

COVID-19 Prevalence and Survival Outcome in Pediatric Cancer Patients Undergoing Chemotherapy: A Study from Tertiary Cancer Center of North-East India

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Background: Pediatric cancer patients are considered one of vulnerable group for Covid-19 infections and its associated complication. We assessed Covid-19 prevalence and implications in pediatric cancer patients of NorthEast India.

Methods: Retrospective study was conducted between July 2020 to June 2021 at Dr B Borooah Cancer Institute (BBCI), Guwahati, Assam, India. Medical records of the childhood cancer patients were analyzed. All patients who were tested for SARS-CoV-2 were collected. All childhood cancer patients with age group between one to eighteen years were included.

Results: Fifty two out of 701 (7%) cancer patients in children were found to be positive for SARS-CoV2 by RT-PCR testing. Among COVID-19 positive patients, the median age was six years. In COVID-19 positive group, thirty (57.6 %) were suffering from hematological malignancy and twenty two (42.4%) have solid malignancy. In COVID-19 positive group, Among the hematological malignancies; acute lymphoblastic leukemia (ALL) comprises 70% (21), acute myeloid leukemia (AML) 16.66% (5) and lymphoma accounting for 13.33%. Fever, cough and sore throat was presenting symptom in majority of patients. Survival outcome has shown statistically significant association ($p=0.0001$) between COVID-19 positive and negative pediatric cancer patients. Eight deaths occurred in COVID-19 positive patients but there was only one death in COVID-19 negative patients.

Conclusion: Among COVID-19 positive childhood cancer patients risk of death was significantly higher compared to COVID-19 negative patients and majority of deaths occurred in hematological malignancies receiving intensive chemotherapy.

Introduction

Childhood cancers are rare comprising of 0.5% to 4.6% of all cancers, but with a very high cure rate. World health organization has under taken many initiatives in low and middle income countries towards improvement of survival among childhood cancer patients [1]. At present, the world is in the middle of a pandemic which is posing as the biggest challenge to public healthcare in many countries. Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is the causative agent of corona virus disease 2019 (COVID-19) [2]. Since its emergence in Dec 2019, it has resulted in 236 million infections and 4.8 million deaths worldwide [3]. India accounts for 7% of the total COVID-19 positive cases as of October 6, 2021 [4]. SIOP-PODC (Pediatric Oncology in Developing Countries) has been instrumental in developing resource adapted treatment protocol for LMIC for six common childhood cancers [Burkitt lymphoma, acute lymphoblastic leukemia (ALL), retinoblastoma, low grade glioma, Hodgkin lymphoma and Wilms tumor [5]. The COVID-19 pandemic has created an unprecedented global challenge in maintenance and continuity of established treatment regimen implementation for children with cancer in both developed as well as developing countries [6].

Due to their immunocompromised status, Pediatric cancer patients constitute one of the most vulnerable groups of individuals for COVID-19 infection as well as its associated morbidity & mortality compared to general population [7]. Memorial Sloan Kettering Cancer Center and New York Presbyterian Hospital have reported 7% and 20% COVID-19 positivity among pediatric cancer patients respectively [8]. In Madrid, incidence of COVID-19 infection in childhood cancer patients was found to be 1.3% higher compared to the general pediatric population [9]. In Turkish patients with hematological malignancy, it was reported that case fatality rate was 13.8% compared to 6.8% in the patients without cancer [10]. It was also reported that pediatric patients with cancer may not be more vulnerable to SARS-CoV-2 infection and resulting morbidity compared to other children [11]. A multicentric and multi country survey showed Covid-19 incidence and severity among children on anticancer treatment might have a mild or asymptomatic COVID-19 [12]. However, in a substantial proportion of pediatric patients with SARS-CoV2, respiratory illness may progress to severe stage requiring hospital care [13]. In pediatric patients with severe COVID-19 symptoms progression to critical illness with hypoxemic respiratory failure can lead to prolonged ventilatory support [14].

Contradicting outcome of studies from different geographical regions of the world about COVID-19 and its associated complications in childhood cancer patients may be a reflection of clinical as well resource setting disparities. In view of scant availability of data from North-East India, current study was undertaken to assess COVID-19 status and its clinical implications in the cancer patients in children of North-East India.

Materials and Methods

Retrospective study was conducted between July 2020 to June 2021 at Dr B Borooah Cancer Institute (BBCI), Guwahati, Assam, India. Medical records of the childhood cancer patients were analyzed. All patients who were tested for SARS-CoV-2 were collected. All childhood cancer patients with age group between one to eighteen years were included and patients with cancer below one year and above eighteen years of age were excluded from study. All cancer patients undergoing chemotherapy were only included in the study. Following set of variables / information were assessed such as age, gender, diagnosis, cancer treatment undergoing before covid-19, indication of testing, laboratory parameters, treatment details (regarding antibiotics, antifungals and steroids), patient status. Routine hematological and biochemistry test required for childhood cancer patients were performed.

The study protocol was approved by institutional ethical committee.

RT-PCR COVID-19 Testing

Nasopharyngeal and oropharyngeal swab specimens were collected in viral transport medium. Total viral RNA extraction was done using Viral RNA mini kit (Qiagen, USA) as per manufacturer instruction. SARS-CoV2 RNA detection in patient specimen was performed on CFX96 Real Time PCR system (Bio-Rad, USA) in one tube RT-PCR protocol as per manufacturer’s instruction (Meril Life Sciences, India). Target confirmatory genes for SARS-CoV2 were ORF1ab gene, Nucleoprotein N gene. RNaseP gene was used as an internal control for RNA quality. Specimen with Ct value ≥ 35 for both ORF1ab gene, Nucleoprotein N gene were only considered positive. All specimen had RNaseP amplification with Ct value ≥ 35 .

Statistical Analysis

Statistical analysis of data was done in Graphpad prism software ver 9.0. The prevalence of SARS-CoV2 infection in test groups were tested using a Fisher’s exact test. Statistical significance was considered for P-value of ≤ 0.05 .

Results

A total 701 childhood cancer patients were tested for SARS-CoV2 between July 2020 till June 2021. All cancer patients were on chemotherapy. Only symptomatic patients and patients due for hospitalization for chemotherapy were screened for SARS-CoV2 infection at our institute according to institution protocol.

Fifty two out of 701 (7%) cancer patients in children were found to be positive for SARS-CoV2 by RT-PCR testing. Among COVID-19 positive patients, the median age was six years whereas COVID-19 negative patients, the median age was seven years. In COVID-19 positive patients, thirty eight (73%) were admitted and treated at hospital whereas fourteen patients were treated in home isolation under the supervision of local health authority with support from our pediatric oncology team. Among COVID-19 positive group, thirty one (59.6%) were male and twenty one (40.4%) were female whereas in COVID-19 negative group 408 (62.9%) were male and 241 (37.1%) were female ($p=0.6568$). In COVID-19 positive group, thirty (57.6 %) were suffering from hematological malignancy and twenty two (42.4%) have solid malignancy. In the COVID-19 negative group, 357 have hematological malignancy (55%) and 292 have solid malignancy (45%). There were no statistically significant association observed with gender and cancer type (Table 1). In COVID-19 positive group, Among the hematological malignancies; acute lymphoblastic leukemia (ALL) comprises 70% (21), acute myeloid leukemia (AML) 16.66% (5) and lymphoma accounting for 13.33% (4) (Table 1).

Characteristics	Total patientsN= 701	PCR positiveN = 52 (%)	PCR NegativeN = 649	P-Value
Age (median) years		6 (2-17 years)	7 (1-16 years)	
Sex				
Male	439	31	408	0.6568
Female	262	21	241	
Cancer Type				
Hematological Malignancy	41	30	357	0.7728
Solid Malignancy	22	22	292	
Covid-19 Symptoms# at the time of diagnosis				
Symptomatic	22	29	99	0.0001\$
Asymptomatic	41	23	350	
Total WBC count (per microliter)				
<1500	4	4	-	

>1500	48	48	-	
Total Neutrophil count (per microliter)				
<500@	4	4	-	
>500	48	48	-	
Survival Outcome				
Dead	9	8	1	0.0001\$
Alive	692	44	648	

Table 1. Demographics and Clinical Characteristics of Childhood Cancer Patients.

High Fever, Cough, Body pain, Diarrhoea; @ 2 patients has <100 neutrophil count (AML induction therapy) in COVID-19 positive group.\$ Statistically significant

Among COVID-19 positive patients, twenty five patients had fever as presenting symptom. Cough and sore throat were seen in seven patients, two patients experienced headache. Sudden onset of breathlessness, vomiting and diarrhea were observed in two patient each. Twenty three patients were asymptomatic of which twenty two were screened before admission and one patient was tested in view of close contact with the COVID positive cancer child. In COVID-19 negative patients, six fifty were asymptomatic and 99 patients were symptomatic where fever was most common symptom followed by cough, sore throat, diarrhea, headache.

Four out of 52 Covid 19 positive patients presented with white blood cell (WBC) and absolute neutrophil count (ANC) less than 1500 and 500 per microliter respectively. Two patients had ANC 20 per microliter and both of these patients had platelet less than 10,000. They also had multiple fever spikes. Both of them were on first induction of acute myeloid leukemia (AML) receiving chemotherapy with daunorubicin and cytosine arabinoside on day 10 and 14 respectively. Both of them required oxygen supplement and ultimately succumbed to death (Table 1).

Majority of COVID-19 positive patients were either asymptomatic or with mild symptoms and received Azithromycin, Dexamethasone, vitamin C, vitamin D and B complex, etc. as per institutional and prevailing national

& international consensus guidelines for childhood cancer patients. Few COVID-19 positive patients with AML and ALL on induction chemotherapy were started on systemic antibiotics along with anti-fungal according to the protocol in suspicion of systemic infection prophylactically in view of fever spike (Table 2).

Treatment received	No. of patients
Azithromycin	19
Other antibiotics (cefepime, meropenam, vancomycin)	15
Antifungal	5
Vitamin B complex, Vitamin D and Vitamin C	30
Steroids	35

Table 2. Details of Covid-19 Treatment Provided to Covid-19 Positive Patients.

Patients with severe COVID-19 symptoms with SpO2 <90% on room air and signs of severe pneumonia or acute respiratory distress syndrome or severe retraction of chest or septic shock or multi-organ dysfunction or pneumonia with cyanosis or grunting or somnolence or seizure, lethargy were shifted to ICU/HDU of designated Covid Care Centre and were treated with immediate oxygen support to maintain target SpO2 94-96% and symptomatic support as per guideline.

Eight out of fifty two patients expired of which seven patients experienced death during treatment

for COVID-19. Out of 52 positive patients nine patients had severe covid 19 symptoms. Out of the eight expired patients two were suffering from AML and both were on induction daunorubicin and cytosine arabinoside chemotherapy and developed multiple systemic bacterial infection along with other comorbidities. Two patients were suffering from ALL and both were on first week of induction chemotherapy and were started on steroids but chemotherapy could not be given in view of severe respiratory difficulty. Three patients were suffering from solid malignancies. One patient suffering from ALL on induction chemotherapy expired after patient has been cured from covid-19 and induction chemotherapy restarted. Patient expired due to systemic bacterial infection and not due to covid-19. One out of 649 covid-19 negative patients expired during study period. Survival outcome between COVID-19 positive and negative group has shown statistically significant association ($p=0.0001$) (Table1).

Two patients had covid-19 reinfection after becoming negative. One 6 year old ALL patient was tested positive 5 months after first infection and another 4 year old retinoblastoma patient tested positive again 2 months after becoming negative. Both patients had mild covid symptoms.

The median days for restarting of chemotherapy is 10 days (Table 3).

Restart Of Chemotherapy After Negative Covid Report	No. of Patients
0-7 Days	7
8-14 Days	22
15-21 Days	13
>21 Days	3

Table 3. Restart of Chemotherapy after Negative Covid Report.

Discussion

In our study, death among COVID-19 positive patients was (8/52) 15.0 % but in COVID-19 negative cancer patients, we observed only one death during the study period. In pooled meta analysis of 3377 hematological malignancy patients of Asia, Europe and North Americans which also included five studies with 102 childhood hematological malignancy patients, pooled risk of death for childhood hematological malignancy was computed at 4% (95% CI) [15]. In Bailey et al retrospective cohort study the case fatality rate among covid positive patients was 0.1% [16]. Hamdy et al. (2021) reported that out of 24 febrile neutropenia pediatric hematology patients, seven were found positive for COVID-19 out of which three (43%) had died [17]. In pediatric population-based data from the US Center for Disease Control and Prevention to COVID-19 hospitalization and in-hospital death, death occurred in 39 (0.19%) of 20,096 hospitalized children [18]. A study reported by Jacqueline Montoya et al. showed similar death rate in childhood cancer patients (10%) as ours. However this study included few myeloid cancer patients (4%) as compared to our study, which included 15.7% AML and majority of death during COVID 19 period in our study were seen in AML and ALL patients only, accounting for 63% of deaths [19]. In our study, deaths in COVID 19 positive patients as compared to COVID 19 negative patients was statistically significant.

Childhood cancer status, early SARS-COV2 infection detection, treatment protocol, resource settings and geographical location may have impact on the varying degree of survival outcome in COVID-19 positive childhood cancer patients. In our study out of eight patients expired, four died in first three months of study period. Two AML patients were severely neutropenic following induction chemotherapy at the time of COVID infection. The ALL patients expired during first week of induction chemotherapy and were hemodynamically unstable. All these patients were severely immunocompromised with bacterial and fungal coinfection leading to increased mortality.

In our study, the COVID-19 positivity among childhood cancer patients was found to be approximately 7%. Forty COVID-19 positive patients became negative in RT PCR testing by

11th day. Only two patients turned negative after more than 16 days. In a study by Rao Et al. from Mumbai public hospital the positivity rate was 12.8% [20]. In New York city up to 20% COVID-19 positivity was reported in childhood cancer patients [5]. In Madrid region COVID-19 positivity in cancer patients in children was found to be 1.3% only [9]. Studies related to COVID-19 in pediatric cancer patients are limited compared to adult cancer patients. Our study was performed in childhood cancer patients during the peak period of COVID-19 infection across India. Therefore the outcome of our study may be reflection of North-East region scenario.

The current rapid global spread of COVID-19 infection prioritizes our intense efforts to identify effective preventive strategies and develop optimal medical management. There is relatively ample information available for adult covid-19 patients but our knowledge of clinical characteristics of childhood covid-19 cancer patients is quite limited. Many of our patients had fever, cough and sore throat as presenting symptoms with majority having fever as presenting complaints which is similar to earlier studies conclusions [21]. Fever has been presenting symptoms even in non-cancer pediatric population and seen in 60% of cases [22]. In our observation we found that Childhood cancer patients with COVID-19 had minor complications and likely to have good prospect of favorable prognosis. In our study, majority of patients with solid malignancy, lymphoma and acute lymphoblastic leukemia had minor complications. Only six patient from this group required oxygen support out of 47 COVID-19 positive patients. In majority of COVID-19 positive patients (n=30) fever subsided by day five of COVID positive status and their clinical course was mild.

Our study may have certain limitations owing to retrospective study design. Our patient sample size may be not very large but it is very well comparable with reference to earlier published COVID-19 studies in childhood cancer patients. We were not able to perform COVID-19 related inflammatory markers, chest radiography, computed tomography scan for all COVID-19 positive patients in our setting as ours is not designated COVID hospital as per government guidelines. All COVID-19 positive patients requiring intensive medical care were transferred on priority basis to designated COVID-19 hospital.

In conclusion, in the present study, it was observed that in pediatric cancer patients of North-East India COVID-19 positivity is similar to other studies. Among COVID-19 positive childhood cancer patients risk of death was significantly higher compared to COVID-19 negative patients and majority of deaths occurred in hematological malignancies receiving intensive chemotherapy. To validate our current observations future studies with larger sample size need to be done.

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Conflict of interest

All the authors declare that there is no conflict of interest.

What is Already Known

Disease severity and survival in pediatric patients with COVID-19 is already known.

What This Study Adds

Clinical picture and characteristics in pediatric cancer patients from North-East India

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