The Impact of COVID-19 Pandemic on Access to Treatment for Children With Cancer in India and Treating Center Practices

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BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic led the Indian government to announce a nationwide lockdown on March 23, 2020. This study aimed to explore the impact of the pandemic on the accessibility of care for children with cancer and to view strategies adopted by hospitals for service delivery. **METHODS:** Weekly average of childhood cancer (\leq 18 years) patient registrations during pre-lockdown period (January 1 to March 23, 2020) were compared with post-lockdown period (March 24 to May 31, 2020). The effect on the scheduled treatment was investigated for post-lockdown period. A survey of health care providers was conducted to determine centers' adopted strategies. **RESULTS:** In 30 participating centers, 1146 patients with childhood cancer (797 pre-lockdown period and 349 post-lockdown period) were registered. The weekly average registration was 67.3 and 35.5 patients during pre-lockdown and post-lockdown respectively (decline of 47.9%). Although most centers experienced this decline, there were 4 that saw an increase in patient registrations. The distribution of patients registered post-lockdown was found significantly different by age (lesser older age, *P* = .010) and distance (lesser travel distance, *P* = .001). 36.1% of patients, who were scheduled for any of the treatment modalities (chemotherapy, surgery, radiotherapy, and hematopoietic stem cell transplantation) during the post-lockdown period, experienced delays. Centers adopted several strategies including modifications to treatment protocols, increased use of growth factors, and increased support from social organizations. **CONCLUSIONS:** This multicenter study from India suggests that the COVID-19 pandemic and the lockdown impacted 2 out of 3 children with cancer. The effect of this on survival is yet to be established. **Cancer 2022;128:579-586**. © *2021 American Cancer Society*.

KEYWORDS: childhood cancer, coronavirus 2019, COVID-19, hospital registration, impact, India.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can result in a flu-like respiratory illness with symptoms such as cough, fever, and in more severe cases, difficulty breathing. It first appeared in Wuhan, China in December 2019 and then spread rapidly throughout the world. By the March 11, 2020, more than 114 countries of the world had patients with SARS-CoV-2 virus and World Health Organization (WHO) declared COVID-19 to be a pandemic.¹ At the time this article was written (May, 2021), the disease had affected more than 168 million people around the world and approximately 3.5 million have died because of it.² India currently has 26.9 million cases and 307,249 deaths, primarily as a result of the second wave that started in March, 2021.²

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In India, the national government, along with the state governments, have taken several measures to curb the rapid spread of the virus, the most significant being the nationwide lockdown of 21 days announced on March 24, 2020³ and the subsequent extension of the lockdown announced on April 14, 2020 and then again on May 4, 2020,⁴ with disruption on travel and related services at a scale that has been unprecedented. This has impacted all aspects of daily living including employment, business, education, and health care.⁵⁻⁸ Although restrictions were subsequently eased, they have now been re-implemented to some degree because of the onset of the second wave.⁹

Successful treatment of childhood cancer needs timely, uninterrupted multimodality treatment backed up by robust supportive social care. Travel restrictions during the pandemic combined with hospitals functioning at curtailed capacity and staffing levels are likely to lead to delays in diagnosis and interruptions in treatment.^{10,11} The lockdown is certain to create additional barriers to accessing health care in low-middle-income countries like India.¹² With this hypothesis, this study explored the impact of COVID-19 pandemic and the associated first national lockdown in March 2020 on the accessibility of care for children with cancer in India. Specifically, our objectives were to see changes in hospital patient registrations, changes in scheduled chemotherapy, radiotherapy, surgery, and hematopoietic stem cell transplantation (HSCT), and to see strategies adopted by hospitals for service delivery during the lockdown.

MATERIALS AND METHODS

Centers treating >50 children (\leq 18 years of age) with cancer annually, and who maintained a registry and/or database, were considered for the study. Participating centers were asked to identify all children ≤18 years old with cancer who were registered in their hospital for the first time (for frontline or relapse treatment) from January 1, 2020, to May 31, 2020. Weekly average patient registrations during the pre-lockdown period (January 1, 2020, to March 23, 2020) were compared with the post-lockdown period (March 24, 2020, to May 31, 2020). These timelines were chosen because the first nationwide lockdown commenced on March 24, 2020, and extended till May 31, 2020; after which there was a phased easing of the lockdown over the next several months.9 We investigated whether the distribution of demographic- (age, gender, and nationality), geographical- (distance to center), and disease- (diagnosis and disease status) related variables was significantly different in the pre-and post-lockdown

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period by χ^2 test. In the case of small frequencies in any category, Fisher exact test was used. A *P* value <.05 was considered significant. SPSS21 was used for calculations.

Of these patients, we then identified those who have scheduled 1 or more modalities of treatment (chemotherapy excluding that given orally), surgery, radiation, and HSCT during the lockdown from March 24, 2020, to May 31, 2020. We determined if these scheduled treatments had been given on schedule or delayed from the schedule. Only those delayed from the schedule because of the pandemic and the lockdown were considered as delays for the analysis. Delays because of clinical reasons (eg, delay in count recovery, sepsis, etc.) were not considered as delays because of the pandemic and/or lockdown. The analysis was descriptive.

We also did a health care provider survey of centers that participated in the study. The survey was completed by the study representatives (22 pediatric oncologists, 4 medical oncologists, 2 hemato-oncologists, 1 radiation oncologist, and 1 ocular oncologist) from each participating center with 1 response per center. The survey was done to understand the effect of the COVID 19 pandemic and lockdown on the hospital practice and strategies that were being used to deliver patient treatment. The first version of the survey was made by the study team and then feedback was obtained from 5 pediatric oncologists who were not involved in the development of the study. The revised survey, along with the study protocol, was then peer-reviewed by 2 national experts and 1 international expert and their feedback was used to finalize the survey (see Supporting Table 1) that was conducted through Google Forms. The analysis was descriptive.

This study was registered with the Indian Pediatric Oncology Group (InPOG-ACC-20-04) and Clinical Trials Registry of India (CTRI/2020/05/025219). Ethical clearance was obtained. The desired patient-specific information was captured from the routine care and registration database of the hospital and did not involve any patient contact for additional information and thus consent was not needed.

RESULTS

Of the 88 centers approached, 30 centers (34%) participated in the study. The responding and nonresponding hospitals were similar for speciality and sector but there was a difference with geographical location with lower participation rates from East India (Supporting Table 1). Of the 30 participating centers, 83% (25 centers) were open for cancer-directed treatment for both existing and new patients during the post-lockdown period, 10% **TABLE 1.** Association of Demographic, Geographical, and Disease-Related Variables to Distribution of Patient Registrations Pre- and Post-Lockdown

Variable	Pre-Lockdown (n = 797), %	Post-Lockdown (n = 349), %	Ρ
Age, y			
00-04	34.6	45.0	.010 ^a
05- 09	28.4	23.2	
10-14	22.5	20.1	
15-18	14.6	11.7	
Gender			
Female	34.1	33.0	.698
Male	65.9	67.0	
Nationality			
International	2.3	0.9	.104
National	97.7	99.1	
Distance, km ^a			
0-50	34.3	47.4	.001 ^a
51-100	8.6	8.4	
101-200	16.3	18.8	
201-500	19.8	17.1	
501-1000	8.5	4.6	
≥1001	12.2	3.5	
Cancer groups			
Group 1 (leukemia)	45.8	51.3	.117
Group 2 (lymphoma)	12.3	10.0	
Group 3 (CNS)	4.4	6.9	
Group 4	6.0	5.7	
(retinoblastoma)			
Group 5 (abdominal tumors) ^b	10.4	10.6	
Group 6 (sarcomas)	14.7	11.7	
Group 7 (others)	6.4	3.7	
Disease status			
Newly diagnosed	94.0	91.7	.155
Relapsed/refractory	6.0	8.3	

Abbreviation: CNS, central nervous system.

^aFor national only.

^bWilms, liver, neuroblastoma, germ cell tumor.

(3 centers) were open only for existing patients and emergencies but not for new patients and 7% (2 centers) were completely shut for all cancer-directed treatment for both existing and new patients.

Patient Registration and Treatment

A total of 1146 children (797 during pre-lockdown period and 349 during post-lockdown period) with cancer were registered in these centers from January 1 to May 31 2020. Of all registered patients, 66% were male and 98% were from India with the reported median age of 6 years. Of these children, 93% were newly diagnosed, whereas 7% were relapsed and/or refractory. Leukemia accounted for 47%, sarcoma 14%, lymphoma 12%, abdominal tumors 10%, retinoblastoma 6%, central nervous system (CNS) tumors 5%, and others 6%.

The weekly average patient registration was 67.3 pre-lockdown (from January 1 to March 23, 2020) and 35.5 post-lockdown (from March 24 to May 31, 2020),

representing a decline of 47.3% (range within centers from 100% decline to 83.7% increase). The weekly trends for this period are shown in Figure 1. Although most centers experienced a decline in registration, 4 centers (2 in the charitable trust sector and 2 in the private sector) saw an increase in patient numbers (Fig. 1).

The decline in weekly registrations was highest for lymphomas and sarcomas (58% decline each) followed by retinoblastoma (50% decline), abdominal tumors (46% decline), leukemias (41% decline), and CNS tumors (20% decline). Our study found that the distribution of patients registered pre- and post-lockdown by age and distance were significantly different, whereas gender, nationality, diagnosis, and disease status were not (Table 1). In the pre-lockdown period, the proportion of children who travelled >500 km was 20.7% and this declined to 8.2% in the post-lockdown period (P = .001). Similarly, the proportion of children 10 years of age and above declined from 37.1% during the pre-lockdown period to 31.8% in the post-lockdown period (P = .010).

Of the 1146 patients registered from January 1 to May 31 2020, 1011 (88.2%) were scheduled to have 1 or more modalities of treatment during the post-lockdown period of March 24 to May 31, 2020. A total of 36.1% of these patients experienced a delay in delivery of 1 or more modalities of the scheduled treatment (chemotherapy, surgeries, radiotherapy, and HSCT) (Fig. 2).

Center Practices

More than usual difficulty to access flow cytometry, cytogenetics, and minimal residual disease were reported by 30%, 50%, and 50% of the centers, respectively. The degree and type of modifications made for induction, consolidation, and maintenance of acute lymphoblastic leukemia, induction treatment of acute myeloid leukemia, and neoadjuvant chemotherapy for sarcoma patients by individual centers are described in Table 2.

For supportive care, 50% of the centers were administering more granulocyte colony-stimulating factors than before. The procurement of morphine was reported as more than usually difficult by 18% of centers. To deal with the relative shortage of blood supply and donors, the threshold for transfusion of blood was higher than usual, special travel passes for donors were arranged, staff members were encouraged to donate, and there was an adaptation of treatment protocols that reduced the need for blood. A total of 79% of the centers reported seeking more support than usual by social support organizations, and Figure 3 displays which specific services were most needed. The social support



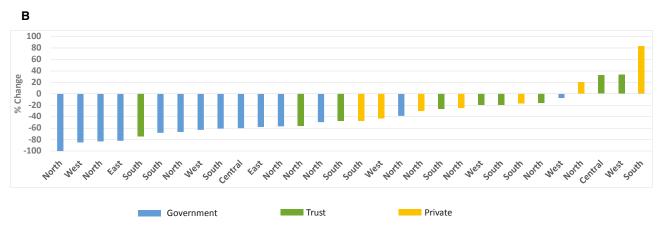


Figure 1. (A) Decline in average per week patient registrations (in numbers). (B) Centerwise trend of percentage change in patients' registrations between pre-coronavirus disease (COVID) (January 1 to March 23, 2020) and post-COVID (March 24 to May 31, 2020) period.

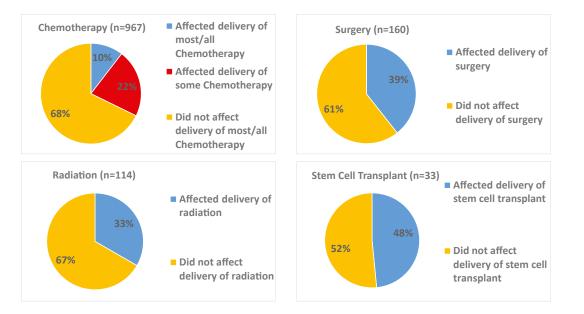
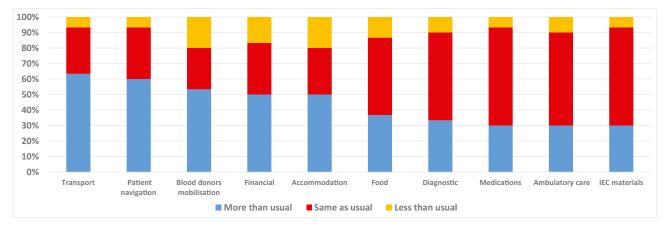


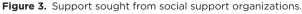
Figure 2. Effect of lockdown on scheduled treatment modalities. "n" is the total number of children scheduled to have respective treatment modalities (chemotherapy, surgery, radiation, and stem cell transplant) during post-COVID (March 24 to May 31, 2020) period.

	No. (%)
Acute lymphoblastic leukemia in induction treatment (n = 28)	
Carrying on treatment as scheduled without any changes	28 (100)
Acute lymphoblastic leukemia in consolidation treatment ($n = 28$)	
Carrying on treatment as scheduled without any changes	25 (89.3)
Decreasing number/doses of iv chemotherapy	1 (3.6)
Switching to oral maintenance therapy	1 (3.6)
Others	1 (3.6)
Acute lymphoblastic leukemia in maintenance treatment (n = 30)	
Continuing giving vincristine and steroid pulses	5 (16.7)
Discontinuing giving vincristine and steroid pulses, even if patient could reach center	5 (16.7)
Does not apply because you do not use a protocol that gives VCR and steroid pulses in maintenance	18 (60.0)
Others	2 (6.7)
Acute myeloid leukemia who were due induction (n = 26)	
Continuing giving induction chemotherapy as usual	19 (73.1)
Giving chemotherapy at reduced dose	2 (7.7)
Eliminating etoposide (if previously using 3-drug protocol) and continuing to give iv cytarabine and anthracycline	1 (3.8)
Switching to oral metronomic chemotherapy	1 (3.8)
Others	4 (11.5)
Sarcomas receiving neoadjuvant chemotherapy (n = 26)	
Continuing iv chemotherapy as planned	19 (73.1)
Continuing iv chemotherapy but decreasing intensity (eg, 3 weekly rather than 2 weekly) or decreasing dose	6 (23.1)
Shifting to oral metronomic chemotherapy	1 (3.8)

TABLE 2. Centers' Practice for Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, and Sarcomas

Abbreviations: iv, intravenous; VCR, vincristine.





organizations are mainly nongovernmental organizations working in partnership with the treating team of the cancer center. They provide holistic support (financial support for treatment and diagnostics, manpower support like nurses and dietitians and/or nutritionists, accommodation to the patients and their families, and other social support) through the cancer continuum of diagnosis to completion of treatment.

DISCUSSION

The impact of the COVID-19 pandemic and the associated lockdown has been widely felt in most areas of life including accessing health care. A survey by WHO done in 155 countries in May 2020 showed the partial or complete disruption of services for cancer treatment in 42% of the countries.¹³ Several studies have examined the impact in the context of childhood cancer by surveying health care providers to provide a national,¹⁴ regional,^{10,11,15} or global picture.¹⁶ Alternatively, investigators have used hospital registration and episode statistics to provide individual patient-level data, however, this has been limited to single-center studies from a few high-income countries¹⁷⁻¹⁹ and a single upper middle-income country.²⁰

Our prospective mixed-quantitative methods study brings forth a national picture of the impact in a low middle-income country like India. India reports a 47.3% decline in weekly average patient registration in the pre- and post-lockdown period that is slightly higher than the decline of 33% and 40% reported from single-center studies in Saudi Arabia and Turkey, respectively.^{16,19} Both these countries have a more comprehensive universal health coverage and greater spending of gross domestic product on health care that could explain the difference, but wider nationally representative data from these countries would allow making a firm conclusion. One in three of the eligible centers participated in the study because many centers had diverted resources to clinical care during the pandemic and were shortstaffed resulting in temporary discontinuation of clinical research and work of the ethics committees. Only 2 centers from East India participated (both from the government sector), however, the decline in their patient registrations was similar to those from other parts of India (Fig. 1B) suggesting that this would not change the inferences that we can draw. A male to female ratio of 2 to 1 in the entire cohort is similar to what has been reported in India before^{21,22} and is believed to partly related to gender bias in seeking health care.²³

Our results also highlight that this decline varied from a maximum of 100% decline in centers that had to shut down childhood cancer services and become COVID-19 hospitals to an actual increase in weekly average patient registrations in 4 of the 30 participating centers with 1 center having an 83.7% increase. The impact was greatest on hospitals in the public sector. Both the pandemic and the lockdown have contributed to the negative impact on patient registrations and treatment. Considering that the total number of patients diagnosed with COVID-19 infection and the associated deaths in the entire country by May 31, 2021 were 190,609 and 5408, respectively,² it follows that the lockdown, rather than the pandemic, had a far greater negative impact.

Although not originally part of the study methodology, we contacted post hoc the investigators at centers which saw an increase in weekly patient registrations and had a conversation to know the reasons connected to this. Diversion of patients to local tertiary centers who otherwise would have travelled greater distances to a regional or national center of excellence was the most common explanation found. Other explanations included nonavailability of services in centers within the government sector that were designated as COVID hospitals and partnership with social support organizations to provide care to patients who were unable to access care.

This is reinforced with the observation that the distribution of patients by distance to the health care center was significantly different in the pre-and post-lockdown period. In the pre-lockdown period, the proportion of children who travelled >500 km was 20.7% and this declined to 8.2% in the post-lockdown period. Although India has many centers providing care to children with cancer, there is a lack of information and guidance on designated centers and referral pathways that results in families travelling long distances to access care.¹² The pandemic and lockdown necessitated these families to seek treatment closer to where they live. Decentralization of treatment enabling its delivery closer to home can have obvious benefits of reducing costs, time taken to travel, and potentially abandonment of treatment. However, this needs to be balanced with the availability of all relevant expertise locally, which is required to achieve optimal outcomes. It is yet to be seen if the changes in health careseeking behavior will persist once travel restrictions are eased and the pandemic resolves.

The distribution of patients registered pre- and post-lockdown significantly varied by age, with a smaller proportion of older children and adolescents being registered in the post-lockdown phase. Sarcomas (particularly of the bone) present in this age group and challenges to achieving timely diagnosis in this age group because of the nonspecificity of symptoms, as well as relative paucity of access to multimodality treatment, could be an explanation. Conversely, there may have been relatively more widespread use of diagnosis and treatment for leukemia, which is seen more in younger children and generally manifests with a shorter time interval. There is a suggestion in our data that the proportion of leukemias increased and the proportion of sarcomas decreased in the post-lockdown period, although this was not statistically significant.

Our study also found that 36.1% of patients scheduled for cancer-directed treatment during the lockdown experienced a delay in delivery of 1 or more modalities of the scheduled treatment. This mirrors the experience of other single-center and multicenter studies and surveys from across the world.^{10,11,14-20} When we combine these data with a near 50% decline in patient registration, we can conclude that approximately 2 out of 3 children with cancer had delayed diagnosis and/or treatment during this time, thus potentially compromising outcomes. Recognizing the devastating effects of the lockdown, the governmental, institutional, and individual response to the second wave has been more nuanced. There has been no nationwide lockdown. However, states and union territories imposed their own state-wide and localized restrictions that have been present for weeks rather than months, and they have been more accommodating for provisions of essential services, travel to access these services, and continued care for those with other illnesses. In relation to this, personal experience suggests that hospitals and health care professionals have become more willing to treat patients with other illnesses including cancer during the second wave.

To achieve a balance between providing vital cancerdirected and supportive treatment and ensuring that the risk of acquiring the SARS-CoV-2 infection was minimum, individual centers adopted several strategies including modifications to treatment protocols and increased use of growth factors. Although not addressed in this study, we know that individual centers in India have also widely used teleconsultation and deferred non-urgent clinical assessments.²⁴⁻²⁷ What has not previously been reported is the increased need and use of support from social organizations with 79% of the centers reported seeking more support than usual. Not surprisingly, the demand and support were greater for nonmedical aspects of care like transport, patient navigation, and accommodation thus reflecting the social impact of the pandemic and lockdown.

A limitation of this study is that it does not examine the impact of the delays in patient registration and interruptions in treatment on the survival of the child. Such information will need more follow-up. Previously, researchers have shown that delays in the start of treatment may adversely impact the outcome of children with certain cancers,²⁸ and recently, models on predicting an excess of mortality in adult patients with cancer because of delays in diagnosis²⁹ and decreased availability of cancer services have been published.³⁰ Another limitation is that this study looks at the immediate period of lockdown in India (March 24 to May 31, 2020) and not the subsequent time period and hence cannot comment on how long the impact has lasted. India has continued through several phases of lockdown and subsequent phases of easing of lockdown that have lasted more than a year.⁹ Hence, it would be logical to conclude that the adverse impact on access to health care would have lasted much longer than the period of this study. Moreover, as of April 2021, the country is in the middle of the second wave with more symptomatic patients and deaths than those reported last year. Although the accompanying lockdown has been less widespread, less intense, and shorter, the impact of those factors on the ability of childhood cancer patients to access health care remains to be investigated. To study the impact of change in the schedule of treatment on the care of children with cancer, the information on vital outcomes, disease outcomes, and treatment outcomes will be collected at 6 months and 12 months after registration at the center. To ascertain the follow-up information, a questionnaire will be sent to each participating center.

In conclusion, our multicenter study from India suggests that the COVID-19 pandemic and the lockdown impacted 2 out of 3 children with cancer. The effect of this on survival is yet to be established. Adapted treatment practices of centers and greater support from social organizations are needed to continue to provide care to these patients.

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AUTHORS CONTRIBUTIONS

Jyotsna Sharma: Conceptualization, literature review, study design, methodology, data curation, formal analysis, writing-original draft, and writingreview and editing. Amita Mahajan: Conceptualisation, investigation, methodology, and writing-review and editing. Sameer Bakhshi: Data entry and writing-review and editing. Veerendra Patil: Data entry and writingreview and editing. Nishant Verma: Data entry and writing-review and editing. Venkatraman Radhakrishnan: Data entry and writing-review and editing. Amitabh Singh: Data entry and writing-review and editing. Amitabh Singh: Data entry and writing-review and editing. Smita Kayal: Data entry and writing-review and editing. Rachna Seth: Data entry and writing-review and editing. Deepam Pushpam: Data entry and writing-review and editing. Ramandeep Singh Arora: Conceptualization, literature review, study design, methodology, data curation, formal analysis, writing-original draft, and writing-review and editing.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author after anonymizing the identifiable information.

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