



COVID-19 in Children with Cancer

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Accepted: 27 October 2021 / Published online: 3 February 2022

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Abstract

Purpose of Review This study aims to describe what is currently known about how children with cancer have been affected by the COVID-19 pandemic, including morbidity and mortality, interruptions in cancer care and delays in diagnosis, and psychosocial effects. Here we summarize the literature on how this patient population has fared during the pandemic, reviewing multiple smaller reports along with two large registries.

Recent Findings Although children with cancer generally have better outcomes with COVID-19 infection than adults with cancer, their risks of hospitalization, ICU admission, and death are greatly increased compared to the general pediatric population. There are socioeconomic and ethnic disparities present in these effects.

Summary Children with cancer experience significant risks from the COVID-19 pandemic. It has yet to be seen how delays and interruptions of cancer treatment and direct organ toxicities caused by the virus itself may affect long-term outcomes in these patients.

Keywords Pediatric · COVID-19 · Oncology

Introduction

March 2020.

A 5-year-old with acute lymphoblastic leukemia (ALL) in induction develops a cough concerning for the new COVID-19 disease. After an exhaustive search for severely limited testing kits, the child is tested for COVID-19 and, 48 h later,

receives a positive test result. We call the worried parents and tell them what we know: yes, COVID-19 is very concerning but thus far, pediatric patients seem to fair much better than adults and no deaths among pediatric oncology patients have been reported. We discuss that the patient is already on steroids, which may help. We note that the known mortality of leukemia is much worse than what appears to be the case with COVID-19 and thus our plan is to continue with induction chemotherapy. We hang up the phone with the family and are left with great uncertainty about the accuracy of our assessment; this is uncharted territory—will

This article is part of the Topical Collection on *Pediatric Oncology*

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pediatric oncology patients do as well as other pediatric patients? Or will their morbidity and mortality be much higher than we expect?

October 2021.

Eighteen months of managing health care during the COVID-19 pandemic has offered the opportunity to investigate the impact of COVID-19 in diverse patient populations. Early on, single site or small patient population reports began to provide snapshots of different clinical scenarios. Pediatric oncologists are known for their cooperative group trials to advance science and clinical care and this pandemic has been no exception. Two large registries for children with cancer and COVID-19 were established early in the pandemic. The Pediatric Oncology COVID-19 Case Report (POCC) [1] distributed by the POCC consortium and the Global Registry of COVID-19 in Pediatric Cancer (Global Registry) [2] established by St. Jude Children's Research Hospital and International Society of Paediatric Oncology (SIOP) have given us a wealth of information and helped pediatric oncologists across the world answer the uncertain questions at the pandemic's onset. We summarize the current but ever-evolving literature regarding pediatric oncology patients with COVID-19—including their clinical course, implications for cancer treatment, and the other effects of the pandemic on children with cancer and their families.

What Symptoms Are Common in Pediatric Oncology Patients with COVID-19 Infections?

Similar to other patient populations, a fair number of pediatric oncology patients are COVID-19 positive and asymptomatic. Pediatric oncology patients are often tested for COVID-19 prior to procedures requiring sedation or anesthesia. Approximately 25% (25/98) of pediatric oncology patients testing positive for COVID-19 were asymptomatic in early data from a New York/New Jersey consortium, which was replicated by the UK, where 28% of COVID-19-positive pediatric oncology patients were asymptomatic. [3, 4] Over time, the frequency of testing increased, which was reflected by an increasing proportion of asymptomatic patients.

Two larger registries have collected data longitudinally throughout the pandemic. The Global Registry of COVID-19 in Childhood Cancer, based at St. Jude Children's Research Hospital, focuses primarily on infections occurring outside the United States (US), including in low- and middle-income countries in South America, Africa, and Asia. [2] They report 35.2% of patients to be asymptomatic and 37.7% with mild disease. Similarly, the US registry (Pediatric COVID-19 Cancer Case [POCC] Report) [1] reports 35% of solid tumor patients and 42% of hematologic malignancy patients

testing positive for COVID-19 have been asymptomatic. Among symptomatic patients, the POCC Report shows fever (37%) and cough (31%) as the most common symptoms, followed by congestion/rhinorrhea (16%), shortness of breath (10%), gastrointestinal symptoms (nausea and vomiting 9%, and diarrhea 6%), headaches (10%), myalgias (9%) fatigue (8%), and sore throat (8%). [1] The Global Registry reports fever (43.3%) and respiratory symptoms (28.6%) as the most common symptoms followed by ENT symptoms (17.6%), gastrointestinal symptoms (9.8%), and neurologic signs or symptoms (8.2%). [2]

What Is the Morbidity and Mortality of COVID-19 in Pediatric Oncology Patients?

Early reports of COVID-19 identified rare severe disease and no deaths in children with cancer. [4–10] Although these initial reports were reassuring, more recent data unveil the larger range of risks that pediatric oncology patients face. The first reported case of COVID-19 in a pediatric oncology patient was that of a child with ALL requiring mechanical ventilation in China, reported as part of a larger pediatric COVID-19 cohort. [11] Small early reports from Italy, France, and the UK included a combined 108 patients, 9 of whom required intensive care with no deaths. [4–6] During the first pandemic surge (January to April, 2020), a cohort of 98 patients in the New York/New Jersey region reported 17 patients (23.2%) requiring ICU admission, with 6 (8.2%) requiring mechanical ventilation. [3] Among the four deaths in that cohort, three had relapsed/refractory disease and one had newly diagnosed acute myeloid leukemia with hyperleukocytosis. While no deaths were solely attributable to COVID-19 infection, the infection was considered to be contributory in two cases. The larger proportion of patients with severe disease in the US compared to Europe may be attributable to more widespread use of asymptomatic testing in Europe at that time.

As of 09/14/2021, the Global Registry reported on 1747 cases from over 50 countries. [2] Among these patients, 8.5% had moderate disease while 11% had severe disease and 7.7% were in critical condition. Nearly 9% were admitted to intensive care, and 3.8% died from COVID-19. The level of care reported by POCC was similar. [1] As of 09/14/2021, there were 1196 patients in this registry from 102 sites, representing more than 50% of US pediatric oncology sites. As compared with solid tumor patients, a larger proportion of patients with hematologic cancers were hospitalized (21% vs. 34%) or required intensive care (6% vs. 9%), while only 3% of patients with hematologic cancers died as compared to 7% of patients with solid tumors. Neither of these registries has evaluated whether variants of concern (such as Delta) [12] have led to more severe disease in children.

How Does the Morbidity and Mortality of COVID in Children with Cancer Compare to Adults with Cancer?

Early on in the pandemic, it quickly became apparent that children in the general population who tested positive for COVID-19 did not become as sick as adults. Children and young adults (0–25 years) with COVID-19 demonstrated a hospitalization rate of 2.5%, ICU admission rate of 0.8%, and a death rate of <0.1% compared to adult rates of 16.6%; 8.6%; and 5% respectively. [13] Among all patients with both cancer and COVID-19, children also experience less morbidity and mortality than adults. Only 4–9% of pediatric oncology patients experience a severe or critical COVID-19 course compared to 55% of adult oncology patients. [1–3, 6–10, 14–29] Table 1 summarizes the mortality rates seen across all of the studies that have reported on

COVID-19-positive pediatric oncology patients with a mortality rate of 4% (140/3445), with most of these deaths specifically being attributed to COVID-19 rather than solely to their oncology diagnosis. [1–3, 6–10, 15–28] In comparison, adults with cancer and COVID-19 have a reported mortality rate of 28%. [29]

The high rates of comorbidities in the adult oncology population (e.g., 31% hypertension, 14% cardiovascular disease, 8% chronic obstructive pulmonary disease, 16% diabetes) [29] may explain the higher mortality rates in adults as comorbidities have been associated with worse outcomes in the general population. [30] In the POCC report, comorbidities in the pediatric oncology population were significantly less common. [1] Obesity (9.5%), asthma (4.9%), and trisomy 21 (4.4%) were the most common comorbidities, with 18% noted as having “other” comorbidity, ranging from autism to panhypopituitarism. [1]

Table 1 Mortality and severe COVID-19 disease in pediatric oncology patients with COVID-19

Patients (N)	Deaths (N)	Severe COVID (N)	Location [Reference]	Publication date
33	0	*5 (15%)	France [6]	May-2020
37	1 (3%)	*5 (14%)	France [15]	Nov-2020
59	0	No ICU/oxygen mentioned	Pakistan [16]	April 2021
7	3 (43%) (1 related to cancer progression)	3 (43%)	Egypt [17]	Oct-2020
57	2 (4%)	6 (11%)	Texas [18]	Mar-2021
20	0	0 (4 hospitalized)	New York [19]	May-2020
16	0	4 (25%)	New York [20]	Jun-2020
6	0	0	[7]	Jun-2020
10	0	0	Italy [8]	Jun-2020
98	4** (4%)	7 (7%)	New York/New Jersey [3]	Dec-2020
18	0	0	Russia [21]	May-2021
1749	65 (3.7%)	152 (8.7%)	50 countries worldwide [2]	Sept 2021
29	0	0	Italy [9]	Jul-2020
19	0	2 required oxygen (11%)	Madrid [10]	May-2020
10	0	0	Saudi Arabia [22]	Nov-2020
20	4 (20%)	3 ICU (15%)	Iran [23]	Jul-2021
33	5 (15%)*	7 (21%)	Columbia [24]	May-2021
38	3 (8%)*	2 ICU (5%)	Mexico [25]	Dec-2020
47	2	11 (23%)	Spain [26]	Jul-2020
15	0	1 (7%)	India [27]	Nov-2020
37	0	14 (38%)	India [28]	Mar-2021
1196	51 (4.3%)	83 (7%)	USA [1]	Sept 2021
Total: 3554	140 (4%)	305 (9%)		

*Appear to be same data set in two different papers

**Deaths not attributed to COVID-19

***Part of the cohort death not attributed to COVID-19

Another explanation may be that the pediatric immune system has a greater ability to produce antibodies to viral illnesses such as COVID-19. Mayanskiy et al. described the presence of COVID-19 antibodies in 92% of pediatric oncology patients 3 weeks after their diagnostic test and in 100% 6 weeks after diagnosis; this is a significantly higher antibody response than seen in adults with cancer, despite most of the children in the cohort receiving chemotherapy that was lymphotoxic. [21]

How Does the Clinical Course for Children with Cancer Compare to Children Without Cancer When Infected with COVID-19?

Even though during the pandemic a high proportion of hospitalized children have tested positive for COVID-19 [31], only 0.8–3.6% of the general pediatric population with COVID-19 has been described as having severe or critical disease. [14, 15] A unique entity related to COVID-19 known as Multisystem Inflammatory Syndrome in Children (MIS-C) has also been identified in a subset of children with previous infection. Children with MIS-C present with fever, hypotension, gastrointestinal symptoms, and cardiac dysfunction as well as laboratory findings of cytokine storm several weeks after primary COVID-19 infection. [32] From March to June 22, 2020, 783 cases of MIS-C in the general pediatric population were reported in the literature. [33]

While 35–45% of pediatric oncology patients positive for COVID-19 have been reported to be asymptomatic in both the POCC and the Global Registry [1, 2], both of these registries have also demonstrated that pediatric oncology patients with COVID-19 have a much more severe clinical course overall and higher death rate than non-oncology patients (see Table 1) [1–3, 6–10, 15–28] Additionally, to date, 23 (1.9%) patients in the POCC report were described as having MIS-C. [1] A comparison cannot be made between pediatric oncology patient with MIS-C and general pediatric patients with MIS-C because of the way the data is collected and the fact that only 59% of the general patients with MIS-C also having a current COVID-19 diagnosis. [33]

What COVID-19 Directed Therapy and Prevention Is Available for Pediatric Oncology Patients?

COVID-19 treatments have evolved over the course of the pandemic for children and adults. Currently, children with cancer who are hospitalized with COVID-19 are treated with Remdesivir and steroids, similar to the approach in children without cancer who have serious disease. [34] Children ≥ 12 receiving cancer therapy qualify for monoclonal

antibodies when they test positive for COVID-19 or for post exposure prophylaxis. [35] Although there are no pediatric oncology-specific data, monoclonal antibodies decrease hospitalization and death on day 29 by 71% in high-risk adults. [35] Additionally, due to their immunocompromised state, children with cancer who meet the age eligibility for vaccination should receive three doses, with the third dose given no sooner than 28 days following the second dose. [36] Adult cancer patients receiving mRNA vaccines have not experienced novel side effects and have had some immune response. [37] There is limited data overall about vaccination in children with cancer, but there is promising preliminary data in vaccination in adolescents with cancer. [38] Revon-Revriere et al. evaluated 10 patients following vaccination with the BNT162b2 mRNA vaccine (Pfizer-BioNTech). Seventy percent had positive serology tests after their first dose and 90% had positive serology 1 month after the second vaccination. [38] Families of children with cancer are encouraged to be vaccinated and to follow applicable CDC and/or state-recommended layered mitigation strategies. [39]

What Happens to Cancer Treatment with a COVID-19 Infection?

Throughout the pandemic, there have been many modifications to children's cancer treatment. [1, 2, 40] These modifications have included some shifts to telehealth visits, delays in imaging and other care, and modifications to chemotherapy. [1, 2, 40] The Global Registry reported a reduction of chemotherapy in 5.4% of patients and withholding of chemotherapy in 37.5% of patients. [2] Similarly, POCC reported chemotherapy withheld in 41% of patients with hematologic malignancies and 30% of patients with solid tumors. [1] In light of the fact that treatment intensity is a hallmark of pediatric cancer therapy, such delays and reductions in chemotherapy may have long-term effects including increased risk of relapse. [41] Disease surveillance has also been impacted, with delays in scans and follow-up monitoring appointments for patients who are off treatment. [40]

Has COVID-19 Caused Delays in Cancer Diagnosis?

Reports during the pandemic surge in Lombardy found that new pediatric oncology diagnoses occurred at half the expected rate. [42] A large pediatric referral center in the region also noted that the volume of new solid tumor diagnoses was nearly half what would have been expected during this time period. [42] Delays in diagnosis continued to be reported worldwide throughout the pandemic, in some cases with children presenting when already critically ill. [40,

43–46] Reports of these delays center on both overwhelmed hospitals and patient fear of going to the hospital. In some situations, delays in diagnosis may have both short-term and long-term effects on morbidity and mortality. [40, 43–46] For example, children may present with overwhelming sepsis or require more aggressive (morbid) surgeries than they would have if they presented earlier. Delays can also impact longer term survival because of changes in stage at presentation. [43, 44]

What Disparities Exist in Children with Cancer and COVID-19?

Both the POCC report and the Global Registry report roughly twice as many hematologic malignancies as solid tumors among children with cancer and COVID-19 even though hematologic malignancies make up less than half of pediatric cancers. [1, 2, 47] This is also consistent with the report from the New York/New Jersey experience, in which the majority (65.3%) of childhood cancer patients with COVID-19 had hematologic malignancies. [3] However, despite comprising only 33% of the POCC patients, approximately half of the deaths in POCC registry were in solid tumor patients. [1] In the Global Registry, hematologic patients had a high rate of deaths attributed to COVID-19 while solid tumor patients had a number of deaths with other attributions. [2] It is conceivable that attribution of COVID-19 to the cause of death poses a challenge according to diagnosis. Because survival rates are higher in children with hematologic malignancies than solid tumors, it may be easier to attribute the cause of death to COVID-19 in hematologic malignancies than in solid tumors. For example, COVID-19 infection may hasten death due to lung metastases in solid tumor patients who would have eventually succumbed to the effects of those metastases.

Racial, ethnic, and socioeconomic disparities have been widely reported in the US COVID-19 population [48, 49], and similar patterns are seen among children with cancer. [1] In the US, a larger proportion of childhood cancer patients identified as Hispanic or having public insurance have been diagnosed with COVID-19 compared with the general pediatric cancer population. [1] Globally, severe and critical illness occurs with greater frequency in low- and lower middle-income countries, although this may also reflect disparities in testing and/or access to care. [50] Age also plays a role in outcome. Both POCC and the Global Registry report older age being associated with severe disease (POCC, ≥ 11 years old; Global, 15–18 years old). [1, 50] In the Global Registry, there was a higher risk of death in adolescent patients than in elementary-aged patients. [2] This is consistent with higher reported rates of disease severity in

adolescents than in elementary-aged children in the general pediatric population. [51]

What Are the Psychosocial Effects of COVID-19 on Children with Cancer and Their Families?

For children with cancer and their families, the psychosocial effects of the pandemic have compounded an already high-stress situation. [52] However, the experience of children and caregivers varies widely throughout the world. During the peak of the pandemic in the UK, the majority of parents of pediatric oncology patients reported that they felt the hospital was no longer a safe place and that they were anxious about the possibility of their child contracting the virus from them. [53] Similarly, parents and young adult cancer patients in the US reported high levels of stress. [54] In the Netherlands on the other hand, there was no difference in quality of life measures for pediatric oncology patients in the months leading up to and following the start of the pandemic, and the proportion of caregivers with distress actually decreased. [55] Caregivers reported that being able to work from home made managing their children's appointments easier, and that sharing concerns with other families about hygiene and homeschooling their children helped them feel more similar to other families. Parents whose children had died of cancer prior to the pandemic revealed that many felt more isolated in their grief, but felt that their experience made them more able to handle the uncertainty of the pandemic. [56]

Families of children with cancer were already at high risk of increased household material hardship due to their child's diagnosis and treatment pre-pandemic. [57] The effects of the pandemic may exacerbate these pre-existing disparities, as families who were already low-income have been further economically strained. [58, 59] Additionally, children with cancer, like all children, are at risk of losing their adult caregivers and other close family members to COVID-19, which has the potential to dramatically increase psychosocial distress and economic hardship. [2]

In addition to changes in the community, families have faced many changes to the care they receive in pediatric oncology centers. For example, child life specialists provide key psychosocial support for children with cancer, including activity centers or "playrooms;" during the pandemic, however, patients hospitalized or requiring frequent or extended clinic visits were not able to participate in such activities with other patients. Some hospital systems and regions limited the patient to one parent or caregiver at the bedside. This left some parents separated from their children for long periods during their child's illness [60], causing distress to children and families. [61] However, patients often were able to participate in virtual schooling with their classmates,

rather than requiring home instruction while their class met in-person. As schools return to in-person instruction, families are faced with deciding whether they are comfortable with their medically able children returning to traditional school in the ongoing pandemic. There are no published data yet on the impact of this change in school dynamics on patient and parent psychological well-being.

Will Children with Cancer Experience Late Effects of COVID-19?

In addition to immediate morbidity and mortality, over the next few years these pediatric oncology patients with a history of COVID-19 will require continued follow-up for late effects from their infection. Both chemotherapy and COVID-19 can affect multiple organs, including notably the heart and lungs. [62, 63] These may have additive or synergistic effects. As children treated for cancer are usually followed in a rigorous, algorithmic fashion to screen for and prevent late effects from cancer and its therapy, an opportunity exists to monitor for late effects from COVID-19. [62] Future comparisons of echocardiograms and pulmonary function testing performed during and after chemotherapy may elucidate differences between infected and uninfected children that will allow us to learn more about the interaction between COVID-19 infection and treatment-related toxicity. Such investigations may inform consideration of any potential modifications to late effects screening guidelines to account for children who have had a COVID-19 infection.

Conclusions

Children with cancer experience severe disease and mortality related to COVID-19 far exceeding the general pediatric population. Sociodemographics are associated with both the likelihood of infection (Hispanic ethnicity, public insurance) and severe disease or mortality (older age, low- and lower middle-income countries). In addition to the risks of hospitalization and death, COVID-19 infection also frequently causes changes in cancer-directed treatment, which may have long-term effects on treatment outcome. The overall impact of the COVID-19 pandemic on children with cancer also includes delays in diagnosis and treatment and the added psychosocial and economic stressors of living during a pandemic while also undergoing cancer treatment. It is conceivable that there will be possible additional late effects on organ function. Fortunately, we are developing a better understanding of COVID-19 in children with cancer, which may help pediatric oncologists and families mitigate some of these effects.

Funding This manuscript was supported by the Concern Foundation.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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