Title: Outcomes of SARS-CoV-2 infection in 126 children and adolescents with Central Nervous System tumors

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Funding**:** This study was funded by the American Lebanese Syrian Associated Charities (ALSAC)

Declaration of interests: The authors declare no competing interests.

Contributors**:** DCM and SM developed the idea. DCM and SM drafted the manuscript and prepared the tables and figures. All authors contributed to the interpretation of the findings and the editing of the article. All authors approved the final submitted version.

ABSTRACT:

Background

The Global Registry of COVID-19 in Childhood Cancer (GRCCC) seeks to describe the natural history of SARS-CoV-2 in children with cancer across the world. Here we report the disease course and management of COVID-19 infection in the subset of children and adolescents with CNS tumors that were included in the GRCCC until February 2021, the first data freeze.

Procedure

The GRCCC is a deidentified web-based registry of patients <19 years of age with cancer or recipients of a hematopoietic stem cell transplant and laboratory-confirmed SARS-CoV-2 infection. Demographic data, cancer diagnosis, cancer-directed therapy, and clinical characteristics of SARS-CoV-2 infection were collected. Outcomes were collected at 30-days and 60-days post infection.

Results

The GRCCC included 1500 cases from 45 countries, including 126 children with CNS tumors (8.4%). Sixty percent of the cases were from middle-income countries, while no cases were reported from low-income countries. Low-grade gliomas, high-grade gliomas, and CNS embryonal tumors were the most common CNS cancer diagnoses (67%, 84/126). Follow up at 30 days was available for 107 (85%) patients. Based on the composite measure of severity, 53.3% (57/107) of reported SARS-CoV-2 infections were asymptomatic, 39.3% (42/107) were mild/moderate, and 6.5% (7/107) were severe or

critical. One patient died from SARS-CoV-2 infection. There was a significant association between infection severity and ANC <500 (p=0.04). Of 107 patients with follow up available, 40 patients (37.4%) were not receiving cancer-directed therapy. Thirty-four patients (50.7%) had a modification to their treatment due to withholding of chemotherapy or delays in radiotherapy or surgery.

Conclusion

In this cohort of patients with CNS tumors and COVID-19, the frequency of severe infection appears to be low, although severe disease and death do occur. We found that greater severity was seen in patients with severe neutropenia, although treatment modifications were not associated with infection severity or cytopenias. Additional analyses are needed to further describe this unique group of patients.

INTRODUCTION:

Although most children and adolescents with COVID-19 infections have favorable outcomes[1-3], early evidence signaled that patients with cancer might have a higher risk of complications.[4] While most children with cancer and SARS-CoV-2 will have a mild disease course, severe cases of COVID-19 and death secondary to infection occur.[5-9] Associations reported with poor outcomes for children with cancer include low absolute lymphocyte or neutrophil count[5], comorbidity, hematologic malignancy diagnosis, or receipt of intensive treatment.[5,6] More severe outcomes have also been reported in patients living in low-and-middle-income countries.[5]

Central nervous system (CNS) tumors are the second most common group of pediatric cancers, accounting for 20-25% of all cases.[10,11] Nevertheless, to date, patients with CNS tumors have contributed a small proportion of published reports of COVID-19 in children with cancer.[12,13] Even in case series from high-income countries, the proportion of patients with CNS tumors ranged from 3% to 9% of included patients.[14-16] The care of children with CNS tumors requires intense multimodal therapy, including neurosurgical procedures, large field radiotherapy and high-dose chemotherapy. In the absence of data to support the safety of proceeding with these treatments in the setting of COVID infection, clinicians may be reluctant to continue these therapies as scheduled.[5,17] It is therefore important to adequately characterize the clinical course of COVID infection in patients with CNS tumors.

The Global Registry of COVID-19 in Childhood Cancer (GRCCC) is a deidentified multi-institutional web-based registry of children and adolescents with cancer and a confirmed diagnosis of COVID-19. In its first report, a cohort of 1500 patients was reported

from 45 countries, including 318 patients treated in low-income or lower-middle-income countries.[5] Here we report the disease course and management of COVID-19 infection in the subset of children and adolescents with CNS tumors that were included in the first data freeze (Februar 1, 2021) of the GRCCC.

METHODS:

Study design and participants

The GRCCC was launched on April 15, 2020 as a joint initiative of St. Jude Global and the International Society of Paediatric Oncology (SIOP). The registry captures cases voluntarily reported by healthcare professionals across the world and is housed in a REDCap (Nashville, USA) database hosted at St. Jude Children's Research Hospital (Memphis, USA). Inclusion criteria include: laboratory-confirmed cases of SARS-CoV-2 infection in children and adolescents (<19 years) with cancer or who have received a hematopoietic stem-cell transplantation. *De-identified data was requested on a maximum of 80 variables in an initial form. Follow up was prompted in a second form for all patients at 30 days to evaluate clinical outcomes, including whether a patient remained hospitalized or had been discharged by the end of the 30-day period. For patients with ongoing evidence of infection at 30 days, an additional follow up form was prompted at 60 days. Comorbidities included history of high-dose steroid within 14 days before diagnosis or illness, pre-existing pulmonary disease, pre-existing cardiac insufficiency, and a free text option for other conditions.* Additional details of study design have been published previously.[5]

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics and outcomes. A five-level composite measure of severity was defined that incorporated the anatomic site of respiratory tract infection (upper versus lower), level of respiratory support, requirement for higher level of care, organ dysfunction, and death attributed to COVID-19. The five levels of severity were: asymptomatic, mild, moderate, severe, and critical.[5]

All data analyses were done using SAS software, version 9.4 and R, version 4.0.4.

Ethical oversight

This study was reviewed by the St. Jude Children's Research Hospital institutional review board and designated as not involving human subjects since no identifiable data is collected. This study was subject to approvals by local ethics committees according to local requirements.

RESULTS:

Data submitted between April 15, 2020, and February 1, 2021 was included for analysis. Data from all institutions which could confirm that all qualifying cases had been entered without bias were included in the first analysis. Of 1500 qualifying episodes, 126 (8.4%) occurred in children with CNS tumors. The clinical characteristics of these patients are summarized in Table 1. The median age of qualifying patients with CNS tumors was 9 years (range 6 months to 18 years). The United States (n=24), Argentina (n=18), and Brazil (n=9) were the countries that submitted the majority of cases (Figure 1). Sixty percent of the cases were from middle-income countries, while no cases were reported from low-income countries. Low-grade gliomas, high-grade gliomas, and CNS embryonal

tumors were the most common CNS cancer diagnoses, accounting for 67% (84/126) of cases. Eighty-one patients (64.3%) were undergoing cancer-directed therapy at the time of infection and 7 (5.6%) were receiving non-curative treatment, including palliative oral chemotherapy. Of patients receiving cancer-directed therapy, 67% (59/88) had received chemotherapy in the 30 days prior to SARS-CoV-2 infection. Furthermore, 4 patients (3.2%) had either undergone myeloablative chemotherapy and autologous hematopoietic stem cell rescue or were receiving preparative therapy at the time of infection. Fifty-seven (45.2%) patients had received radiotherapy, including 27 who received craniospinal irradiation.

SARS-CoV-2 infection was detected most frequently based on nasopharyngeal (77.8%, 98/126), nasal (16.7%, 21/126), or oropharyngeal swabs (15.9%, 20/126). Fifty-two (41.3%) patients were symptomatic at the time of SARS-CoV-2 detection (Table 2). The most common reported symptoms were fever (67.3%, 35/52), cough (42.3%, 22/52), rhinorrhea (21.2%, 11/52), and headaches (21.2%, 11/52). The mean duration of symptoms when the patient was tested for SARS-CoV-2 was 2.7 days (range 0-11 days). Radiologic characteristics are described in Table 2, with most patients having no diagnostic imaging performed to evaluate COVID-19 pulmonary complications. At SARS-CoV-2 infection, 17 patients (13.5%) had an absolute neutrophil count (ANC) of less than 500 cells/μL, while 17 (13.5%) had an absolute lymphocyte count (ALC) of less than 300 cells/μL. Twenty-five (19.8%) patients had an identified comorbidity, including endocrinopathies (n=10), preexisting pulmonary disease (n=5) and history of high-dose steroid use within 14 days of infection (n=5). At presentation, 33 patients (26.2%) were

admitted specifically for management of COVID-19, while 31 (22.6%) were already admitted to the hospital when infection was detected.

Follow up at 30 days was available for 107 (85%) patients (Table 3). Of these, 55 patients (51.4%) were never hospitalized, and 42 patients (39.3%) were discharged after a stay of less than 30 days. Based on the SARS-CoV-2 diagnosis, 14 (13.1%) patients received COVID-19-directed treatment. Azithromycin (n=11), corticosteroids (n=7), hydroxychloroquine (n=6), remdesivir (n=3), and oseltamivir (n=2), ivermectin (n=1), and tocilizumab (n=1) were the utilized medications. Of patients with follow up available, 40 patients (37.4%) were not receiving cancer-directed therapy. Of patients receiving cancer-directed treatment, 34 patients (50.7%) had a modification to their treatment due to withholding of chemotherapy or delays in radiotherapy or surgery. Treatment modification was not associated with COVID-19 severity (p=0.64), ANC lower than 500 cells/µL (p=0.05), ALC lower than 300 cells/µL (p=1.0), or age group (p=1.0).

Six (5.6%) patients were admitted to the intensive care unit (ICU) or intermediate care unit. Furthermore, 2 patients (1.9%) were intubated, while CPAP/BiPAP was used in 1 patient (0.9%). The duration of non-invasive respiratory support had a mean of 12.5 days (range 5-38 days), while the duration of intubation had a mean duration for 5 days (range 1-9). At follow-up (30 days after symptom onset), most patients (75/3%, 96/107) had laboratory-confirmed or clinical resolution of COVID-19. Only 1 patient (0.9%) expired from COVID-19 or its complications. This patient was a 15-year-old male with a diagnosis of high-grade glioma who had a lower-respiratory infection leading to respiratory failure and death. At the time of SARS-CoV-2 infection, the last chemotherapy was given in the

prior 30 days and the ANC was 250 cells/µL and ALC was 330 cells/µL. Two additional deaths (1.9%) were unrelated to COVID-19.

Based on the composite measure of severity, 53.3% (57/107) of the patients were asymptomatic, 39.3% (42/107) had mild or moderate infection, and 6.5% (7/107) had severe or critical infection. Disease severity was associated with ANC lower than 500 cells/µL (p=0.04), but not with recent chemotherapy administration, existence of comorbidities, or ALC lower than 300 cells/µL (Table 4).

DISCUSSION:

In this study, we report on the largest cohort of children and adolescents with CNS tumors and COVID-19. In these 126 patients, we have shown that although rare, poor outcomes do occur with an overall mortality of close to 1%, and 7% of patients having severe or critical infection. Although multiple variables that have been associated with poor outcomes and mortality, only an ANC of less than 500 cells/µL was associated with worse outcome in this cohort. In contrast to the whole GRCCC cohort, an ALC of less than 300 cells/µL and age at infection were not associated with severe or critical illness.

It is important to note, that patients with CNS tumors only represented 8.4% of the whole GRCCC cohort. This is less than half of what would be expected based on the relative frequency of pediatric CNS in relation to childhood cancers. This may indicate multiple level of biases, from reporting to testing to access to care. A large variability of incidence of pediatric CNS tumors exists, with high-income countries having a higher incidence[11], and could be associated with the distribution of cases in our cohort. Hence these data may be a general reflection of the status of access to care for children with

CNS tumors, especially in LMICs. This is a relevant factor to consider as poor outcomes have been reported in LMICs for the full cohort of the GRCCC.[5] Furthermore, CNS tumor patients are frequently managed as outpatients, another possible selection bias.

The COVID-19 pandemic has changed health care delivery, creating additional barriers to diagnosis and treatment for children with cancer. It is important to point out that, although the direct effects of COVID-19 were generally mild in this cohort, almost one-third of patients had a modification to their cancer-directed therapy. This is consistent with other reports that describe important interruptions to cancer therapy, especially in low- and middle-income countries.[17,18] Results to date suggest that in most patients, particularly in those with minimal or absent symptoms, cancer-directed therapy can be continued although progression to more severe disease is still a risk. The ultimate consequences of these interruptions remain unquantified but are likely to influence cancer outcomes. Health systems interventions must be considered for this vulnerable population in order to minimize avoidable mortality and morbidity.

There are several limitations to this study. First, the requirement to only include patients with laboratory confirmed SARS-CoV-2 infection likely influenced the underrepresentation of low-income settings, as seen by the fact we had no patients from low-income countries. Furthermore, regional representation of the included patients is varied, with little contribution from Eastern Europe, Africa, and Southeast Asia. Contribution to the GRCCC was voluntary and have been associated with awareness of the existence of the registry. Second, we did not capture testing practices at the institutions that contributed patients to the GRCCC. It is possible that testing practices or recall biases might have contributed to patient characteristics and outcomes.

Nonetheless, to limit this possibility, we did request that all institutions submitting cases include all patients that were found to have COVID-19. Third, the registry did not capture the specific SARS-CoV-2 variant infecting patients, hence it is unknown if this factor may have contributed to clinical presentation or infection outcomes. Finally, although it is the largest cohort reported, only a small number of severe cases were included. This limited that capacity to analyze factors, inherent to cancer treatment or patients, that may contribute to infection severity in children with CNS tumors.

Although this is the largest cohort of patients reported to date, additional insight is needed, including the effects of treatment modifications on long-term outcomes and the description of clinical outcomes of COVID-19 in low-income countries. Furthermore, the included data describes the first year of the pandemic and outcomes may have changed with greater access to testing, increased knowledge of clinical course, and with the possible availability of COVID-19 vaccinations for children and adolescents. Finally, some of the included data in this study point to possible biases that exist in the care of pediatric CNS tumors and warrant further investigation, as these may have worsened during the pandemic.

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LEGENDS:

Table 1: Demographic, World Bank country income level, and basic cancer-related descriptors of cohort.

Table 2: Baseline characteristics of patients and SARS-CoV-2 infection.

Table 3: COVID-19 outcomes and modifications to cancer therapy.

Table 4: Distribution of clinical severity. This measure included the following levels of severity: asymptomatic, mild or moderate, and severe or critical. Fisher test was used for comparison.

Figure 1: Countries submitting data to the GRCCC on patients with CNS tumors and COVID-19.