

## Retrospective Study

**Manifestations of COVID-19 infection in children with malignancy: A single-center experience in Jordan**

Mousa Ahmad Qatawneh, Moath Altarawneh, Ruba Alhazaimah, Mais Jazazi, Omaiema Jarrah, Alaa Shorman, Laila Alsadah, Maher Mustafa

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**Mousa Ahmad Qatawneh, Moath Altarawneh, Ruba Alhazaimah, Mais Jazazi, Omaiema Jarrah, Maher Mustafa**, Department of Hematology and Medical Oncology and Stem Cell Transplantation Unit, Queen Rania Children's Hospital, Royal Medical Services, Amman 11183, Jordan

**Alaa Shorman**, Department of Neonatology, Queen Rania Children's Hospital, Royal Medical Services, Amman 11183, Jordan

**Laila Alsadah**, Department of General Pediatrics, Queen Rania Children's Hospital, Royal Medical Services, Amman 11183, Jordan

**Corresponding author:** Mousa Ahmad Qatawneh, MD, Consultant Physician-Scientist, Staff Physician, Department of Hematology and Medical Oncology and Stem Cell Transplantation Unit, Queen Rania Children's Hospital, Royal Medical Services, Dabouq, Amman 11183, Jordan.

[dr\\_m\\_qatawneh@yahoo.com](mailto:dr_m_qatawneh@yahoo.com)

**Abstract****BACKGROUND**

The coronavirus disease 2019 (COVID-19) has been the cause of a global health crisis since the end of 2019. All countries are following the guidelines and recommendations released by the World Health Organization to decrease the spread of the disease. Children account for only 3%-5% of COVID-19 cases. Few data are available regarding the clinical course, disease severity, and mode of treatment in children with malignancy and COVID-19.

**AIM**

To evaluate the treatment plan and outcome of children with malignancy who contracted COVID-19.

**METHODS**

A retrospective study of the medical files of patients with malignancy who contracted COVID-19 between July 2020 and June 2021 was performed. The following data were reviewed for all patients: primary disease, laboratory data, admission ward, clinical status upon admission, disease course, treatment plan, and outcome. Eligible patients were those with malignancy who tested positive for COVID-19 by reverse transcription polymerase chain reaction.

## RESULTS

A total of 40 patients who had malignancy contracted COVID-19 from July 1, 2020 to June 1, 2021. Their primary diseases were as follows: 34 patients (85%) had hematological malignancies (30 had acute lymphoblastic leukemia, 2 had acute myeloblastic leukemia, and 2 had Hodgkin lymphoma), whereas 6 patients (15%) had solid tumors (2 had neuroblastoma, 2 had rhabdomyosarcoma, and 2 had central nervous system tumors). Twelve patients (30%) did not need hospitalization and underwent home isolation only, whereas twenty-eight patients (70%) required hospitalization (26 patients were admitted in the COVID-19 ward and 2 were admitted in the pediatric intensive care unit).

## CONCLUSION

COVID-19 with malignancy in the pediatric age group has a benign course and does not increase the risk of having severe infection compared to other children.

**Key Words:** COVID-19; Malignancy; Disease severity score; Children; Jordan

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**Core Tip:** Coronavirus disease 2019 (COVID-19) has caused a global health crisis since the end of 2019. This retrospective study describes the manifestation of COVID-19 in our oncology patients who were treated at Queen Rania Children's Hospital between July 2021 and June 2021, focusing on the initial presentation, clinical course and management plan and comparing these results with the international data worldwide to determine the optimal way to care for oncology patients during the COVID-19 crisis.

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) has caused a global health crisis since late 2019[1]. As there were more than 2 million cases of COVID-19 worldwide, the World Health Organization (WHO) declared COVID-19 a pandemic in March 11, 2020[2,3]. By June 1, 2021, a total of 170448610 cases of COVID-19, including 3663570 deaths, had been reported worldwide. In Jordan, a total of 737284 cases of COVID-19 and 9472 deaths had been reported by June 1, 2021[4].

The incubation period of the virus is between 2 and 14 d with an average of 5 d[5,6]. The main routes of virus transmission are droplets and close contact[7]. COVID-19 affects all age groups; however, the pediatric population accounts for only 3%-5% of total cases[8]. Oncology patients generally shed respiratory viruses for longer than immunocompetent people and this is mostly true for COVID-19 as well[9]. In children, most cases of COVID-19 are asymptomatic, and studies have revealed that children have less severe symptoms compared to adults[10-12]. However, some patients develop life-threatening complications such as acute respiratory distress syndrome, thrombosis, and multiorgan failure[13-15]. Children with malignancy are frequently immunocompromised because of the therapy they receive, putting them at high risk for severe infections, which are the major cause of mortality in these patients [16-18]. However, there is growing evidence that the mortality rate in pediatric cancer patients with COVID-19 is extremely low[19,20]. The international pediatric oncology community acted quickly in response to the COVID-19 pandemic and made many recommendations to decrease the risk of infection in pediatric cancer patients[21,22].

This study analyzed and evaluated the treatment plans and outcomes of children with malignancy who contracted COVID-19 in Queen Rania Children's Hospital (QRCH; Amman, Jordan), and compared our results with the international results.

## MATERIALS AND METHODS

This retrospective study was approved by the ethics committee of the Jordanian Medical Services. The medical records were reviewed of patients at QRCH who had malignancy and tested positive for

COVID-19 between July 2020 and June 2021.

All pediatric oncology patients under 14-years-old who had received anticancer treatment and were diagnosed with COVID-19 by polymerase chain reaction (PCR) nasopharyngeal swab were eligible for this study. The primary endpoint was death, discharge from the hospital, or end of active care for COVID-19 for patients who needed further treatment of their primary disease in the hospital, or 14 d after initial diagnosis of COVID-19 in patients who did not need hospitalization.

Data were collected on primary disease, age, white blood cell count, absolute neutrophil count, lymphocyte count, place of admission, clinical status on admission, mode of treatment, radiological findings, and outcome.

PCR for COVID-19 was done for symptomatic patients, patients who had close contact with a confirmed case of COVID-19, and before any admission to the hospital, as our hospital guidelines recommend PCR for COVID-19 for any patient who needs admission, whatever the cause of admission.

Detailed clinical histories including primary disease, status of the disease, comorbidities, and detailed chemotherapy history were taken from all of our patients. We also performed full physical examinations, investigations, and chest X-rays, and if indicated, a high-resolution chest computed tomography (CT) scan was performed. After obtaining all of these data, researchers assigned patients a “disease severity score” categorizing the severity of their disease into the following categories: asymptomatic, mild, moderate, and severe disease (as described in [Table 1](#)).

For patients who needed admission, they were admitted in an isolation room in a specialized ward in the hospital (COVID-19 ward). When they met the criteria for discharge, they were discharged home with precautions and remained in home isolation until 14 d from the day of their COVID-19 diagnosis.

COVID-19 recovery was defined by the disappearance of the clinical symptoms in symptomatic patients or 14 d from the diagnosis of COVID-19 in asymptomatic patients.

## RESULTS

About 400 oncology patients were seen in QRCH during the study period between July 2020 and June 2021. A total of 40 oncology patients tested positive for COVID-19 during the same period. Twenty-four patients (60%) were males and sixteen (40%) were females. Twenty-eight patients were below the age of 6 years; they accounted for the majority of our patients in this study (70%). Five patients (12.5%) were between the ages of 6-years-old and 12-years-old whereas seven patients (17.5%) were between the ages of 12-years-old and 14-years-old. Hematological malignancies were the predominant primary disease in this study, as they accounted for about (85%) of the cases. The patients’ characteristics are summarized in [Table 2](#).

Upon presentation, full investigations were done for the patients in addition to chest X-rays. A high-resolution chest CT scan was done if there were any chest X-ray abnormalities or moderate to severe respiratory symptoms. Only 10 patients required a chest CT scan. Laboratory and radiological findings are summarized in [Table 3](#).

According to the disease severity score, 10 patients (25%) were asymptomatic, 20 patients (50%) had mild symptoms, and 8 patients (20%) had moderate symptoms whereas just 2 patients (5%) had severe symptoms. Of these patients, 12 (30%) were kept in home isolation whereas 28 patients were treated in the hospital, where 26 patients (65%) were treated in the COVID-19 ward and 2 patients (5%) were treated in the pediatric intensive care unit (PICU). The solid tumor patients were asymptomatic or had mild symptoms, whereas the moderate and severe symptoms were found only in patients with hematological malignancies; however, some patients who had hematological malignancies were asymptomatic or had mild symptoms. The hospital management was case by case and the treatment plan comprised intravenous (IV) antibiotics, azithromycin, dexamethasone, oxygen support, IV immunoglobulin (IVIG) for patients with hypogammaglobulinemia, and vitamins. Details about the clinical course of COVID-19 are summarized in [Table 4](#).

## DISCUSSION

Few data are available worldwide regarding the effect of COVID-19 on pediatric oncology patients; however, multiple studies have been published on the COVID-19 clinical course in these patients. In our center, 10% of our oncology patients contracted COVID-19 between July 2020 and June 2021. This percentage of COVID-19-infected oncology patients was higher than that reported in the general pediatric population in Jordan in the same period, which was about 5%-6% [4]. This increase in the percentage of COVID-19 among our oncology patients can be explained by the frequent testing of these patients for COVID-19 even if they were asymptomatic, as they require recurrent admissions to the hospital for different reasons including chemotherapy, fever, blood, and platelet transfusions and surgeries. Screening for COVID-19 was done before each admission as part of our hospital protocol regarding admissions during the era of COVID-19. However, this was not the case for healthy pediatric patients. Screening for COVID-19 was not done for healthy children who did not need hospital

**Table 1 Coronavirus disease 2019 disease severity score**

Disease severity	Definition
Asymptomatic	No symptoms at all during the course of COVID-19
Mild disease	Symptoms that did not require hospital admission; if hospitalization was required, the indication was for a cause other than the management of COVID-19 associated symptoms or signs
Moderate disease	Symptoms that required inpatient management of COVID-19 associated symptoms, but without the need for PICU care
Severe disease	Symptoms that required PICU care for COVID-19 related signs and symptoms

COVID-19: Coronavirus disease 2019; PICU: Pediatric intensive care unit.

**Table 2 Characteristics of pediatric oncology patients with coronavirus disease 2019**

Patient characteristics	Number	Percentage (%)
Sex		
Male	24	60
Female	16	40
Age		
1-6 yr	28	70
6-12 yr	5	12.5
12-14 yr	7	17.5
Primary disease		
Acute lymphoblastic leukemia	30	75
Acute myeloid leukemia	2	5
Neuroblastoma	2	5
Rhabdomyosarcoma	2	5
CNS tumors	2	5
Hodgkin lymphoma	2	5

CNS: Central nervous system.

admission unless they were symptomatic or in close contact with a confirmed COVID-19 case.

The median age of our oncology patients at the time of COVID-19 diagnosis was 5 years (range between 1.5 years and 13.5 years). This is similar to what was reported by Millen *et al*[23] in a study done in the United Kingdom involving 54 patients under the age of 16 years with malignancy. The median age in our study was less than that reported by Al Odda *et al*[24] in a study done in al Sulaimani-Kurdisan involving 54 malignancy patients and by Dong *et al*[25] in a Chinese study involving 2143 patients with malignancy, as the median age for these two studies was 7 years. We also reported that the majority of our patients were less than 6 years (70%), followed by patients who were more than 12 years (17.5%), consistent with the study by Navaeian *et al*[26] that was conducted in Iran in 20 oncology patients.

In our study, 24 patients were males (60%) and 16 patients were females (40%). This male predominance was reported in a study done in our center about patients who underwent hematopoietic stem cell transplantation and had COVID-19 infection post-transplant; all of them were males[27]. Madhusoodhan *et al*[28] also reported male predominance in a multicenter retrospective study involving 578 pediatric oncology patients in the New York-New Jersey region; 70% of their patients were males.

The majority of our cases had hematological malignancies (85%); 30 patients (75%) had acute lymphocytic leukemia (ALL), 2 patients (5%) had acute myeloid leukemia, and 2 patients had Hodgkin lymphoma. Solid tumors accounted for a smaller percentage (20%) of the cases. Similar results were reported by most of the international studies done worldwide[10,20,29,30]. This predominance of hematological malignancies among oncology patients who had COVID-19 can be explained by the fact

**Table 3 Laboratory and radiological details for coronavirus disease 2019 in our oncology patients**

Parameters	Numbers	Percentage (%)
WBC count		
Leukopenia < 4000	16	40
Normal WBC count	20	50
Leukocytosis > 16000	4	10
Lymphocytes count		
Lymphopenia	23	57.5
Normal count	17	42.5
Lymphocytosis	0	0
Neutrophil count		
Severe neutropenia	10	25
Mild-Moderate neutropenia	10	25
Normal count	16	40
Neutrophilia	4	10
CRP titer		
Negative < 6	3	7.5
Positive 6	37	92.5
D-Dimer		
Positive	6	15
Negative	34	85
IgG level		
< 700 mg/dL	9	22.5
> 700 mg/dL	31	77.5
Chest X-ray findings		
Normal chest X-ray	18	45
Perihilar infiltrates	12	30
Bilateral patchy consolidation	10	25
High-resolution chest CT scan findings		
Bilateral infiltration > 25%	8	20
Bilateral infiltration 25%-50%	2	5
Bilateral infiltration > 50%	0	0

CRP: C-reactive protein; CT: Computed tomography; IgG: Immunoglobulin G; WBC: White blood cell.

that hematological malignancies are the most common malignancies in pediatric age groups, and they require longer duration of treatment, especially for ALL patients. Furthermore, the hematological malignancies themselves and the chemotherapy used for the treatment of these types of malignancies have a greater effect on T lymphocyte function compared to solid tumors[31,32].

Regarding our patients, fever was the most common presenting symptom, as 24 patients (60%) had a temperature higher than 37.8 axillary at the time of the COVID-19 test. All of these patients were admitted to the COVID-19 ward in our hospital and were treated with IV antibiotics, as bacterial infection cannot be ruled out and has to be covered by IV antibiotics, especially in neutropenic patients.

Most of the international studies also reported that fever was the most common presenting symptom of COVID-19 in oncology patients[33,34].

Most of our patients had mild symptoms (50%), whereas just 2 patients (5%) had severe symptoms. The moderate and severe symptoms were found exclusively in patients who had hematological malignancies, whereas the patients who had solid tumors were asymptomatic or had mild symptoms.

**Table 4** Details of the clinical course of coronavirus disease 2019 in oncology patients

Parameters	Number	Percentage
Presenting symptoms		
Fever	24	60
Cough	15	37.5
Sore throat	3	7.5
Dyspnea	2	5
Diarrhea	2	5
Disease severity		
Asymptomatic	10	25
Mild disease	20	50
Moderate disease	8	20
Severe disease	2	5
Place of care		
Home isolation	12	30
COVID-19 ward	26	65
PICU	2	5
Treatment required		
No treatment	10	25
IV antibiotic	24	60
Azithromycin	30	75
Vitamins	30	75
Dexamethasone	26	65
Oxygen support	4	10
CPAP	2	5
IVIG	9	22.5

COVID-19: Coronavirus disease 2019; CPAP: Continuous positive airway pressure; IVIG: Intravenous immunoglobulin; PICU: Pediatric intensive care unit.

This can be explained by the fact that the hematological malignancies themselves and the chemotherapy used for the treatment of these types of malignancies have a greater effect on T lymphocyte function compared to solid tumors[31,32], in addition to the role of granulocyte-colony stimulating factor (G-CSF) administration after completing chemotherapy in solid tumor patients, which prevents the development of severe neutropenia.

Asymptomatic patients and patients with mild symptoms except fever were discharged home with instructions for strict home isolation and were followed by video and phone calls.

The patients with severe symptoms were treated in the PICU as they required the use of continuous positive airway pressure (CPAP) to maintain oxygen saturation of more than 94%. The primary disease for these 2 patients with severe symptoms was ALL. Both of them were in remission and in the consolidation phase of their treatment; however, these 2 patients had severe neutropenia at the time of COVID-19 infection. The treatment plan for these 2 patients was IVIG, dexamethasone, azithromycin, and IV antibiotics in addition to the CPAP, which was needed for 2 d for the first patient and 3 d for the second patient. Gradual improvement in clinical status was noticed for both of them and they were discharged home without any complications after about 2 wk of admission. As severe neutropenia might have played a major role in the development of severe symptoms of COVID-19 in these 2 patients, modifications of the chemotherapy doses for all of our patients in the hospital were made to prevent severe bone marrow suppression, especially severe neutropenia. Furthermore, we administered G-CSF at 48 h after finishing the chemotherapy protocol for non-hematological malignancies to perform bone marrow rescue.

Patients with moderate symptoms were admitted to the COVID-19 ward and they received dexamethasone and azithromycin. IV antibiotics were also given for patients with fever. IVIG was given

for patients with secondary hypogammaglobulinemia, which may have occurred due to chemotherapy; only 9 of our patients (22.5%) received IVIG.

These results are similar to what was reported by Millen *et al*[23], who reported that 6.6% of their oncology patients had severe symptoms of COVID-19. On the other hand, our results are higher than what was reported by Madhusoodhan *et al*[28], as they reported that only 17 of 578 oncology patients (3%) developed severe symptoms of COVID-19.

However, studies done on COVID-19 in the general pediatric population have shown similar rates of severe symptoms of COVID-19 among children who tested positive for COVID-19. Bellino *et al*[35] reported in a study done in Italy that 4.3% of patients who had COVID-19 developed severe symptoms. Meena *et al*[36] reported in their systematic review and meta-analysis that 4% of pediatric patients who had COVID-19 developed severe symptoms.

These similar results of severe symptoms of COVID-19 among oncology patients compared to the general pediatric population suggest that, even though the oncology patients have more risk factors for developing severe symptoms of COVID-19, children with malignancy who have COVID-19 are not at greater risk of having severe symptoms of COVID-19.

None of our patients died or developed any of the chronic complications of COVID-19, including multisystem inflammatory syndrome in children, after recovering from the infection. These results may be explained by the role of chemotherapy-related immune suppression in the protection against the development of cytokine release storm[37]. The mortality rate in our study is comparable to the overall death rate reported by Verity *et al*[38], as the estimated rate in their study was 0.66% and decreased to 0.0016% in children under the age of 9 years.

For all of our patients who tested positive for COVID-19, chemotherapy was withheld for at least 10 d, even in asymptomatic patients. We did not notice any increase in the malignancy-related morbidity nor mortality due this delay of chemotherapy.

On the other hand, we did not notice an increase in the incidence of any malignancy groups during the COVID-19 era, which indicates that the virus is not an oncogenic virus, at least in the short term.

As there is a risk of exposure to COVID-19 in both the community and hospital settings, resulting in extreme anxiety in the families of patients with malignancies, standard precautions for basic and respiratory hygiene must be strictly applied to reduce the risk of transmission of COVID-19.

One limitation of this study was the small number of cases, as it included just one institution's experience in a short period of time. Another limitation was the short follow-up period of these patients, which prevented us from detecting the possible long-term complications.

## CONCLUSION

Patients with malignancies are more likely to be infected with COVID-19, especially patients with hematological malignancies. However, these patients are not more likely to develop severe symptoms of COVID-19 compared to children in general. Furthermore, mortality and morbidity due to COVID-19 infection are not increased in patients with malignancies. Therefore, chemotherapy should be continued for patients with cancer during the era of COVID-19, provided that the WHO recommendations are strictly applied and that patients are not severely suppressed and have tested negative for COVID-19. However, the prevention of severe neutropenia by administering G-CSF as a bone marrow rescue is mandatory to prevent the moderate to severe symptoms of COVID-19 in malignancy patients.

## ARTICLE HIGHLIGHTS

### Research background

The coronavirus disease 2019 (COVID-19) has been the cause of a global health crisis since the end of 2019. All countries are following the guidelines and recommendations released by the World Health Organization to decrease the spread of the disease. Children account for only 3%-5% of cases of COVID-19. Few data are available regarding the clinical course, the severity of the disease, and mode of treatment in children with malignancy and COVID-19.

### Research motivation

COVID-19 has caused a global crisis worldwide, with few data available on this new health crisis. Patients with comorbidities are more susceptible to COVID-19 complications, especially oncology patients who are receiving different modalities of treatment making them immunocompromised most of the time. We would like to share our experience in these patients to compare it with the published data worldwide.

### **Research objectives**

The main objective of this study was to evaluate the outcome of oncology patients who contracted COVID-19, compare it with the results of the healthy population in the same age group, and compare the outcomes among different malignancy groups. Also we compared our patients' outcome with the international data published worldwide to share our experience and try to improve our management plan for these patients to provide the best care for them during this health crisis.

### **Research methods**

A retrospective review of the medical files of patients who have malignancy and developed COVID-19 between July 2020 and June 2021 was performed. The following data were reviewed for all patients: primary disease, laboratory data, admission ward, clinical status upon admission, disease course, treatment plan, and outcome. Eligible patients were patients who had malignancy and tested positive for COVID-19 by reverse transcription polymerase chain reaction.

### **Research results**

A total of 40 patients with malignancy who contracted COVID-19 from July 1, 2020 to June 1, 2021. Their primary diseases were as follows: 34 patients (85%) had hematological malignancies (30 of them had acute lymphoblastic leukemia, 2 had acute myeloblastic leukemia, and 2 had Hodgkin lymphoma), whereas 6 (15%) had solid tumors (2 had neuroblastoma, 2 had rhabdomyosarcoma, and 2 had central nervous system tumors). Twelve patients (30%) did not need hospitalization and underwent home isolation only, whereas 28 patients (70%) required hospitalization (26 patients were admitted in the COVID-19 ward and 2 patients were admitted to the pediatric intensive care unit).

### **Research conclusions**

Children with malignancy who contracted COVID-19 have a benign course and do not have increased risk of severe infection compared to healthy children.

### **Research perspectives**

The findings of this study will help us share our experience worldwide and give an idea of what is occurring in developing countries during this health crisis, especially in oncology patients who need special care.

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## **FOOTNOTES**

**Author contributions:** Qatawneh MA, Jazazi M, and Mutafa M substantially contributed to the conception and design of the work; Altarawneh M, Jazazi M, and Shorman A substantially contributed to the data collection; Alhazaimeh R, Shorman A, and Alsadah L substantially contributed to the acquisition, analysis, or interpretation of the data; Qatawneh MA, Alhazaimeh R, and Jarrah O contributed to drafting or revising the manuscript critically for important intellectual content; Qatawneh MA, Altarawneh M, and Mustafa M gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Institutional review board statement:** This retrospective study was approved by the Ethical committee of the Jordanian Medical Services.

**Informed consent statement:** Informed consent forms were obtained from all the patients.

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

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**Country/Territory of origin:** Jordan

**ORCID number:** Mousa Ahmad Qatawneh 0000-0002-5400-8804; Moath Altarawneh 0000-0001-9526-9181; Ruba Alhazaimeh 0000-0002-2579-8915; Mais Jazazi 0000-0003-0400-6840; Omaiema Jarrah 0000-0003-0719-7822; Alaa Shorman 0000-0002-9760-0904; Laila Alsadah 0000-0002-8667-5142; Maher Mustafa 0000-0001-5975-3400.

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