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# COVID-19 infection in children with cancer in Armenia: report for the whole pandemic period*

**I. Melnichenko[1], R. Papyan[1–3], Y. Margaryan[4], E. Minasyan[1, 2], S. Hovhannisyan[1], M. Minasyan[1, 2], M. Petrosyan[1], L. Hambardzumyan[2], H. Grigoryan[1, 2], S. Hovsepyan[1–3], L. Krmoyan[1, 2], L. Hakobyan[1, 2], S. Iskanyan[1], S. Danielyan[5], L. Vagharshakyan[1, 2], N. Azizyan[6], M. Grigoryan[1, 7], S. Atoyan[8], G. Tamamyan[1–5], L. Sargsyan[1, 2]**

*[1]Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan; 7 Nersisyan St., Yerevan 0014;*
*[2]Department of Hematology and Pediatric Oncology, Yerevan State Medical University; 2 Koryun St., Yerevan 0025;*
*[3]Immune Oncology Research Institute; 7 Nersisyan St., Yerevan 0014;*
*[4]The Institute of Cancer & Crisis; 7 Nersisyan St., Yerevan 0014;*
*[5]Hematology Center after Prof. R.H. Yeolyan; 7 Nersisyan St., Yerevan 0014;*
*[6]National Center of Oncology after V.A. Fanarjian;76 Fanarjian St., Yerevan 0052;*
*[7]Department of Infectious Diseases, Yerevan State Medical University; 2 Koryun St., Yerevan 0025;*
*[8]National Infectious Diseases Center of Armenia; 2 Acharyan St., Yerevan 0041*

**Contact details:** *Irina Melnichenko Irinamelnichenko2009@gmail.com*

***Background and aims.*** *Immunocompromised pediatric patients with cancer are more susceptible to experiencing severe COVID-19 infection compared to other children. In a global registry study of childhood cancer with COVID-19, involving 1500 patients, severe of critical infections were detected in 20 % of the cases. The mortality rate of 4 % excelled that of the general pediatric population. Data about the development of COVID-19 complications in children with cancer remains limited and varies across different countries. This study aims to describe the incidence and characteristics of COVID-19 infection in children with cancer in Armenia.*

***Methods.*** *A prospective analysis was conducted on PCR-confirmed cases of COVID-19 infection in children with cancer aged 0–18 years from 2020 to 2022 at the Pediatric Cancer and Blood Disorders Center of Armenia, Yeolyan Hematology Center, the only pediatric hematology/oncology institution in our country.*

***Results.*** *Between June 2020 and March 2022, we studied 201 children with cancer in Armenia, of whom 35 cases of COVID-19 infection were confirmed. The median age was 8.4, and the male/female ratio was 1.3. Among the COVID-19-positive patients, 15 had acute lymphoblastic leukemia, 5 had lymphomas, 4 patients had neuroblastoma, and 2 each had medulloblastoma, rhabdomyosarcoma and Ewing sarcoma. There were single cases of osteosarcoma, acute myeloid leukemia and malignant triton tumor. Twenty patients (57 %) were asymptomatic, and the rest presented with fever, sore throat, and cough. Among the patients with hematological malignancies, four developed pneumonia, and two of them experienced cancer progression subsequently. Additionally, four patients had pancytopenia/thrombocytopenia, likely due to the infection with the Omicron in the last three months of the mentioned period. Overall, the incidence of COVID-19 complications was 11 %, and mortality was zero.*

***Conclusion.*** *This is the first nationwide report on COVID-19 in children with cancer in Armenia. The findings indicate lower rates of severe infection and mortality among compared to global estimates. Further studies are emerging to explore these differences.*

**Key words:** COVID-19 infection, childhood cancer, study, incidence, mortality, complications

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***Information about the authors***
*I. Melnichenko: MD, Pediatric Oncologist/Hematologist and Head of the Survivorship Clinic at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan, e-mail: Irinamelnichenko2009@gmail.com*
*R. Papyan: MD, Pediatric Oncologist, Head of Musculoskeletal Multidisciplinary Working Group at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan; Assistant Professor at the Department of Hematology and Pediatric Oncology, Yerevan State Medical University; Clinical Research Physician at Immune Oncology Research Institute, e-mail: ruzannapapyan92@gmail.com*
*Y. Margaryan: MD, MPH, Executive Director and co-founder of the Institute of Cancer and Crisis, e-mail: margaryanyeva@gmail.com*
*E. Minasyan: MD, Third-year fellow of the Hematology and Pediatric Oncology Department of Yerevan State Medical University, based in the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan, e-mail: elya.minasyan.pns@gmail.com*
*S. Hovhannisyan, MD, MPH, Pediatric Oncologist/Hematologist at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan, e-mail: satenhovhannisyan93@gmail.com*
*M. Minasyan: MD, Pediatric Oncologist/Hematologist at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan, e-mail: mariam.minasyan.nsk@gmail.com*
*M. Petrosyan: MD, Pediatric Oncologist/Hematologist at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan, e-mail: mpt950522@gmail.com*
*L. Hambardzumyan: MD, Fellow of the Hematology and Pediatric Oncology Department of Yerevan State Medical University, e-mail: lianahambardzumyan00@gmail.com*
*H. Grigoryan: MD, Pediatric Oncologist/Hematologist at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan, e-mail: henrik.grigoryan93@gmail.com*
*S. Hovsepyan: MD, Pediatric Oncologist and Hematologist, Research Fellow at the Immune-oncology Research Institute, e-mail: Shushhovsepyan96@gmail.com*

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*L. Krmoyan: MD, Pediatric Hematologist at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan; Assistant Professor at the Department of Hematology and Pediatric Oncology, Yerevan State Medical University, e-mail: lusinekrmoyan3@gmail.com*
*L. Hakobyan: MD, Pediatric Oncologist/Hematologist at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan; Assistant Professor at the Department of Hematology and Pediatric Oncology, Yerevan State Medical University, e-mail: lusinehakopian77@mail.ru*
*S. Iskanyan: MD, Pediatric Oncologist/Hematologist at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan, e-mail: samveliskanyan@yahoo.com*
*S. Danielyan: MD, PhD, Director of Hematology Center after Prof. R.H. Yeolyan, e-mail: danielsamvel@yahoo.com*
*L. Vagharshkayan: MD, Pediatric Hematologist and Head of Pediatric Hematology Department at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan; Assistant Professor at the Department of Hematology and Pediatric Oncology, Yerevan State Medical University, e-mail: lalavagarshakyan@yahoo.com*
*N. Azizyan: MD, Pulmonologist and the Deputy Head of the Diagnostic Service at the National Center of Oncology after V.A. Fanarjian, e-mail: nazizyan@mail.ru*
*M. Grigoryan: MD, Pediatric Infectious Disease Specialist at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan; Department of Infectious Diseases, Yerevan State Medical University, e-mail: Markgrigoryan@gmail.com*
*S. Atoyan: MD, MPH, Director of the National Infectious Diseases Center of Armenia, e-mail: stepan.atoyan@gmail.com*
*G. Tamamyan: MD, MSc, PhD, DSc, Head of the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology Center after Prof. R.H. Yeolyan; Chairman and Professor of the Department of Hematology and Pediatric Oncology, Yerevan State Medical University; CEO of the Immune Oncology Research Institute; President-Elect of the Pediatric Oncology East and Mediterranean (POEM) Group; Editor-in-chief of OncoDaily.com, e-mail: gevorgtamamyan@gmail.com*
*L. Sargsyan: MD, Pediatric Oncologist/Hematologist and the Head of Pediatric Oncology Department at the Pediatric Cancer and Blood Disorders Center of Armenia, Hematology center after Prof. R.H. Yeolyan; Assistant Professor at the Department of Hematology and Pediatric Oncology, Yerevan State Medical University, e-mail: lilitrsargsyan@gmail.com*

***Authors' contributions***
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**Introduction**

Cancer ranks second leading cause of pediatric death in the developed world. In high-income countries, the survival rate in pediatric oncology exceeds 80 percent, whereas in low- and middle-income countries this value remains significantly lower, at – 40 % or less [1]. The lack of specialized centers with appropriate expertise is one of the significant factors contributing to the higher mortality rates [2]. However, there has been a gradual improvement in the situation in the world, and Armenia, classified as a middle-income country, serves as a prime example of this progress. Based on the experiences of foreign countries, Armenia unified all the existing pediatric oncology and hematology units into the Pediatric Cancer and Blood Disorders Center of Armenia in 2019. Since its establishment, this dedicated center has achieved remarkable success in pediatric oncology, leading to a significant increase in the survival rate, which now stands at 75–80 % [3].

The coronavirus infection (COVID-19) that became quickly spread all over the world at the end of 2019 was one of the unprecedented challenges pediatric oncology faced.

Immunocompromised children with cancer face a higher vulnerability to severe COVID-19 infection than other children. In a global registry study of COVID-19 in childhood cancer involving 1500 patients reported that 20 % had severe or critical infections with a 4 % mortality rate exceeding that of the general pediatric population. The earlier literature reports on COVID-19 complications in children with cancer were limited. [4]. Due to the absence of specific guidelines regarding the continuity and modification of anti-cancer therapies, hospital admission procedures, and infection protection precautions the pandemic period has presented challenges for oncology units [5]. Hence, collaborative studies and comprehensive information collection from various clinics and institutions became vital to manage and prioritize pediatric cancer treatment strategies during the COVID-19 pandemic. Moreover, these endeavors were crucial for the further development of strategies against other infections and to estimate the infection fatality risk for childhood cancer. Recent studies showed positive outcomes in pediatric oncology and COVID-19, with most cases experiencing mild symptoms. Moreover, these studies reported minimal changes to cancer outcomes during the pandemic.

This study is aimed to describe the incidence of COVID-19 infection in children with cancer and its impact on childhood cancer outcomes in Armenia.

This type of research holds immense value as comprehensive and integrated strategies used at regional and national levels complement each other, culminating in a comprehensive and standardized approach to combating childhood cancer during the pandemic at a global level.

**Methods**

A prospective analysis of PCR (polymerase chain reaction)-confirmed COVID-19 infection cases in children with cancer aged 0–18 years was conducting at the Pediatric Cancer and Blood Disorders Center of Armenia from 2020 to 2022. Information was collected through questionnaires, covering various aspects such as patients' age, sex, type and stage of the disease, cancer treatment plan and modifications and outcome, COVID-19 symptoms, and duration. Initially, the data was gathered in a manual database and later transferred to an electronic database.

It is important to acknowledge the limitations of the study. Our focus was only on the children who were already diagnosed with cancer and undergoing treatment during the pandemic, excluding those who completed their treatments or tested negative for COVID-19 but displayed typical clinical symptoms related to the infection (false-negative tests).

**Results**

Between June 2020 and March 2022, a total of 201 children with cancer in Armenia were studied, and 35 cases of COVID-19 infection were confirmed. The median age was 8.4 years, male/female ratio – 1.3. Among the confirmed COVID-19 cases, 57 % of children were asymptomatic. Acute lymphoblastic leukemia (ALL) was diagnosed in 15 children, Hodgkin lymphoma (HL) – 3, Burkitt lymphoma – 1, primary cutaneous T-cell lymphoma – 1, neuroblastoma – 4, medulloblastoma – 2, Ewing sarcoma (ES) – 2, rhabdomyosarcoma – 2, osteosarcoma – 1, acute myeloid leukemia (AML) – 1, malignant peripheral nerve sheath tumor (MPNST) – 1.

Most symptomatic patients experienced common COVID-19 symptoms, such as fever, sore throat, and cough. Four patients, two with HL, one with ALL, and one with AML, developed pneumonia, and two of them experienced cancer progression after recovering from the infection.

One of the HL patients had already received the 5$^{th}$ cycle of chemotherapy when tested positive for COVID-19. Subsequently, 10 days later the patient exhibited number of COVID-19 symptoms such as persistent fever up to 39 °C, pericardial effusion, diarrhea, rash, and lymphadenopathy. Laboratory findings were consistent with Pediatric Inflammatory Multisystem Syndrome associated with COVID-19. The patient started receiving IVIG, but persistent fever remained. Computer tomography and biopsy of cervical lymph nodes revealed disease progression.

In another case, a patient diagnosed with AML received chemotherapy according to AML-MRD 2018 protocol. After AME and HAM chemotherapeutic regimen the patient developed a fever and cough. A positive PCR test result for COVID-19 confirmed the infection which was followed by hypoechogenic lesions in the liver, spleen, and leukemia cutis discovered by ultrasound examination. The progression of the disease was confirmed by biopsy.

Since February 2022, when the omicron variant of COVID-19 spread, some of the patients had a fever, and sore throat, and complete blood count analysis showed thrombocytopenia/pancytopenia (three patients were after a chemotherapy course, but had severe aplasia which was not detected before (ES – 1, MPNST – 1, ALL – 1). One of the patients with neuroblastoma experienced severe symptoms right before a myeloablative stem cell transplant.

Overall, the incidence of COVID-19 complications was 11 %, and there were no reported deaths.

**Discussion**

The information collected from all the medical records available at the Pediatric Cancer and Blood Disorders Center of Armenia reflects the situation that prevailed in pediatric oncology of Armenia during the pandemic. The comprehensive analysis of the registered data has revealed that more than half of the oncological patients diagnosed during routine screening were asymptomatic and needed no special treatment but observation. Among the remaining patients, who constituted about 43 % of the cohort, the typical symptoms of COVID-19 were observed. Fever was the most common symptom, comprising 73.3 %, followed by respiratory symptoms in 46.7 % of cases, and 26.7 % developed pneumonia. Despite significant immunosuppression in most children, they did not experience severe manifestations of the COVID-19 infection.

Regarding mortality, no fatal cases were reported.

It is worth noting that similar findings have been reported by other reviews as well [6–8]. Worldwide, a larger proportion of COVID-19 infections in pediatric patients have been asymptomatic. Among symptomatic children, fever was the most commonly reported symptom [9]. Remarkably, several countries, including the United States, France, Italy, Spain, and Mexico have also reported a 100 % survival rate for pediatric COVID-19 cases [4]. Moreover, some studies highlighted that the mortality rate directly related to COVID-19 in the pediatric population is much lower (less than 1 %) in contrast to other seasonal epidemics, including respiratory viruses, like respiratory syncytial virus and H1N1 [6, 9].

Despite all the children experiencing delayed treatment including chemotherapy, stem cell transplantation, and surgeries, oncological disease progression only developed in two cases.

Therefore, it is unreasonable to definitively confirm that the delay in treatment serves as the sole reason for relapse or disease progression. While treatment delays could contribute to certain cases, various factors could influence relapse or disease progression, making it challenging to attribute it solely to treatment delays during the pandemic. Indeed, the modifications of treatment schedules and delays in diagnosis caused by the pandemic are likely to have both short-term and long-term effects on morbidity and mortality, as well as longer-term survival outcomes [9].

**Conclusion**

Despite challenges and serious issues related to the COVID-19 pandemic, children with cancer have continued to receive proper cancer care. It should be noted that the predictions that children with cancer, particularly the immunocompromised patients would experience severe disease has not been realized. In pediatric oncology COVID-19 has a mild effect and the mortality rate related to the infection is extremely low. Changes in cancer-directed therapies have not significantly affected treatment outcomes.

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