complications, but robust data from low- and middle-income countries is lacking. This study was designed with the primary objective of finding the prevalence and outcome of COVID- 19 in children with hematological or oncological diseases. Clinical characteristics of COVID-19, outcomes in terms of need for respiratory support, intensive care, mechanical ventilation or mortality, delay in therapy, and use of COVID-19 directed therapy were analyzed.

Method: Retrospective review of all children with hematological or oncological diseases with confirmed COVID-19 managed at Patan Hospital from Jan 2020 to Sep 2021. Patients were screened according to the hospital screening protocol. The clinical characteristics and outcomes of COVID-19 along with the delay in chemotherapy or local therapy were recorded.

Result: Twelve children tested positive for SARS- CoV-2 during the study period, and one had reinfection with COVID-19, 9(75%) were oncology patients, while 3(25%) were hematology patients. Fever (83.3%) was the most common symptom, followed by cough (58.3%). Four (33.3%) children had mild infections, and 4(33.3%) had severe infections. Eight oncology patients had delays in starting or continuing chemotherapy or undergoing surgery due to COVID-19. The median duration of delay was 10.5 d (range-7-21 d). The delay in therapy in patients with COVID-19 was significant in comparison to children without COVID-19.

Conclusion: The majority of pediatric hematology-oncology patients recovered from COVID-19 without sequelae. There was a delay in providing treatment to oncology patients due to changing protocols.

Keywords: Cancer, children, COVID-19

Introduction

Coronavirus disease 2019 (COVID-19) caused by novel severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) has created havoc all over the world.[1] Most countries are struggling to control the spread of virus and healthcare systems are struggling to stay afloat.[2] The brunt of infection has been taken by the elderly and people with co-morbidities.[1] Studies show immunocompromised adults succumbed more to COVID-19 in comparison to the healthy population.[3] Children remain comparatively safer age group, but the same might not hold for immunocompromised children as comprehensive data is not available.[1,4,5] The dilemma for pediatric oncologists is whether to go ahead with intensive immunosuppressive therapy versus low dose bridging therapy or withhold therapy given the ongoing pandemic. Challenge remains as recent reviews show higher mortality and increased severity of disease in pediatric oncology patients[4] in contrast to previous studies showing risk at par to normal children.[6,7]

Data regarding the prevalence and outcome of COVID-19 in children with malignancies is scarce. A retrospective study from the USA revealed higher morbidity and mortality in pediatric oncology patients than normal children[1] whereas an Indian study revealed that 7% of patients required respiratory support.[8] The status of this group of children in Nepal is under-reported, thus this study will help in further management of this cohort of children. As the pediatric hematology-oncology services at Patan Hospital, Patan Academy of Health Sciences (PAHS) was started 2 y ago, this study aimed to describe the clinical characteristics, natural history, and outcome of COVID-19 in children with hematological and oncological diseases.

Method

This is a retrospective chart review of all the children with underlying hematological or oncological diseases with COVID-19 confirmed by RT-PCR or COVID antigen detection test managed at Patan Hospital, Patan Academy of Health Sciences (PAHS) from January 2020 till September 2021. Ethical approval was obtained from the Institutional Review Committee of PAHS following which data collection was done. Patient information was extracted from medical records and electronic data using hospital numbers. Patients with incomplete data were excluded from the study. The data were deidentified to ensure strict anonymity. For COVID-19 positive patients, data on demographics, clinical symptoms, the severity of COVID-19[6](Table 1), investigations, imaging, hospital course, stage of cancer-related therapy, the severity of chemotherapy[1](Table 2), and impact of COVID-19 on the therapy were extracted from records.

As per the protocol, on presentation to the hospital for inpatient or outpatient care, children were screened for the presence of COVID-19 related symptoms or exposure to contacts with SARS-CoV-2 infection. The screening criteria for COVID-19 was based on the hospital protocol which was revised thrice during the study period in September 2020, October 2020, and June 2021 respectively. Children with fever and respiratory symptoms were tested for SARS-CoV-2 infection in their nasopharyngeal and oropharyngeal swabs using reverse transcriptase-polymerase chain reaction (RT-PCR) test while with fever with gastrointestinal or any other symptoms related to COVID-19 without respiratory symptoms were tested with either COVID antigen detection or RT-PCR test. The RT-PCR test was also instituted in asymptomatic children before elective surgery, radiation, deep sedation for invasive procedures, or each cycle of myelosuppressive chemotherapy. The elective surgery was withheld in children who tested positive till RT-PCR for COVID-19 was negative and the patient was clinically stable. The decision to start or continue myelosuppressive chemotherapy was based on the clinical status of the patient and the urgency of treatment.

All hematology patients with fever and respiratory distress were admitted and treated with empirical intravenous antibiotics and

were continued till the child was afebrile for at least 24 h and blood culture at 72 h of inoculation was sterile. All oncology patients with fever and neutropenia (Absolute neutrophil count<500/mm^3) were admitted and treated with empirical intravenous antibiotics after sending blood culture irrespective of the RT-PCR report. The antibiotics were continued till blood culture at 72 h of inoculation is sterile and the patient was afebrile for at least 24-48 h. Antibiotics were started depending upon the departmental protocol for febrile neutropenia patients. Oncology patients on mild chemotherapy with fever and without neutropenia and respiratory distress and symptomatic patients were managed at home with intermittent review by the treating physician over the phone.

Descriptive analysis was performed using Microsoft Excel. Categorical data are presented with frequency and percentage. The sub-group analysis to find the association between the delay in chemotherapy or surgery in oncological patients with COVID-19 was performed using the Chi-square test. p-value $\leq$0.05 was considered statistically significant. All patient identifiers were replaced in the study by case identification numbers to protect the privacy of the patient.

Result

There was a total of 35 patients under the age of 14 y with various hematological and oncological diseases managed at Patan Hospital, PAHS till September 2021 out of which 27 had various malignancies. Among them, 12 tested positive for SARS-CoV-2 during the study period and one child with Acute Lymphoblastic Leukemia (ALL) had reinfection with COVID-19 after a period of 9 mo. Among children with various malignancies and COVID-19, 4(33.3%) had acute leukemia making it the most common diagnosis. Among children with non-malignant diseases 1(8%) had hemophilia and 2(16%) had iron deficiency anemia. For symptomatic infection, 9(75%) patients were admitted for treatment whereas one patient with mild disease and two asymptomatic patients were managed at home under the physician's guidance.

All were symptomatic except for 2(16.7%) patients. Both asymptomatic patients tested positive on screening before surgery. Three patients were diagnosed with COVID-19 at the time of diagnosis of malignancy. Out of these, two patients were symptomatic with fever, headache, body ache without respiratory symptoms and both underwent bone marrow aspiration and biopsy under intravenous sedation with ketamine and midazolam for confirmation and categorization of leukemia while suffering from COVID-19.

Only 1(8.3%) patient had a critical illness and he was neutropenic as well as lymphopenic at the time of diagnosis of COVID-19. Mild and severe diseases accounted for 4(33.3%) patients each while 1(8.3%) had moderate disease, Figure 1. The patient with reinfection with COVID-19 had a mild disease in both episodes. He was admitted and given empirical antibiotics during the first episode as he was receiving severe myelosuppressive chemotherapy and was neutropenic. The chemotherapy was withheld during this period. During reinfection, he was receiving mild myelosuppressive chemotherapy and was non-neutropenic thus he was managed at home, and chemotherapy was continued throughout the period and was not started on empirical antibiotics. There were 4(33.3%) neutropenic and lymphopenic patients at the time of diagnosis of SARS-CoV-2 infection. Out of the four patients with neutropenia and lymphopenia, one had critical illness while two had mild disease and one had a moderate disease. Out of four patients with severe disease, one was an oncology patient while three were hematology patients. The patient with critical COVID-19 disease who was referred from another center and was hypoxic

at presentation died within 4 h of hospital admission. The remaining patients recovered from COVID-19 without sequelae. One patient with hemophilia developed intracranial bleeding while suffering from COVID-19 and had to be transferred to another center with a neurosurgical facility. One patient died due to progressive malignancy after recovery from COVID-19. The data regarding the duration of negative RT-PCR reports were available in 7(58.3%) patients. The duration was 4 w in 1(14%) patient, 3 w in 2(28.5%) patients and 2 w in 4(57%) patients.

Out of nine oncology patients, 2(22.2%) were receiving severe, 3(33.3%) moderate, and 1(11.1%) mild intensity chemotherapy; 1(11.1%) was receiving targeted therapy and 3(33.3%) patients were RT-PCR positive for SARS-CoV-2 at the time of diagnosis. Among three patients who were diagnosed with COVID-19 at the time of diagnosis of malignancy, two patients received cancer-directed therapy after testing negative for COVID-19, while one was started on chemotherapy despite a positive COVID-19 report. The patient with COVID-19 at the diagnosis of ALL was started on steroids as a part of chemotherapy rather than as COVID-19 directed therapy. The patient was persistently febrile without respiratory symptoms at the time of starting steroids. None of the children with hematological or oncological diseases received COVID-19 directed therapy like steroids, remdesevir or tocilizumab, or plasmapheresis.

Out of nine oncology patients with positive COVID-19 reports, 8(88.9%) had a delay in starting or continuing chemotherapy or undergoing surgery, which was statistically significant (p value<0.01), Table 5. The median duration of delay in therapy was 10.5 d (range 7-21 d). Two leukemia patients receiving mild intensity chemotherapy continued chemotherapeutic drugs while suffering from COVID-19. Both the patients with mild and moderate diseases recovered without sequelae.

Table 1. Coronavirus severity index[6]

Asymptomatic	Asymptomatic but positive diagnostic test (undertaken for other reasons).
Mild	Symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Clear chest on auscultation. Some cases may have no fever or have only digestive symptoms such as nausea, vomiting, abdominal pain, and diarrhea
Moderate	Signs of pneumonia including fever, cough, and crepitations. No increased work of breathing. No manifestations related to severe disease
Severe	Respiratory distress—respiratory rate ≥70 breaths/min for infants, ≥50breaths/min for children>1year. Oxygen saturation<92%. Dehydration requiring intravenous fluid support.
Critical	Acute respiratory distress syndrome (ARDS) or respiratory failure requiring ventilator support. Signs of shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, or acute kidney injury. Need for ICU support for other reasons

Table 2. The severity of the chemotherapeutic regimen is classified based on the degree of myelosuppression[1]

Mild	Maintenance therapy in leukemia or targeted therapy
Moderate	Interim maintenance therapy for ALL, solid tumor protocols
Severe	Induction, Consolidation, Delayed Intensification therapy for ALL, All AML therapy, Induction therapy for lymphomas

Table 3. Demographics of hematological or oncological patients with positive COVID-19 reports, N=12

Demography	N(%)
Gender	
Male	9(75)
Female	3(25)
Age	
<5years	3(25)
5-10years	1(8.3)
11-14years	8(66.7)
Disease type	
Oncology	9(75)
Acute Lymphoblastic Leukemia (ALL)	3*(25)
Acute Myeloid Leukemia (AML)	1(8.3)
Embryonal Rhabdomyosarcoma	1(8.3)
Hepatoblastoma	1(8.3)
Osteosarcoma	1(8.3)
Chronic Myeloid Leukemia (CML)	1(8.3)
Langerhans Cell Histiocytosis (LCH)	1(8.3)
Hematology	3(25)

*One patient had reinfection with COVID-19.

Table 4. Clinical features, treatment and outcome of hematological or oncological patients with positive COVID-19 reports, N=12

Characteristics	**N(%)**
Clinical features	
Fever	10(83.3)
Cough	7(58.3)
Altered bowel habit	2(16.7)
Headache	2(16.7)
Bodyache	2(16.7)
Treatment	
Oxygen support	5(41.7)
Antibiotics use	9(75)
Outcome	
Mechanical ventilation	1(8.3)
Inotrope support	1(8.3)
ICU care	1(8.3)
Mortality	1(8.3)

Table 5. Association of COVID-19 status with delay in chemotherapy/local therapy among hematology and oncology patients, N=27

COVID-19	**Delay in Chemotherapy**		**Total**	χ^2	p value
	Yes	No			
Positive	8	1	9	12.963	<0.01*
Negative	3	15	18		

*p value - significant

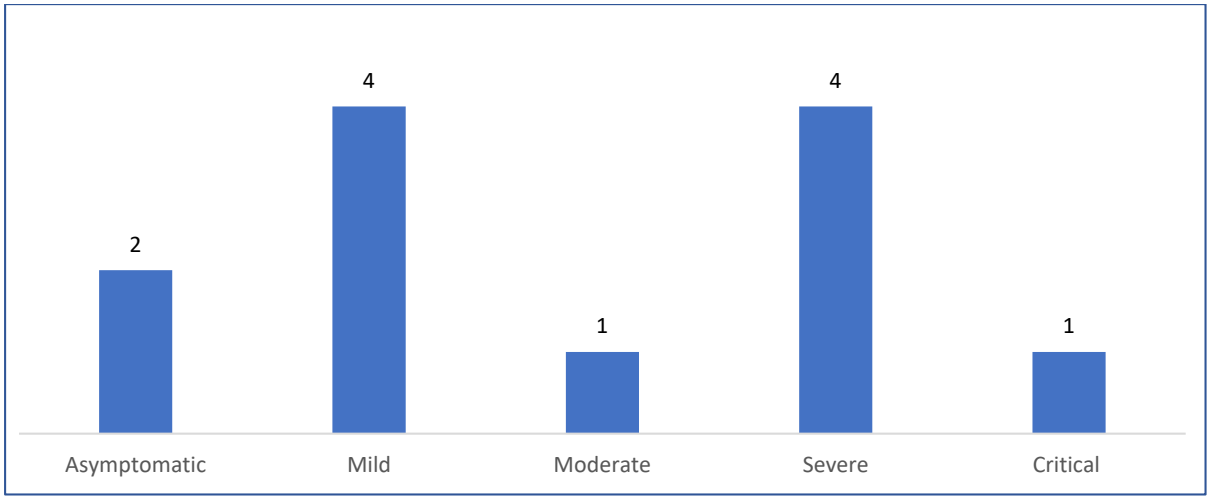

Figure 1. Severity index of hematological and oncology patients presenting with SARS-COV-2 infection.

Discussion

In this study, most children, 6(50%) with malignancies had a mild or asymptomatic infection, which is similar to the findings of other studies reviewing children with COVID-19 and hematological or oncological diseases.[7,9,10] The incidence of symptomatic infection 10(83.3%) in our cohort was also comparable to the incidence of symptomatic infection 26(72.2%) in children without underlying illness in a retrospective study from China.[4] Retrospective review of 19 pediatric hematology-oncology patients from the USA reported that 84% of their children were symptomatic and 32% required respiratory support.[7] One study from a cancer center in Chennai, India reported only 33% symptomatic infection in their cohort of 15 patients, and 7% required respiratory support while 5(41%) of our cohort required respiratory support.[8] The study in Chennai was performed in the early days of the pandemic where all children with malignancies were screened irrespective of the symptoms, which likely explains the contrasting findings from our cohort.[8]

The majority of our COVID-19 positive patients were hospitalized, 10(83.3%), which was in concordance with the retrospective study conducted in New York City where 55(75%) of COVID-19 patients required hospitalization.[1] In contrast to our findings, only 5% of children with cancer required hospitalization for COVID-19 related symptoms in a study from New York City.[11] Similarly, another study of six pediatric oncology patients from the USA showed mild infection in all their cohorts, none requiring hospitalization for COVID-19 or respiratory support.[7] The higher incidence of hospitalization in our cohort is due to the departmental policy of admitting all febrile patients on active treatment for any oncological disease irrespective of their blood counts and clinical status.

In our cohort, treatment was modified in the form of delaying chemotherapy or postponing surgery in more than half of the oncology patients who were positive for COVID-19. The delay was significant in comparison to COVID-19 negative patients. The majority of the delay in therapy was due to the physician's decision to defer the planned therapy rather than due to COVID-related complications. A study conducted in New York City revealed a similar delay in providing cancer-related treatment to patients.[9] The international consensus guidelines also advise to treat oncology patients as per clinical scenario with reasonable adaptations.[12] A group of pediatric oncologists from China recommended to continue chemotherapy in pediatric oncology patients on an intensive phase of therapy

unless they are suspected or confirmed to have COVID-19 and to avoid delay >7 d while children on maintenance therapy delays should be <14 d.[13] The decision to delay critical cancer-directed therapy may adversely affect the long-term outcome in these children, thus pediatric oncologists face challenges regarding therapy. The findings in our study and other studies from USA and Italy indicate that in children without comorbidities except for cancer diagnosis, COVID-19 may not pose a significant threat in comparison to other viral illnesses, and in asymptomatic oncology patients whose therapy cannot be deferred, the myelosuppressive chemotherapy may be considered with close monitoring of patients.[7,9] These results are fairly encouraging as most childhood cancers are aggressive requiring treatment and significant treatment delays can lead to disease progression eventually affecting the prognosis of the disease.

Due to the ongoing pandemic, the problem was not only in providing treatment but also in performing complete risk stratification of patients. One patient with ALL had to be upgraded from intermediate to high-risk category as post-induction Minimal Residual Disease (MRD) remission could not be assessed. Various studies have been published regarding the impact of COVID-19 and delay in diagnosis as well as treatment due to COVID-19 but few studies are depicting the effect of incomplete risk stratification due to unavailability of services in low- and middle-income countries like Nepal.[14,15] As the patient's treatment had to be escalated, the long-term effects of toxic therapy remain unknown. The pediatric hematology-oncology services at PAHS despite being in the very early stages of operation could continue to provide regular services throughout the first and second wave of COVID-19 despite some obstacles in risk stratification and acquiring chemotherapy medications. A cross-sectional study conducted by St Jude Global Alliance and International Society for Pediatric Oncology, Memphis USA including 213 institutions in 79 countries from all WHO regions to study the global effects of COVID-19 pandemic on pediatric cancer care reported complete closure of pediatric cancer care services (median 10 d, range 1-75 d) in 15(7%) centers.[16] They found substantial disruption in cancer diagnosis and management particularly in low- and middle-income countries. Patan Hospital, being one of the treatment centers for suspected and confirmed cases of COVID-19, played a vital role in continuing pediatric hematology and oncology services during the pandemic.

One of the main limitations of our study is the sample size. As the pediatric hematology-oncology services have been recently set up (2 y) at Patan Hospital, PAHS, the number of children undergoing treatment is limited thus contributing to the small number of children in our study which might not depict the true picture in the community. Another limitation is the nonuniform Covid-19 testing policy of patients during the study period. At the beginning of the study, asymptomatic patients admitted for chemotherapy were tested with RT-PCR. During the study, the testing policy was revised as the pandemic situation changed so that asymptomatic patients requiring admission during the study were tested with antigen detection tests, and symptomatic patients with fever and /or respiratory and/or gastrointestinal symptoms requiring admission were tested with RT-PCR test. Our study is thus prone to potential selection bias, exaggerated by the small sample size and the changing policies on testing children during the study period. The third limitation of our study relates to the use of tests for the diagnosis of COVID-19. We have used antigen detection test as the screening test in our study but the sensitivity of this test is limited.[17] The study conducted in Nepal in rapid antigen test in asymptomatic population revealed sensitivity and specificity of 85% and 100% respectively with an accuracy of 93%.[18] This is in contrast to the findings in various studies conducted in other countries where the sensitivity has ranged from 30-

71%.[17,19,20] There are also well-documented concerns regarding the sensitivity of RT-PCR for diagnosis of COVID-19.[21] The study conducted in China revealed only 30-60% sensitivity for RT-PCR test done from oropharyngeal and nasopharyngeal secretions with the highest sensitivity (93%) from lower respiratory secretions.[22] As we test oropharyngeal and nasopharyngeal secretions, we might have missed the cohort of children with cancer and COVID-19 who were not unwell enough to present to the hospital or who had negative antigen or RT-PCR test.

Conclusion

Most of the pediatric hematology and oncology patients with COVID-19 recovered. There was a delay in the treatment of oncology patients with COVID-19 due to changing protocols.

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Conflict of Interest

None

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None

Author Contribution

Concept, design, planning: ALL (ST, PA, RR, AM, ARO, GS); Literature review: ST, PA, AM; Data collection/analysis: ST, PA, RR, AM; Draft manuscript: ST, PA, RR; Revision of draft: ALL; Final manuscript: ALL; Accountability of the work: ALL

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