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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Abstract

BACKGROUND: Pediatric cancer patients are considered one of vulnerable group for covid-19 infections and its associated complication. We assessed in this study, covid-19 prevalence and implications in pediatric cancer patients of North-East India METHODS: A total of sixty three pediatric cancer patients were tested for covid-19 by RT-PCR between July 2020 to September 2020. All the patients received chemotherapy as per their cancer types. Patients within age group one year to eighteen years were included. Retrospectively medical records of pediatric cancer patients were analyzed for clinical outcome between COVID positive and negative group. RESULTS: Among sixty three patient, 19(30%) were found positive for COVID-19. Among COVID-19 positive patients, fourteen patients have hematological malignancies. Fever was the main presenting symptom along with cough and sore throat there were no statistically significant association observed between COVID-19 positive and negative group for gender, cancer type, total WBC count and absolute neutrophil count. Survival outcome has shown statistically significant association (p=0.0065) between COVID-19 positive and negative pediatric cancer patients. Four deaths occurred in COVID-19 positive patients but there was no death in COVID-19 negative patients. Statistically significant association was also observed between COVID-19 positivity in patients being symptomatic (p=0.0001). CONCLUSION: We conclude from our present study that among pediatric cancer patients of North-East India, COVID-19 positivity was significantly high in symptomatic patients compared to asymptomatic. Among COVID-19 positive pediatric cancer patients risk of death was significantly higher compared to COVID-19 negative patients.

INTRODUCTION

World health organization led initiative in low and middle income countries towards improvement of survival among childhood cancer patients[1.] 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 gliomas , Hodgkin lymphoma and Wilms tumor[2]. 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 coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19)[2.] Since its emergence in Dec 2019, it has resulted in 63.7 million infections and 1.4 million deaths worldwide. India accounts for 15% of the total COVID-19 positive cases as of November 30, 2020. 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 settings[3].

Due to their immunocompromised status, Pediatric patients constitute one of the most vulnerable group of individuals for COVID-19 infection and its associated morbidity & mortality as compared to general

population[4]. Memorial Sloan Kettering Cancer Center and New York Presbyterian Hospital have reported 7% and 20% COVID-19 positivity among pediatric cancer patients[5]. In Madrid, Incidence of COVID-19 infection in childhood cancer patients was found to be 1.3% higher compared to the general pediatric population[6]. 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[7]. 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[8]. A multi centric and multi country survey showed Covid-19 incidence and severity among children on anticancer treatment might have a mild or asymptomatic COVID-19[9].However, in a substantial proportion of pediatric patients with SARS-CoV2, respiratory illness may progress to severe stage requiring hospital care[10]. In pediatric patients with severe COVID-19 symptoms progression to critical illness with hypoxemic respiratory failure can lead to prolonged ventilatory support[11].

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 India and more specifically 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. All the cancer patients of children were treated at Dr. Bhubaneswar Borooah Cancer Institute, Guwahati, Assam from July 2020 till September 2020

MATERIALS AND METHODS

Retrospective study was conducted between July 2020 to September 2020 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 year 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 cancer treatment 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, 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 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 sixty three childhood cancer patients were tested for SARS-CoV2 between July 2020 till September 2020. All cancer patients had undergone active chemotherapy. Only symptomatic patients and patients due for hospitalization for chemotherapy were screened for SARS-CoV2 infection at our institute due to limited resources during the specific time period

Nineteen out of sixty three (30%) 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 eight years whereas COVID-19 negative patients, the median age was five years. In COVID-19 positive patients, sixteen (84%) were admitted and treated at hospital whereas three patients were treated in home isolation under the supervision of local health authority with support from our pediatric oncology expert. Among COVID1-9 positive group, Twelve (63.2%) were male and seven (36.8%) were female whereas in COVID-19 negative group thirty one (70.4%) were male and thirteen (29.6%) were female (p=0.7724). In COVID-19 positive group, Fourteen (73.6 %) were suffering from hematological malignancy and Five have (26.4%) solid malignancy but in COVID-19 negative group, twenty seven have hematological malignancy and seventeen have solid malignancy (p=0.5654). There were no statistically significant association observed with gender, cancer type, total WBC count and absolute neutrophil count (Table1). In COVID-19 positive group, Among the hematological malignancies; acute lymphoblastic leukemia (ALL) comprises 57%, acute myeloid leukemia (AML) 21.5% and non-hodgkins lymphoma accounting for 21.5% (Table1).

Survival outcome between COVID-19 positive and negative group has also shown statistically significant association (p=0.0065). Statistically significant association was observed between COVID-19 positivity and patients being symptomatic (p=0.0001) (Table1).

Among COVID-19 positive patients, fourteen had fever as presenting symptom. Cough and sore throat were seen in four patients, two patients experienced headache. Sudden onset of breathlessness, vomiting and diarrhea were observed in one patient each. Five patients were asymptomatic of which four 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, thirty six patients were asymptomatic and eight patients were symptomatic where fever was most common symptom followed by cough, sore throat, diarrhea, headache.

Three patients had preexisting signs of infection and were started on antibiotics prior to covid 19 infection. They were continued on antibiotics during the course of covid 19 hospitalization. Demographics and clinical characteristics have been detailed in TABLE 1.

Routine blood count done in our covid-19 positive patients showed three patients 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 and 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 oxygenation supplement and ultimately succumbed to death (TABLE 1).

COVID-19 Treatment:

Majority of COVID-19 positive patients received azithromycin, dexamethasone, vitamin C, vitamin D and B complex, steroids 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 and prophylactically in view of fever spike (TABLE 2).

Four patients out of 19 expired of which three patients experienced death during treatment for COVID 19. One patient expired after he had been cured of COVID 19 due to complication of chemotherapy. Out of the three 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. One osteosarcoma patient on week 3 MAP protocol (high dose methotrexate, doxorubicin and cisplatin) tested positive for covid-19 and was started on antivirals, antibiotics and supplement oxygen. This patient developed sudden onset of breathlessness and patient needed urgent ventilator support and succumbed to death. One patient suffering from ALL on induction chemotherapy expired after patient has been cured from covid-19 and induction chemotherapy had been restarted. Patient expired due to systemic bacterial infection and not due to covid-19

DISCUSSION

In our study, death among COVID-19 positive patients was (4/19) 21.0 % but in COVID-19 negative cancer patients we had not observed any 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)[12] . Hamdy et al. (2021) in 24 febrile neutropenia pediatric hematology patients seven were found positive for COVID-19 among them three (43%) had died[13]. Childhood cancer status, early SARS-COV2 infection detection, treatment protocol, resource settings, geographical region may have impact on the varying degree of survival outcome in COVID-19 positive childhood cancer patients.

In our study, the COVID-19 positivity among childhood cancer patients tested for SARS COV2 was found to be approximately 30%. Fourteen COVID-19 positive patients become negative in RT PCR testing by 11^{th} day. Only two patients turn negative after more than 16 days. In New York city up to 20% COVID-19 positivity was reported in cancer patients in children[5]. In Madrid region COVID-19 positivity in cancer patients in children was found to be 1.3% only[14]. Pediatric cancer patients studies related to COVID-19 very limited compared to adult cancer patients studies. Our study was performed in cancer patients in children during the peak period of COVID-19 infection across India therefore the outcome of our study may be reflection of North-East region scenario.

In our study we found that COVID-19 positivity (73.6%; 14/19) was significantly high in cancer patients with suspected covid-19 symptoms compared to asymptomatic patients (26.4%; 5/19). There has been studies which concluded that pediatric cancer patients may have mild or asymptomatic COVID-19 infection[8,9].

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 of symptomatic patients having fever as presenting complaints which is similar to earlier studies conclusions[15]. Fever has been presenting symptom\souts even in non-cancer pediatric population and seen in 70-80% of cases[16]. 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 two patient from this group required oxygen support out of 16 COVID-19 positive patients. In majority of COVID-19 positive patients (n=15) fever subsided by day five of COVID positive status and their clinical course was mild. Total deaths in COVID 19 positive patients in our study was four comprising about 21%. A study reported by Jacqueline Montoya et al. showed similar death rate in childhood cancer patients of 10%. 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 patients only, accounting for 66.7% of deaths[17]. In our study, deaths in COVID 19 positive patients as compared to COVID 19 negative patients was statistically significant Primarily deaths occurred to AML patients with COVID-19 positive status and they were treated with intensive chemotherapy regimen and during course of time after both AML patients expired all subsequent AML patients regardless of COVID status were treated with adequate isolation.

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 designate COVID hospital as per government guidelines. All COVID-19 positive patients with immediate intensive medical requirement were transferred on priority basis to designate COVID-19 hospital ICU.

CONCLUSION

We would like to conclude from our present study observation that in pediatric cancer patients of North-East India COVID-19 positivity was significantly high in symptomatic patients compared to asymptomatic patients. Among COVID-19 positive childhood cancer patients risk of death was significantly higher compared to COVID-19 negative patients. To validate our current observation future studies with larger sample size need to be done.

Conflict of interest : All the authors declare that there is no conflict of interest

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