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# Outcomes of COVID-19 in children with cancer – Report from the Indian Pediatric Oncology Group (InPOG) COVID-19 registry in India

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ABSTRACT

*Introduction:* The clinical outcomes of COVID-19 infection in children with cancer have been variable worldwide. Therefore, we aimed to collect data from all regions in India through a national collaborative study and identify factors that cause mortality directly related to COVID-19 infection.
*Methods:* Data was collected prospectively on children across India on cancer therapy and diagnosed with COVID-19 infections from 47 centers from April 2020 to October 2021. Information was recorded on the demographics, the number of children that required intervention, and the outcome of the infection. In addition, we analyzed the impact of the delta variant in 2021.
*Results:* A total of 659 children were studied, of whom 64% were male and 36% were female. The data from the eastern region was sparse, and this was a collection bias. COVID-19 infection was predominantly seen in children less than five years. The delta variant had a higher impact in the southern region, and this was statistically significant. Of the 659 children, 30 children died (4.5%), however only 7 of the deaths were directly attributed to COVID-19 infection (1%).
*Conclusion:* The study reports the largest nationally representative cohort of children with cancer and COVID-19 to date in India. We identified demographic and clinical factors associated with increased all-cause mortality in patients with cancer. Complete characterization of the cohort has provided further insights into the effects of COVID-19 on cancer outcomes. The low mortality allows us to recommend that specific cancer treatments be continued without delays in therapy.


## 1. Introduction

COVID-19 has had a significant impact on cancer services across the world. The pandemic has resulted in delayed diagnosis, therapy interruptions, and considerable morbidity and mortality. The most recent COVID-19 and Cancer Consortium (CCC-19) found a 28% increased risk of COVID-19 severity and 61% increased risk of 30-day mortality with cytotoxic agents [1]. Specific therapies such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, platinum-etoposide, and DNA methyltransferase inhibitors were associated with increased 30-day all-cause mortality. In contrast, the UK Coronavirus Cancer Monitoring Project did not find an increased risk of death with immunotherapies, targeted therapies, and hormone therapies after adjusting for age, sex, and comorbidities [2,3].

Each year, there are around 50,000 new children diagnosed with cancer in India, and the impact of COVID-19 on this population has given us unique insights into the pathophysiology of the infection. Management of children with COVID-19 across the country has been as per Indian Council for Medical Research (ICMR) guidelines which have been frequently updated [4]. However, real world data was required to analyze the effects of COVID-19 in children undergoing cancer therapy. In April 2020, the Indian Pediatric Oncology Group (InPOG) helped establish the COVID-19 registry for all physicians to report minimal outcome data across the country. The registry captured multicenter outcome data from India, including patients from the first wave in 2020 and the delta variant seen during the second wave in 2021.The latter was reported to be more virulent resulting in a higher mortality [5].

## 2. Patients and methods

The study collected prospective data on children diagnosed with COVID-19 infection between April 14th, 2020, to October 14th, 2021, for 18 months across a total of 47 centers in India. All centers had obtained clearance from their ethical committee, and the data was accrued using a Google form with regular reminders set for uploading the data. The minimal data set included the age and sex of the child, the region from India – north, south, east, or west and the initial diagnosis of hematolymphoid or a solid tumor. All children included had a confirmed RT PCR for the SARS COVID-19 virus. We collected data on the need for intervention with paracetamol, antihistamines, and hospitalization for COVID-19 infection. Interventions for active disease included steroids, oxygen, ventilation, remdesivir, and anticoagulation. The outcome of the event and information on direct deaths due to COVID-19 infections were collected. Data analysis was performed using the SPSS software. The study has been approved by the institutional review board and written informed consent was obtained from parents of all children.

## 3. Results

We collected data on a total of 659 children with a median age of 7 years, number of males being 419 (63.5%) and females being 240 (36.4%), with a male-female ratio of 1.7:1. The initial peak incidence was in May 2020, and the second wave due to the delta variant occurred in May 2021. Fig. 1 depicts COVID-19 in India, and Fig. 2 illustrates the parallel data in children with cancer. The age distribution data has been described in Fig. 3, with the less than five-year-old children being maximally affected (n = 277, 42%). Leukemia and lymphoma were the underlying diagnoses in most of the patients in the registry 484/659 (73.4%) and solid tumors in 175/659 (26.6%).

All regions of the country were equally affected during the pandemic. However, data was collected from 339 children from the southern region, 189 from the northern region, 126 from the western region, and five from the eastern region, and this was a reporting bias. The second wave in 2021 due to the delta variant affected the southern part more than the north and western areas. Of the 406 children affected during the first wave in 2020, 230 (56.6%) were from the north and western regions of India; while 176 (43.3%) were from the southern and eastern parts of India. However, during the second wave in 2021, of the 253 affected, 85 (33.5%) were from north and western India, and 168 (66.4%) belonged to south and east India. This increased incidence was statistically significant with a p-value of <0.0001.

The majority of the children (72%) was diagnosed during screening and did not have any symptoms. They recovered with observation and did not require intervention. The number of

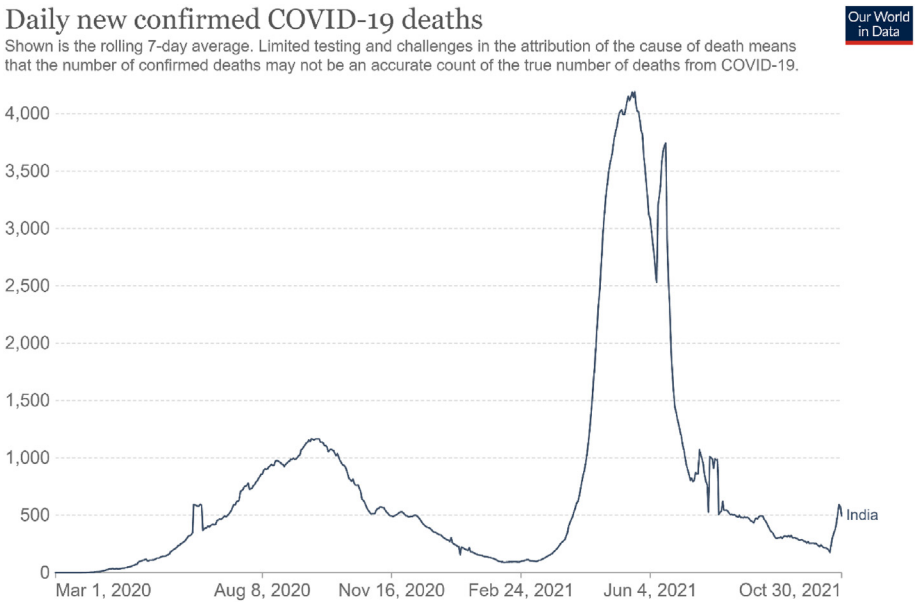


**Fig. 1.** The incidence of COVID-19 infection in India over an 18 month period.

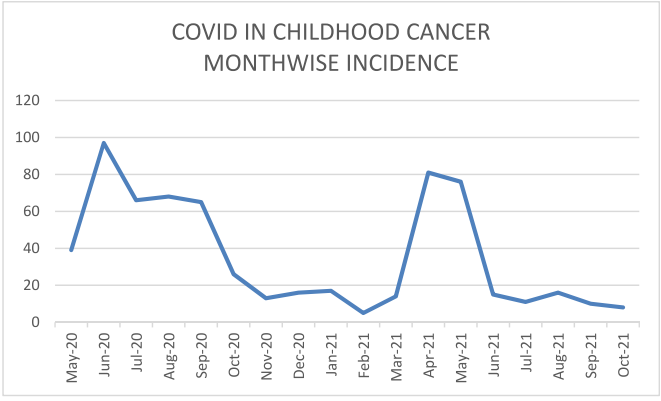


**Fig. 2.** Month wise incidence of COVID-19 in children with cancer in India.

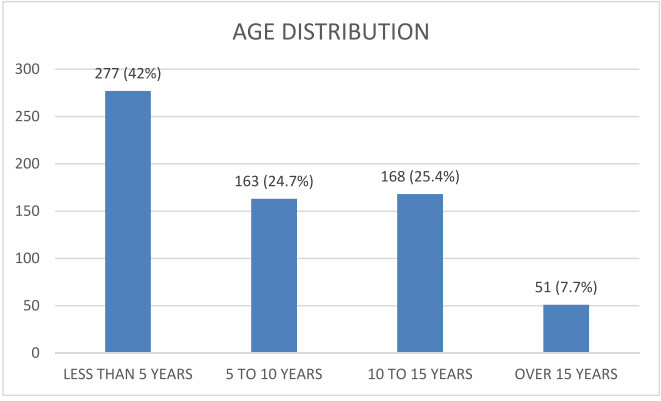


**Fig. 3.** The age distribution of children with cancer and COVID-19 infection.

children that presented with symptoms were 124/659 (18.8%). They required treatment such as intravenous fluids, antibiotics, oxygen supplementation, and steroids. Less than ten children received remdesivir. Of the 659 children, 30 children died, however only 7 of the deaths were directly attributed to COVID-19 infection. Table 1 summarizes the cause of mortality in children in the cohort. Therapy-related deaths included bacterial sepsis during the neutropenic phase with concomitant COVID-19 in 4 children. Relapsed or refractory malignancy resulted in 19 deaths. There were 5 children with leukemia or lymphoma and 2 in the solid tumor group who died of COVID-19 related symptoms. The direct COVID-19 related mortality was 1%, and the overall mortality rate was 4.5%.

**Table 1**
Distribution of the causes of mortality (n = 30).

| Cause of death | Number (overall percentage) |
|---|---|
| Progression of cancer | 19 (2.8%) |
| COVID 19 related | 7 (1%) |
| Regimen related | 4 (0.6%) |

## 4. Discussion

The diagnosis and therapy of childhood cancers requires access to care in the form of travel to a referral center, financial resources, medical and nursing teams, blood donors, and health care workers to work as a team to deliver optimal therapy to every single child. The COVID-19 pandemic resulted in considerable barriers to care, especially in this cohort. Data from all regions in India reflects the enormous struggle faced by the families affected and the care providers. The registry data has clearly shown that most of the children were asymptomatic and were diagnosed during a routine screening and needed only observation. Symptomatic children formed only a third of the cohort, and the mortality rate was low.

The unusual pathophysiology of COVID-19 infection is that the clinical severity is related to the immune system's response to the viral antigen, and the resulting cytokine release causes organ damage [6]. Children undergoing cancer chemotherapy have suboptimal immune responses to infections and thereby are less vulnerable to the severe forms of the disease [7,8]. Seasonal epidemics including respiratory viruses such as respiratory syncytial virus(RSV), H1N1, and dengue result in morbidity and mortality each year in children, including those undergoing cancer treatment.

In a multivariate analysis, Rodriguez et al. had clearly shown that a diagnosis of cancer was the strongest predictor of mortality in children affected with RSV [9]. In contrast, the H1N1pandemic resulted in interruptions in cancer therapy with low mortality [10]. Similarly, the mortality directly related to COVID-19 was low at 1% in our cohort with major interruptions in therapy.

The experience during the first wave helped cancer services across the country prepare better for the second wave. Aggressive testing, reducing hospital visits, avoiding visitors during an inpatient stay, teleconsultation, home testing, and published guidelines for care ensured that the mortality was kept low even during the emergence of the Delta variant [11]. In addition, the registry helped connect physicians across the country to share experiences and provide optimal care. The main drawback of this registry data is the lack of comprehensive data as we failed to capture all children with cancer diagnosed with COVID-19 infection. Most physicians were posted as frontline workers and most cancer centers did not have a dedicated data manager resulting in a reporting bias.

The more significant effect of COVID-19 in India is already seen in our services across the country as the number of relapses in all curable childhood cancers is on the increase as there have been interruptions in therapy for several patients [12]. In addition, rigid lockdowns, lack of healthcare workers, loss of jobs, and financial constraints have resulted in suboptimal care. Collateral damage in terms of challenges in the delivery of care has thus been more evident than the direct impact of COVID-19 in children with cancer.

## 5. Conclusion

The InPOGCOVID-19 registry data has tracked the incidence of the infection during 2020 and 2021 and recorded data on a total of 659 children. There is a preponderance of male children (63.5%) and children less than five years (42%) and a diagnosis of leukemia and lymphoma in the registry (73.4%). The first wave affected the northern and western parts of the country, while the second wave had a higher impact in the southern regions. The direct COVID-19 related mortality was low at 1%, and less than one-third of the cohort required intervention. This data will help health care providers across our country improve services and optimize care during crises so that children with cancer can access seamless care in the future.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

There are no conflicts of interest.

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