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ONCOLOGY: RESEARCH ARTICLE

Low numbers of COVID-19 in Swedish pediatric oncology patients during the first pandemic year despite an open society

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Abstract

Background: Sweden adopted a different strategy than many other countries to combat the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and kept most schools open. Initial reports from China suggested that coronavirus disease 2019 (COVID-19) was milder in children compared to adults, but there was a lack of data from immunocompromised children. Therefore, we investigated the rate of verified SARS-CoV-2 infections in our Swedish pediatric oncology patients.

Procedure: This was a multicenter retrospective study. A questionnaire including patient data as well as SARS-CoV-2 data was sent to the six Swedish childhood cancer centers in May 2021.

Results: During the first pandemic year, 49 patients were identified as SARS-CoV-2 positive, and 22 (45%) children were hospitalized with COVID-19. Two children needed intensive care, but no COVID-19-related deaths were reported. Most patients ($n = 36$, 73%) were on active chemotherapy treatment and 23 children (49%) attended school or daycare at least part-time. Half of the SARS-CoV-2-positive patients experienced a delay in cancer treatment.

Conclusions: Despite the rapid spread of SARS-CoV-2 in Sweden, without a strict lockdown of the society, the number of nationally reported pediatric oncology patients with polymerase chain reaction (PCR)-verified infection was low, and the majority of children had mild disease. Our data show that treatment interruptions occurred frequently and this should clearly be avoided for the coming years.

KEYWORDS
COVID-19, hematology, oncology, pediatrics, SARS-CoV-2

Abbreviations: Ag, antigen; ALL, acute lymphoblastic leukemia; COVID-19, coronavirus disease 2019; ICU, intensive care unit; PCR, polymerase chain reaction; PHA, Public Health Agency Sweden; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1 | INTRODUCTION

In late 2019, the first cases of atypical pneumonia were reported from Wuhan, China. Within a few months, the spread of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a global pandemic, and significant morbidity and mortality in high-risk populations were reported due to the associated coronavirus disease 2019 (COVID-19).[1] As of the end of September 2021, 232 million cases and almost 5 million deaths have been reported globally. Early in the pandemic, in the absence of effective testing strategies, treatment or prevention by vaccines, countries applied different strategies to limit virus spread. Many regions around the world went into strict lockdown for all age groups and it is estimated that the resulting school closures have affected >90% of students globally. In contrast, Sweden adopted a different approach to contain the virus, and chose to keep schools and daycare facilities open for children, except for a 3-month school closure for students >16 years of age starting in March 2020.[2] The adult population was encouraged to work from home, practice social distancing, and adhere to common hygiene measures. Initially, Sweden reported higher case counts and attributable mortality than other Nordic countries, but lower compared to other European countries.[3]

Children were in general reported to experience asymptomatic infection or to have milder disease than adults.[4] Early reports from China suggested that adult oncology patients were at higher risk of severe COVID-19 than patients without cancer.[5] Encouraging early data from Italy suggested that despite their immunosuppressed state, children with cancer may have a benign, self-limiting disease.[6] This was further supported by a global flash survey including 25 countries, reporting asymptomatic/mild COVID-19 in eight of nine polymerase chain reaction (PCR)-confirmed cases.[7] A meta-analysis of COVID-19 data from pediatric oncology patients compiled in June 2020 also showed a low COVID-related mortality of 0.6%, with no difference in the risk of hospitalization between children with hematological malignancies or solid tumors.[8]

During the second year of the pandemic, more data have been available on the impact of COVID-19 for pediatric oncology. A recent report from the United States on the New York–New Jersey regional experience covering 13 institutions, showed that while most pediatric oncology patients with PCR-verified COVID-19 experienced asymptomatic or mild disease, they suffered a higher morbidity than reported for the general pediatric population.[9] A major concern highlighted by this study is the high risk for delays in chemotherapy that accompanies COVID-19.

In Sweden, children with cancer are diagnosed at one of six childhood cancer centers located at the regional university hospitals in Umeå, Uppsala, Stockholm, Linköping, Gothenburg, and Lund. Approximately 300 new cases of childhood cancer are diagnosed in Sweden yearly, with Stockholm and Gothenburg treating approximately 25%–30% each, Uppsala and Lund 15%–20% each, and Linköping and Umeå 5%–10% each of new cases. After clinical and diagnostic workup, treatment is initiated at the university hospital. Thereafter, some chemotherapy regimens and supportive care, including infections without need for intensive care unit (ICU), transfusions, nutrition, physiotherapy, and psycho-social support, are taken care of at shared care local hospitals.

In this report, we present national data on COVID-19 cases in pediatric oncology patients from Sweden; a country that adopted a different strategy than many other countries to combat the pandemic by never implementing a full lockdown and keeping schools mostly open. We report on the geographic and demographic distribution of COVID-19 cases and on the clinical outcomes observed in this patient cohort, including observed treatment delays.

2 | MATERIAL AND METHODS

2.1 | Study population

This was a multicenter retrospective study, where a questionnaire was sent to the six Swedish childhood cancer centers in May 2021 (Umeå, Uppsala, Stockholm, Linköping, Gothenburg, and Lund). The questionnaire included basic data on age, gender, underlying cancer diagnosis, date of positive SARS-CoV-2 test, and preferred test platform. In addition, questions related to clinical symptoms of infection, length of hospital stay, intensive care, and consequences for cancer chemotherapy were included. The treating physician could also add relevant patient information in free text. Data on clinical testing routines at the different centers were also retrieved through the questionnaire.

2.2 | Data collection and analyses

Based on epidemiological data on the number of new cases per day from the Public Health Agency Sweden (PHA), we defined the first pandemic wave as occurring from March 2020 to September 2020 and the second wave from October 2020 to February 2021. Data from the time period March 2020 to February 2021 were collected to cover the first year of the pandemic in Sweden, including both the first and second waves of the pandemic. Cases were defined by a positive test (PCR or antigen detection [Ag]) recorded in the patient chart. A local representative from the Supportive Care Group within the Swedish Pediatric Oncology consortium was responsible for identifying cases and for data collection from patient medical records, using both university and local hospital records to complete the survey. Descriptive statistics were performed using Prism 9, GraphPad. This study was approved by the Swedish Ethical Review Authority (reference number 2021-01256).

2.3 | Recommendations for social life during the pandemic for children with cancer

In Sweden, most children with cancer (except for those who have received a stem cell transplant) and their families are recommended

to participate in normal age-appropriate activities as long as the child is in a general good condition, despite treatment effects such as neutropenia, thrombocytopenia, and other stress factors. This strategy is supported by a Swedish study that reported that children undergoing oncological treatment and attending school did not suffer an increased risk of starting antimicrobial treatment, compared to those who did not attend school.[10] During the pandemic, it was recommended by the Supportive Care Group[11] that most children with cancer should follow the general recommendations for children provided by the PHA. Local exceptions existed and included the Gothenburg region, where physicians were cautious during the first 3–6 months of the pandemic and recommended daycare/school absence for patients who were in the intensive treatment phase of hematological malignancies.

3 | RESULTS

3.1 | Data on SARS-CoV-2 testing in Swedish pediatric cancer centers

In Stockholm and Lund, all asymptomatic patients were tested for active SARS-CoV-2 infection before admission to the ward or before anesthesia for procedures, and children with fever or respiratory symptoms were tested as part of diagnostic workup. In Gothenburg, symptomatic patients and patients scheduled for anesthesia were tested during the first and second waves. In Linköping and Uppsala, only children with upper respiratory symptoms were tested for SARS-CoV-2, while asymptomatic children were admitted without testing. In Umeå, only patients with respiratory symptoms were tested for SARS-CoV-2 during the first pandemic wave, while all patients and their parents were tested before admission during the second wave. In general, asymptomatic staff were not routinely tested for active SARS-CoV-2 infection, but were required to wear face masks at all patient contacts and at staff meetings, when unable to keep a 2-m distance.

3.2 | SARS-CoV-2-positive patient characteristics

In total, 49 SARS-CoV-2-positive children were identified from March 2020 to February 2021, the first pandemic year in Sweden. Cases were identified in five of the six centers, with no cases reported from Linköping, where the first PCR-verified case was identified in March 2021. Most centers used viral PCR for detection of SARS-CoV-2 rather than Ag tests. Patients ranged from 6 months to 18 years of age, with a median of 9.2 years. Children were equally distributed in the different age groups and two-thirds of children were school-aged. There were more boys ($n = 29$, 59%) than girls diagnosed with SARS-CoV-2 infection. In two-thirds of cases, children were symptomatic when tested for SARS-CoV-2. As expected, children with a hematological diagnosis dominated ($n = 24$, 49%), and 19 cases were observed in patients with acute lymphoblastic leukemia (ALL), of whom three had relapsed ALL. Three children had underlying severe anemia and one child had giant cell astrocytoma on the basis of tuberous sclerosis. Most patients ($n = 36$, 73%) were on active chemotherapy treatment, but only four children had received daily corticosteroids for the last 2 weeks. Patient characteristics are shown in Table 1. Almost half of the children were attending school or daycare at least part-time, despite the pandemic.

TABLE 1 Patient characteristics March 2020–February 2021

Patients	Total $n = 49$
Age group, years	
<6	17
6–12	16
13–18	16
Median (range)	9.2 (6 months to 18 years)
Gender, *n* (%)	
- Girls	20 (41)
- Boys	29 (59)
Diagnosis, *n* (%)	
- Hematological malignancy[a]	24 (49)
- CNS tumor	7 (14)
- Solid tumor	13 (27)
- Miscellaneous[b]	5 (10)
Cancer treatment, *n* (%)	
- Active	36 (73)
- Daily steroids	4 (11)
- Follow-up	13 (27)
Reason for testing, *n* (%)	
- Symptoms of infection	34 (69)
- Screening	15 (31)
Attending daycare or school[c], *n* (%)	23 (49)

Abbreviation: CNS, central nervous system.

[a]Including lymphomas.

[b]Miscellaneous, including HLH, giant cell astrocytoma, and autoimmune hemolytic anemia.

[c]One child was aged 6 months and thus not eligible for daycare. Missing data for 13 patients as information was lacking in the patient medical record.

COVID-19 cases in pediatric cancer patients in the first wave were observed primarily in the Stockholm area and more cases were identified in other parts of the country during the second wave (Figure 1).

3.3 | Clinical course of COVID-19

Of the 49 SARS-CoV-2-positive patients, 22 children were hospitalized due to COVID-19 (Table 2). There were no differences in age between hospitalized and non-hospitalized children ($p = .70$, Mann–Whitney test), nor within any diagnosis group when comparing among all positive hospitalized children ($p = .79$, Fisher's exact test). Two children were SARS-CoV-2 positive at the time of initial diagnosis of their malignancy, which may have contributed to hospitalization, as they showed only minor symptoms of COVID-19. The median length of hospital

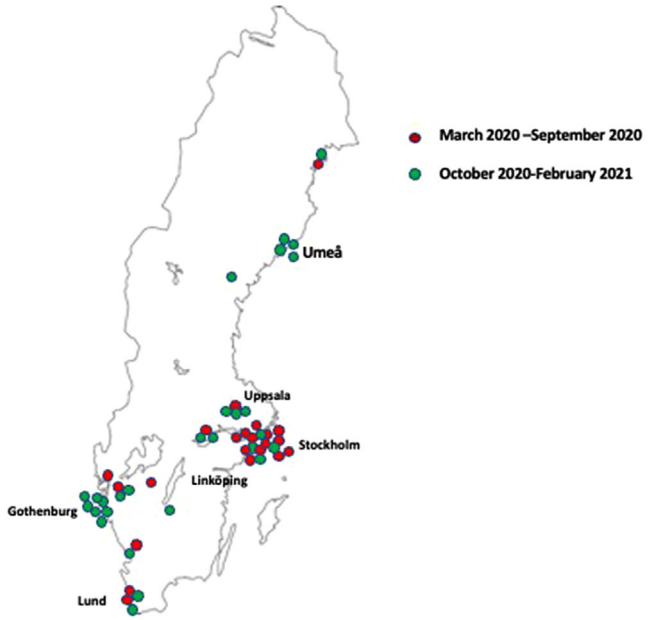

FIGURE 1 Identified SARS-CoV-2-positive cases during the first (March 2020 through September 2020, red dots) and second (October 2020 through February 2021, green dots) pandemic waves in Sweden

TABLE 2 Characteristics of hospitalized SARS-CoV-2 patients

Hospitalization, *n* (%)	
- Number of patients	22 (45)
- Length of stay, median (range)[a]	5 (1–42) days
- Intensive care treatment, *n* (%)	2 (4)
Age in hospitalized patients	
- Median (range)	9 (1.5–16.5) years
Diagnosis in hospitalized patients, *n* (%)	
- ALL and lymphoma	10 (45)
- CNS tumor	3 (14)
- Solid tumor	8 (36)
- Miscellaneous[b]	1 (5)
Delay in cancer treatment, n (%)	23 (47)

Abbreviations: ALL, acute lymphoblastic leukemia; CNS, central nervous system.

[a]Missing data for two children.

[b]Miscellaneous, including HLH, giant cell astrocytoma, and autoimmune hemolytic anemia.

stay was 5 (range 1–42) days. In the majority of hospitalized patients, COVID-19 did not cause significant morbidity. However, almost half of the children (23/49) experienced a delay in cancer therapy.

Two children required treatment in the ICU. The first patient was 16 years old and regularly seen in the outpatient clinic due to a low-grade brainstem glioma, previously treated with surgery and chemotherapy according to the LGG 2003 protocol. MRI in November 2019 showed an extensive rest tumor in the cerebellum and brainstem. Post therapy, the patient was diagnosed with chronic respiratory insufficiency caused by the tumor and had on one previous occasion required hospitalization due to viral pneumonia. In June 2020, the patient was admitted to the ICU with respiratory distress and high fever, and the clinical workup demonstrated a positive PCR test result for SARS-CoV-2 and a computed tomography scan of the chest with typical COVID-19 findings. At day 8 after admission, the patient required intubation for a 5-day period. Still, more than a year later, the patient needs respiratory support during the night, and it is possible that COVID-19 has contributed to the chronic respiratory insufficiency.

The second child was 4 years old, recently diagnosed with a large solid lung tumor that filled most of the left thoracic cavity where PAD showed desmoid-type fibromatosis. The patient was feeling well when admitted to the oncological ward to start the first course of chemotherapy as the tumor was inoperable. The child had received dexamethasone for 5 days before admission to hospital. At the ward, the child became ill with symptomatic COVID-19 and transferred to the ICU after 5 days. Six days after testing positive with PCR, the child was intubated on vital indication but recovered; however, remaining PCR positive for approximately 1.5 months before clearing the virus. Thus, chemotherapy was significantly delayed.

4 | DISCUSSION

During the first SARS-CoV-2 pandemic year, Sweden adopted a different COVID-19 strategy than, for example, most of Europe and the United States, and kept the society open. For example, most schools and daycare facilities remained open but with strict hygiene routines put in place. The pediatric hematology and oncology departments mostly adhered to the recommendations from the PHA. This retrospective study indicates that Swedish pediatric oncology patients were not at risk for more severe COVID-19 than other children in Sweden.[12]

In this study cohort, 49 children with cancer tested positive for SARS-CoV-2 infection at the childhood cancer centers in Sweden. The first wave primarily affected children treated in Stockholm and Uppsala, which is in accordance with the national geographical spread of SARS-CoV-2 infection.[13] The lower number of cases in the Gothenburg region during the first wave of the pandemic may also be attributed to strict, region-specific recommendations provided to families of children with cancer. The majority of PCR-positive children reported in this study were under active cancer treatment and as such, more likely to be tested than children who were in a follow-up phase after childhood cancer. During the first year of the pandemic, seroprevalence studies from the Swedish PHA showed an increase of SARS-CoV-2-specific antibody titers from 1.7% in April 2020 to 23.4% in March 2021 in pediatric outpatients who were sampled for reasons other than COVID-19,[14] which indicates a wide spread of SARS-CoV-2 also among children. Interestingly, the same publication reported that in March 2021, the observed seroprevalences were similar across different age groups (0–11, 12–15, and 16–19 years of age). This differs from the findings in our study, where the majority of SARS-CoV-2 PCR-positive patients were younger children. However, this most likely reflects the age

distribution of childhood cancer rather than SARS-CoV-2 epidemiology, as many of our patients were tested before admission to the ward or before procedures involving anesthesia, and not as outpatients, as in the PHA report mentioned above.

SARS-CoV-2 infection was mainly detected by PCR rather than by Ag testing in our cohort. Ag testing reliably detects samples with high viral loads, although it is not as effective in detecting low viral loads, whereas PCR also may differentiate between negative and low viral load samples.[15] As asymptomatic children tend to present with quite low viral loads, the number of asymptomatic SARS-CoV-2-positive children reported in this study may in part be explained by the aforementioned fact that many centers screened children using PCR rather than with Ag tests. The difference between positive cases among the Swedish pediatric cancer centers may rather be attributed to different testing strategies in combination with the fact that Swedish regions were affected differently between the first and second pandemic waves than different test methods.

Although most children presented with mild symptoms, almost 50% were hospitalized due to COVID-19. In a few cases, hospitalization was required due to cancer treatment rather than the infection. The high rate of hospitalization observed in this study may reflect the initial lack of knowledge on COVID-19 in immunocompromised children, thereby resulting in an overly cautious clinical approach, despite early reports, for example, from Italy,[6] indicating a mild clinical course in most pediatric hemato-oncology and transplanted patients. Other reports have claimed a higher incidence of ICU admittance (9%) or death (4%), something that is not reflected in our population.[16]

Of the two children admitted to ICU, one was in cancer follow-up and had been without cancer treatment for many years. This patient showed typical signs of COVID-19, including respiratory failure requiring intubation and ventilator-assisted breathing. The previous malignancy had resulted in chronic respiratory insufficiency, which likely contributed to the severity of disease in this case. The second child, however, was suffering from a pre-existing large solid lung tumor, which most likely impacted the respiratory failure.

There were no deaths due to severe COVID-19 during the study period, which is in accordance with data from a meta-analysis showing an overall COVID-19 mortality of 0.6% in children with cancer.[8] Recently, national Polish data also indicated that children with cancer have a low mortality risk related to SARS-CoV-2.[17] Similar to our findings, however, a high proportion (63%) of children experienced a delay in cancer treatment. However, it should be emphasized that recent global data indicate that COVID-19 in children with cancer can cause significant mortality in low or low-middle-income countries.[18]

Contrary to reports from many parts of the world, a high proportion of children with cancer reported continued school or daycare attendance, following the recommendations from the Swedish PHA. After the initial 3–6 months of the pandemic, all cancer centers reverted to the practice of no shielding and schools were open to a high extent. In conclusion, despite the rapid spread of SARS-CoV-2 in Sweden, without a strict lockdown of the society, the number of nationally reported pediatric oncology patients with PCR-verified infection was low, and the majority of children had mild disease. These data are promising, as we now are almost 2 years into the pandemic. With the rapid roll-out of SARS-CoV-2 vaccines in Sweden, where children from the age of 12 have been offered vaccination from September 2021, we will hopefully see less children with cancer infected and in need of hospitalization or with postponed cancer treatment.

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AUTHOR CONTRIBUTIONS

Anna Nilsson was the principal investigator, and responsible for the study design, data compilation and analysis, and writing the initial draft. Emil Sundberg, Kleopatra Georgantzi, Josefin Palle was responsible for regional data collection and Torben Ek were responsible for initial review and editing. Emil Sundberg, Kleopatra Georgantzi, Hartmut Vogt, Frans Nilsson, Ladislav Król, Cecilia Langenskiöld, and Torben Ek were responsible for regional data collection. All authors reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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