IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

Clinical Outcomes of Pediatric Cancer Patients with COVID-19: A Cross-Sectional Study

Yasaman Arian, Pooya Faranoush, Fahime Ehsanipour, Negin Sadighnia, Ali Elahinia, Mohammad Faranoush

Pediatric Growth and Development Research Center, Institute of Endocrinology, Iran University of Medical Sciences, Tehran, Iran

Corresponding Author: Pooya Faranoush, Pediatric Growth and Development Research Center, Institute of Endocrinology, Iran University of Medical Sciences, Tehran, Iran
E-mail: p-faranoush@razi.tums.ac.ir

Received: 25, Dec, 2023
Accepted: 27, Jul, 2024

ABSTRACT

Background: Considering the widespread COVID-19 pandemic and its impact, especially on children, particularly those with cancer, in terms of transmission risk, mortality, and the occurrence of the disease based on various studies in different countries, we decided to conduct this study to improve the care of children with cancer regarding COVID-19.

Materials and Methods: A descriptive cross-sectional study with a confirmed diagnosis of COVID-19 consisted of obtaining 20 mL of blood samples from the participants in a random manner. Diagnostic examinations, including CT scans, chest X-rays, and a range of hematologic and blood tests, such as complete blood count, ESR, CRP, and D-Dimer, were performed on all patients.

Results: This study contains 26 males and 12 females. The mean age of the patients was 3.81 ± 6.35 years. The majority of cancer patients with COVID-19 were diagnosed with Acute Lymphoblastic Leukemia (ALL) (47.7%). The most common symptoms of COVID-19 in the patients were fever (73.7%), cough (39.5%), and nausea/vomiting (21.1%). 40.4% of the patients had pathological findings suggestive of COVID-19 on their chest CT scans. 60.52% of the patients had an elevated Erythrocyte Sedimentation Rate (ESR), and 73.68% had an elevated C-reactive protein (CRP) level.

Conclusion: Despite the outcomes of COVID-19 in most children with cancer in this study, children with cancer still experience risks from COVID-19, and it is unclear how delays and interruptions in cancer treatment and direct damage from the virus may impact long-term outcomes in these patients.

Keywords: Covid-19; Cancer; Pediatric oncology

INTRODUCTION

Coronaviruses are single-stranded RNA-enveloped viruses belonging to the Corona viridae family, divided into four genera: Alpha, Beta, Delta, and Gamma. The membrane protein (M protein) and the envelope protein (E protein) are involved in virus morphogenesis. In contrast, the spike protein (S protein) facilitates virus entry into host cells and is a key target in vaccine development. SARS-CoV-2 uses the ACE2 receptor in various tissues such as the lungs, heart, liver, kidneys, and more to enter human cells. ACE2 is crucial in lung injury, heart function, and blood pressure regulation, and its levels correlate with interleukin 6, which is significant in cytokine storm syndrome. The clinical spectrum of symptoms is highly variable and can impact both mental and physical health, ranging from asymptomatic forms to severe respiratory failure requiring specialized care. Children with moderate to severe immune deficiencies, severe genetic, neurological, metabolic disorders, severe asthma, chronic respiratory diseases, and severe cardiac conditions are at higher risk for severe disease progression and leading to harm to human mental and physical health.

COVID-19 in children generally presents with similar clinical features and pathogenesis as in adults, though asymptomatic and mild cases are more

common among children. Respiratory complications can include croup and bronchiolitis, and some children may develop multisystem inflammatory syndrome (MIS-C) after the acute infection phase, which can be dangerous despite its rarity. Children generally have a better prognosis and lower mortality rates compared to adults, though newborns and children under five are more susceptible to severe disease manifestations.

Cancer continues to be a major worldwide contributor to mortality, with its incidence steadily increasing, leading to a significant surge in death rates. Pediatric cancer patients infected with COVID-19 tend to experience more severe symptoms and worse outcomes, with about 20% of cases becoming severe or critical. Chemotherapy further weakens their immune systems, leading to delays in cancer diagnosis and treatment due to the pandemic.

The effects of COVID-19 on pediatric cancer patients, including risk factors and clinical symptoms, are not fully understood, particularly in Iran. More information is needed to manage and plan treatment for this vulnerable group effectively. This study aimed to evaluate the prevalence of COVID-19 in cancer patients under 18 years old and analyze their clinical and laboratory characteristics to improve treatment outcomes and quality of care for this vulnerable population.

Materials and Methods

Study description

We conducted a descriptive cross-sectional study on 38 patients under the age of 18 with a confirmed diagnosis of COVID-19. Using a simple random sampling method, we selected patients hospitalized at Rasoul Akram or Ali Asghar hospitals, affiliated with the Iran University of Medical Sciences in Tehran, Iran, between April and September 2020.

Study design

The study involved collecting 20 mL of blood samples from each participant. A questionnaire was created to gather demographic and clinical details, including gender, age, presence of fever, and history of chemotherapy. Diagnostic procedures were conducted for all patients, including CT scans, chest X-rays, and various hematologic and blood tests such as complete blood count, ESR, CRP, and D-Dimer. The clinical symptoms experienced by the patients, such as respiratory or digestive complications, were carefully documented.

The NAAT-PCR test is the gold standard for diagnosing COVID-19. Patient samples were collected via nasopharyngeal and oropharyngeal swabs. The timing of this test affects its sensitivity, with the highest sensitivity (89%) in the first four days of symptom onset. It should also be noted that a positive RNA virus detection does not necessarily indicate active infection, as the test can remain positive for up to 90 days after the illness.

All the examinations were conducted with the ethical code of (IR.IUMS.FMD.REC.1400.229) certified by the ethical committee of the Iran University of Medical Sciences.

Inclusion criteria

The inclusion criterion for participation in the study is a confirmed diagnosis of COVID-19 through RT-PCR in patients under the age of 18 with cancer who have been referred to Rasoul Akram or Ali Asghar hospitals between April and September 2020 and have been hospitalized for any reason, and express their consent to participate in the research project.

Exclusion criteria

Patients whose information and medical records were incomplete regarding the variables of the study, who were over 18 years old, or who did not agree to participate in the research project were excluded (Figure 1).

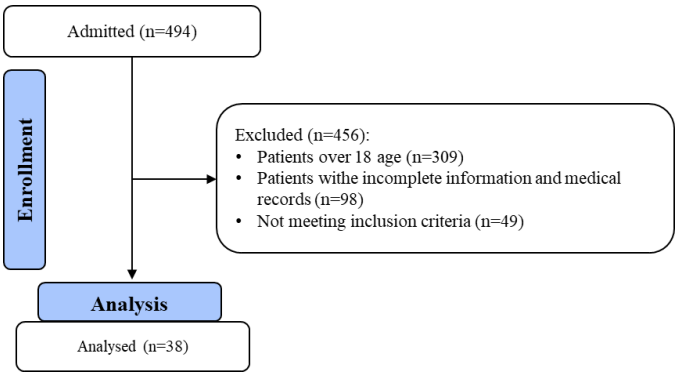


Figure 1. Flow diagram

Virus detection

Serological tests play a distinct role in the diagnostic landscape of COVID-19, detecting IgM and IgG antibodies against viral proteins. IgM indicates a recent infection, while IgG suggests a past infection within the last six months. However, these tests should not replace PCR or antigen tests, especially for confirming active infection. CDC guidelines recommend PCR confirmation for positive antigen tests, particularly in asymptomatic individuals or those with no COVID-19 exposure history.

Serological tests are valuable in occupational health, public health, and specific clinical settings. They are particularly useful in diagnosing recent infections in conditions like Multisystem Inflammatory Syndrome in Children (MIS-C) and indicating potential immunity against reinfection. Nonetheless, their primary role remains supplementary to PCR and antigen tests for active infection diagnosis.

Data analysis

The correlations between the variables were analyzed using t-tests or one-way ANOVA. Continuous variables were presented as mean values accompanied by their standard deviation (SD), while qualitative variables were reported as frequency percentages. The statistical analysis was conducted using SPSS 20 software, with a significance level of $p < 0.05$, indicating statistical significance.

RESULTS

Demographics of pediatric cancer patients

The study included 38 patients, most of whom were male. Specifically, there were 26 males (68.4% of participants) and 12 females (31.6% of participants). The patients ranged in age from 1 to 15 years old, with an average age of 6.35 years and a standard deviation of 3.81 years. Notably, half of the participants (19 patients) were under the age of 5 years (Figure 2).

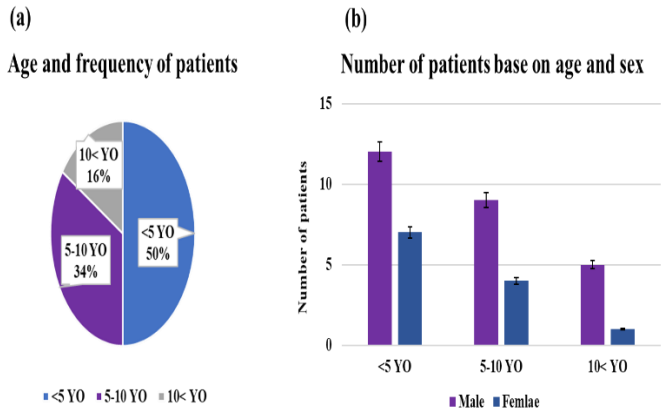


Figure 2. Frequency and number of patients based on age and sex

Clinical characteristics of pediatric cancer patients with COVID-19

Most of the pediatric cancer patients with COVID-19 (47.7%) had Acute Lymphoblastic Leukemia (ALL). Other diagnoses included Neuroblastoma, Retinoblastoma, and brain tumors. The majority of the patients (84.2%) were undergoing chemotherapy, and four patients had undergone surgery in addition to chemotherapy (Table 1). This Table shows the number and percentage of pediatric cancer patients with COVID-19 for each cancer type included in the study.

COVID-19 testing and symptoms in pediatric cancer patients

The majority of pediatric cancer patients (71.1%) tested positive for COVID-19 via RT-PCR during their initial visit, while 28.9% tested positive after being hospitalized. The most common symptoms observed were: Fever (73.7%), Cough (39.5%), Nausea/Vomiting (21.1%), Diarrhea, and Rhinitis. Moreover, 40.4% of the patients had pathological findings of COVID-19 on their lung CT scans. (Figure 3). This figure highlights the prevalence of different complications among the pediatric cancer patients in the study.

Table 1: The number of patients with various type of cancers

Cancer types	Male (%)	Female (%)
Acute lymphoblastic leukemia (ALL)	11 (28.9%)	6 (15.7%)
Acute myeloid leukemia (AML)	1 (2.63%)	0
B-cell lymphoma	1 (2.63%)	0
Hodgkin's lymphoma	1 (2.63%)	0
Burkitt lymphoma (BL)	2 (5.26%)	0
Rhabdomyosarcoma	2 (5.26%)	0
Osteosarcoma	2 (5.26%)	0
Neuroblastoma	1 (2.63%)	2 (5.26%)
Brain tumor	1 (2.63%)	2 (5.26%)
Retinoblastoma	2 (5.26%)	1 (2.63%)
Hepatoblastoma	1 (2.63%)	0
Glioblastoma (GBM)	0	1 (2.63%)
Autoimmune lymphoproliferative syndrome (ALPS)	1 (2.63%)	0

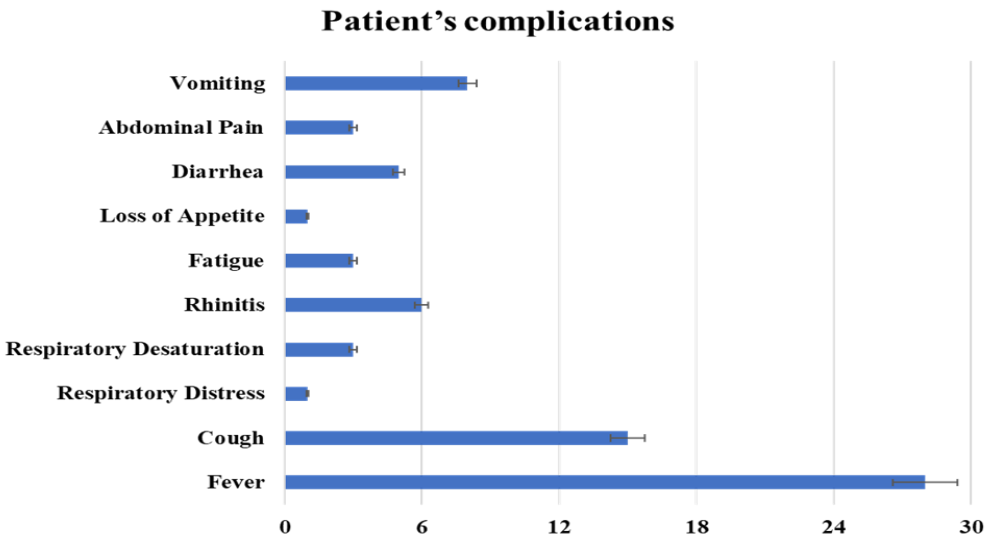


Figure 3. Patient's complications were demonstrated. Most of the patients had fever in their history

Laboratory findings and treatments in pediatric cancer patients with COVID-19

Laboratory findings

In terms of serum factors, there were no significant differences among the patients, except for the C-reactive protein (CRP) level, which was higher in patients with severe involvement compared to those with mild to moderate involvement. This difference was statistically significant, as determined by t-test analysis (P-value < 0.05). Furthermore, 13.5% of the patients had thrombocytopenia, and 21.1% had leukocytosis. The distribution of thrombocytopenia and leukocytosis did not show a significant difference among the three groups of patients. The main results included leukopenia in 55.26% of patients (21 patients), leukocytosis in 21.05% (8 patients), normal BUN and creatinine levels in all patients, elevated D-dimer in 15.79% (6 patients, above 600 ng/ml), high Erythrocyte sedimentation rate (ESR) in 60.52%, high CRP in 73.68%, and thrombocytopenia in 13.5%. A statistically significant finding was that higher CRP levels were associated with severe cases (P-value < 0.05).

Treatments administered

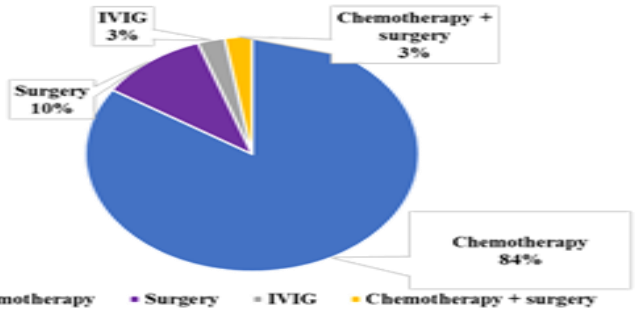
Most patients received antibiotics (76.3%), including azithromycin, cefazolin, and amikacin. Antiviral agents were used in 76.3% of patients (e.g., remdesivir, favipiravir), and Corticosteroids in 36.8% of patients (e.g., prednisolone, dexamethasone). Intravenous immunoglobulin (IVIG) was used in 36.8% of patients and only in 1 patient prescribed hydroxy urea (Figure 4).

The study reveals a high prevalence of leukopenia and elevated inflammatory markers such as ESR and CRP in pediatric cancer patients with COVID-19. Higher CRP levels were significantly associated with severe disease. Most patients received a combination of antibiotics, antiviral agents, corticosteroids, and IVIG, reflecting a comprehensive approach to managing this vulnerable population.

(a) Hematologic and Blood analyses

CBC-CBT	Mean (SD)
WBC (count/L)	6.17 (6.58)
Segment (%)	57.40 (25.71)
Hemoglobin (gr/dl)	10.30 (2.58)
Platelet (*1000/ml)	169.56 (176.06)
ESR (mm/h)	41.60 (40.73)
CRP (mg/l)	27.46 (27.71)
D-dimer (ng/ml)	504.27 (745.50)
AST (U/L)	66.81 (83.75)
ALT (U/L)	75.39 (99.76)
ALP (IU/L)	364.74 (171.67)
BUN (mmol/L)	10.01 (4.36)
Creatinine (mg/dl)	0.57 (0.14)

(b) Cancer treatment protocol



(c) Frequency of medication administration

Medications	Frequency (%)
Antibiotics	29 (76.3%)
Antivirals	29 (76.3%)
Corticosteroids	14 (36.8%)
IVIG	15 (39.5%)
Hydroxychloroquine	1 (2.6%)

Figure 4. (a) Patient's hematologic and blood tests; (b) The protocol of cancer treatment for patients; (c) Frequency of medication administration in patients

DISCUSSION

Although SARS-CoV-2 infection is less prevalent in the pediatric population compared to adults, the presence of malignancy and its underlying treatments may increase the risk of contracting this disease in children with malignancies. On the other hand, infection control measures and hospital conditions may restrict the access of sick children and their parents to diagnostic and therapeutic facilities in hospitals and negatively impact the psychological well-being of both children and parents. Therefore, we aimed to investigate the prevalence and symptoms of SARS-CoV-2 infection in children with malignancies referred to two medical centers in Iran, one of which was a pediatric referral center. In this study, among 494 patients under 18 years of age with cancer who were included in the analysis, we found 38 patients (7.69%) with a positive RT-PCR test. In the study by Millen et al., the estimated incidence of SARS-CoV-2 infection identified in hospitalized children under 16 years of age with cancer was 3%. In the study by Madhusoodhan et al., 16.95% of pediatric oncology patients tested positive for SARS-CoV-2. In two other studies in the United States, approximately 11% of pediatric oncology patients tested positive for SARS-CoV-2(21, 22). These differences may be attributed to variations in the extent and accuracy of screening among immunocompromised patients, the availability of tests, and temporal differences in the stage of the COVID-19 pandemic. In a study conducted by Navaiyan et al. in Iran (Tehran), 7.4% of children under 15 years of age with cancer had a positive RT-PCR test, which is similar to our study. The mean age of the patients was 3.81 ± 6.35 years, with 50% being under five years old. Among the study participants, 68.4% were male. In the study by Schlage et al., out of the 79 patients with SARS-CoV-2 infection, 45 were male (57.0%), with a mean age ranging from 6 months to 17 years. In the study by Navaiyan et al., 55% of the patients were male, with a mean age of 6 years, and 45% were under 5 years old. Considering that ALL is the most common malignancy in childhood and that it is more prevalent in males, the higher proportion of males in our study can be justified.

Most of the cancer patients who had COVID-19 were diagnosed with Acute Lymphoblastic Leukemia (ALL) (47.7%). The next most common cancers were Neuroblastoma, Retinoblastoma, and brain tumors (each at 7.9%). In the study by Madhusoodhan et al., 53% of patients had ALL. Similarly, Schlage et al. reported that the most common malignancy was Acute Lymphoblastic Leukemia (ALL). These results were also observed in the studies by Navaiyan and Mehrvar. The predominance of ALL among pediatric cancer patients with COVID-19 can be attributed to leukemia being the most frequent malignancy in this age group.

The most common symptoms in patients with COVID-19 were fever (73.7%), cough (39.5%), and nausea/vomiting (21.1%). In the studies by Navaiyan et al. and Mehrvar et al., fever and cough were also the most common symptoms (38, 41). Similarly, in a study by Shahnaz Armin et al. conducted on children under 18 years old with COVID-19 in five major cities in Iran, fever and cough were the most common clinical symptoms. In a global study of 1,747 cases from over 50 countries, including low- and middle-income countries in South America, Africa, and Asia, fever (43.3%) and respiratory symptoms (28.6%) were reported as the most common symptoms, followed by ear, nose, and throat symptoms (17.6%) and gastrointestinal symptoms (9.8%). Similarly, the US Pediatric Oncology COVID-19 Consortium (POCC) registry reports that 35% of solid tumor patients and 42% of hematologic malignancy patients tested positive for COVID-19 were asymptomatic. Among symptomatic patients, fever (37%) and cough (31%) were the most common symptoms, followed by congestion/rhinorrhea (16%), shortness of breath (10%), gastrointestinal symptoms (nausea and vomiting 9%), and diarrhea (6%), headache (10%), myalgia (9%), fatigue (8%), and sore throat (8%).

71.1% of the patients had a positive RT-PCR test at the time of referral, and 28.9% tested positive during hospitalization. In a study by Teresa de Rojas in Madrid, 63% of hospitalized patients were admitted due to COVID-19 infection. The number of patients who tested positive for COVID-19 during hospitalization highlights the need for healthcare providers to follow protective protocols and implement physical measures to protect patients

from infections. It also emphasizes the importance of continuously monitoring and testing patients for COVID-19 and other infections during their hospital stay or considering outpatient treatment and home-based care. According to the experience of Mehrvar, outpatient treatment without antivirals or antibiotics was a suitable option for pediatric oncology patients with mild COVID-19 symptoms, and all patients with mild COVID-19 symptoms who avoided hospitalization recovered at home. Although children with cancer have generally had better outcomes with COVID-19 compared to adults with cancer, the risk of hospitalization, ICU admission, and death has increased compared to the general pediatric population. In this study, 21 people (55.26%) had leukopenia, eight people (21.06%) had leukocytosis, 13.5% had thrombocytopenia. Also, in 6 patients, D-dimer was high. About 60 percent of patients had high ESR, and 73 percent of patients had high CRP. In this study, no relationship was found between thrombocytopenia, leukocytosis, and the severity of the disease. The only laboratory factor with a statistically significant relationship with disease severity was CRP (p-value <0.05). In Noviani et al.'s study, most patients had lymphopenia. The mean ESR and CRP in patients was 62 and 67 mg/dl. In Shahnaz Armin et al.'s study, 24.5% of children with COVID-19 had leukocytosis, and 9.33% had leukopenia. According to two systematic reviews, most children with COVID-19 have normal WBC counts, and the most common abnormalities are leukopenia and lymphopenia. In a study conducted by Madhusoodhan, no relationship was found between inflammatory factors such as CRP and D-dimer and the severity of disease in children with cancer. According to Benjamin Gallo Marin et al.'s study, some laboratory markers may predict COVID-19 prognosis. Findings typically associated with worse outcomes include increased D-dimer, C-reactive protein (CRP), LDH, and highly sensitive cardiac troponin -I. In a meta-analysis by Sujan Badal et al., leukopenia, lymphopenia, procalcitonin elevation, and high CRP and D-dimer were common laboratory abnormalities in children. In another cross-sectional analytical study conducted in children with underlying disease, high CRP, procalcitonin, and lymphopenia had a significant correlation with disease severity. Hend A. Nooh et al.'s study showed no clear significant relationship between the evaluated inflammatory indices and outcome in children with cancer and COVID-19, except for PLR (platelet to lymphocyte ratio). Increased RDW and lymphopenia may also play a role in undesirable outcomes. Increased CRP in adults with cancer has had a significant association with disease severity. CRP is an inflammatory marker secreted in response to inflammatory cytokines secreted from activated macrophages. Therefore, its serum level can reflect the intensity of inflammation and cytokine storm associated with COVID-19. Unlike adults, information on laboratory markers in the pediatric cancer population with COVID is less. It requires further evaluation in a larger population over a longer period. In our study, 76.3% of patients received antibiotics, including azithromycin, ceftazidime, amikacin, etc., 76.3% received antiviral drugs, including remdesivir and favipiravir, 36.8% received corticosteroids including prednisolone and dexamethasone, 39.5% received IVIG and one patient also received hydroxychloroquine. There are multiple reports on various therapeutic options against COVID-19 in pediatric cancer patients. To date, no randomized controlled trial has demonstrated the benefits of hydroxychloroquine administration in pediatric cancer patients with COVID-19. However, some studies have reported hydroxychloroquine administration in the early phases of the COVID-19 outbreak. Studies have shown that antiviral therapy can be beneficial in managing severe phases of SARS-CoV-2 infection by shortening recovery time. There is no specific antiviral therapy for SARS-CoV-2, so increased surveillance and preventive strategies should be considered to reduce exposure risk. Many unanswered questions remain in managing pediatric cancer patients infected with COVID-19. In this environment, treatment decisions must be individualized based on each case, and patients should receive their anticancer treatment under strict SARS-CoV-2 screening. In our study, 10.5% of patients were severe or critical. One patient who had a brain tumor (glioblastoma) was intubated and (probably) died of COVID-19. Similar studies in Italy, France, and Britain did not report death. However, in

Noviani et al.'s study, 20% of patients died during treatment, which was significantly higher than the reported mortality in other studies. In another study in the United States consisting of 98 patients in the New York/New Jersey area, two deaths (possibly) related to COVID-19 infection were reported. In a meta-analysis study, mortality in children with cancer was 0.6 percent. In a global review of 1,747 cases, 3.8 percent had died due to COVID-19.

In a global study in 45 countries, a higher proportion of severe or critical outcomes was observed in patients in low-income and lower-middle-income countries (41.7 percent versus 16.5 percent in upper-middle-income countries and 7.4 percent in high-income countries) compared to patients in other income groups. In most studies, children with cancer generally have a more severe clinical course and higher mortality compared to the general pediatric population. Children with cancer and undergoing treatment for it are a vulnerable population. Cancer and its treatment suppress the immune system and increase the risk of infection and severity of any infection. Frequent hospital visits for treatment make it difficult to follow social distancing and the use of masks.

In our study, most children with cancer who contracted COVID-19 had a benign outcome. However, the broader implications for pediatric cancer patients during the pandemic are concerning. The risks are multifaceted, including potential treatment delays, interruptions in ongoing cancer therapies, and direct harm from the virus. These factors collectively raise uncertainties about the long-term outcomes for these vulnerable patients. The impact of COVID-19 on children with cancer extends beyond immediate health effects. Delays or disruptions in cancer treatment schedules can compromise prognosis and overall survival rates. Furthermore, the direct physiological effects of COVID-19 on individuals undergoing cancer treatment are not fully understood, adding complexity to their management and care.

Comprehensive strategies are needed to mitigate these risks, including robust infection control measures, adapted treatment protocols, and ongoing research better to understand the intersection of COVID-19 and pediatric oncology. Efforts must minimize treatment disruptions while ensuring patient safety and optimizing long-term health outcomes.

CONCLUSION

Although COVID-19 resulted in relatively mild outcomes for most pediatric cancer patients in this study, those undergoing cancer treatment remain vulnerable to the virus. The implications of potential treatment delays or interruptions, as well as direct harm from COVID-19 itself, on the long-term prognosis of these young patients are uncertain. While immediate COVID-19 effects were mild in this cohort, pediatric cancer patients still face unique vulnerabilities, and questions remain regarding the virus's potential long-term impacts on treatment outcomes.

To validate the findings of this study, additional clinical trials involving pediatric cancer patients from various regions and multiple hospitals are necessary. Future prospective studies should also focus on assessing the long-term efficacy of different treatments and preventive strategies. This approach will help optimize care protocols and improve outcomes for pediatric cancer patients affected by COVID-19.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Hu T, Liu Y, Zhao M, et al. A comparison of COVID-19, SARS and MERS. PeerJ. 2020;8:e9725.

2. Cao Y, Yang R, Lee I, et al. Characterization of the SARS-CoV-2 E Protein: Sequence, Structure, Viroporin, and Inhibitors. Protein Sci. 2021;30(6):1114-30.

3. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. Circ Res. 2020;126(10):1456-74.

4. Zarebavani M, Baghaei Naeini F, Farahvash A, et al. Resveratrol attenuates chronic social isolation stress-induced affective disorders: Involvement of NF-κB/NLRP3 axis. J Biochem Mol Toxicol. 2023;37(5):e23311.

5. Naeini FB, Hassanpour S, Asghari A. Resveratrol exerts anxiolytic-like effects through anti-inflammatory and antioxidant activities in rats exposed to chronic social isolation. Behav Brain Res. 2023;438:114201.

6. Heart MD, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry. 2011;10(1):52-77.
7. Çelik I, Öztürk R. From asymptomatic to critical illness: decoding various clinical stages of COVID-19. Turk J Med Sci. 2021;51(SI-1):3284-300.
8. Vidya G, Kalpana M, Roja K, et al. Pathophysiology and Clinical Presentation of COVID-19 in Children: Systematic Review of the Literature. Maedica (Bucur). 2021;16(3):499-506.
9. Chow EJ, Englund JA. Severe Acute Respiratory Syndrome Coronavirus 2 Infections in Children. Infect Dis Clin North Am. 2022;36(2):435-79.
10. Zhu F, Ang JY. COVID-19 Infection in Children: Diagnosis and Management. Curr Infect Dis Rep. 2022;24(4):51-62.
11. Khalaji A, Yancheshmeh FB, Farham F, et al. Don't eat me/eat me signals as a novel strategy in cancer immunotherapy. Heliyon. 2023;9(10):e20507.
12. Tahavvori A, Alizadeh F, Mousavian A, et al. Achievements, Challenges, And Limitations Of Car-T Cell Therapy In Cancer Treatment, A Comprehensive Review. J Pharm Negat Results. 2022: 13(9):11145-52.
13. Farrokhi M, Taheri F, Farrokhi M, Heydari Z, et al. advancements in the management of pediatric cancers. In Faranoush P (ed). *Advancements and Innovations in Cancer Management: A Comprehensive Perspective*. Zenodo, USA, 2024. pp 24-31.
14. Revon-Riviere G, Ninove L, Min V, et al. The BNT162b2 mRNA COVID-19 vaccine in adolescents and young adults with cancer: A monocentric experience. Eur J Cancer. 2021; 154: 30–34.
15. Terrance B, Greiner JV, Maxwell-Schmidt E, et al. Guidelines for Frontline Health Care Staff Safety for COVID-19. J Prim Care Community Health. 2020; 11: 2150132720938046.
16. Charla Y, Kalra M, Chopra N, et al. COVID-19 vaccination in pediatric cancer patients: A high priority. Pediatr Blood Cancer. 2021;68(12):e29397.
17. Smart M, Puopolo O, Chang MR, et al. Clinical course and native antibody development after COVID-19 infection in 50 pediatric oncology patients. J Clin Oncol. 2023;41(16_suppl):10063.
18. Hasnat F, Noman F, Moben AL, et al. Difference in Clinical Patterns between COVID-19 Affected Children and Adults. Mymensingh Med J. 2021;30(4):1093-1099.
19. Tran A, Hou SHJ, Forbes C, et al. The Impact of the Early COVID-19 Global Pandemic on Children Undergoing Active Cancer Treatment and Their Parents. Curr Oncol. 2023;30(2):2441-56.
20. Millen GC, Arnold R, Cazier JB, et al. Severity of COVID-19 in children with cancer: report from the United Kingdom Paediatric Coronavirus Cancer Monitoring Project. Br J Cancer. 2021;124(4):754-759.
21. Boulad F, Kamboj M, Bouvier N, et al. COVID-19 in children with cancer in New York City. JAMA Oncol. 2020;6(9):1459-1460.
22. Gampel B, Lucas AGT, Broglie L, et al. COVID-19 disease in New York City pediatric hematology and oncology patients. Pediatr Blood Cancer. 2020;67(9):e28420.
23. Schlage S, Lehrnbecher T, Berner R, et al. SARS-CoV-2 in pediatric cancer: a systematic review. Eur J Pediatr. 2022;181(4):1413-1427.
24. Navaeian A, Mahmoudi S, Pourakbari B, et al. COVID-19 infection in children with underlying malignancies in Iran. J Basic Clin Physiol Pharmacol. 2021;33(1):79-84.
25. Madhusoodhan PP, Pierro J, Musante J, et al. Characterization of COVID-19 disease in pediatric oncology patients: the New York-New Jersey regional experience. Pediatr Blood Cancer. 2021;68(3):e28843.
26. Mehrvar A, Qaddoumi I, Tashvighi M, et al. Treatment and outcomes of pediatric patients with cancer and COVID-19 at MAHAK pediatric cancer treatment and research center, Tehran, Iran. Semin Oncol. 2021;48(4-6):295-303.
27. Armin S, Mirkarimi M, Pourmoghaddas Z, et al. Iranian Pediatric COVID-19 Epidemiology and Clinical Characteristics. Can J Infect Dis Med Microbiol. 2021;2021:4914371.
28. COVID-19 and Childhood Cancer Registry [Internet]. St. Jude Global. [cited 2021 Sep 14]. Available from: https://global.stjude.org/en-us/global-covid-19-observatory-and-resource-center-for-childhood-cancer/registry.html.
29. Johnston EE LJ, Kahn A, Sharma A, Schwalm C, Brackett J, et al. reports and updates 2023 [cited 2023. Available from: https://www.uab.edu/medicine/icos/icos-research/the-pocc-report/reports-updates.
30. de Rojas T, Pérez-Martínez A, Cela E, et al. COVID-19 infection in children and adolescents with cancer in Madrid. Pediatr Blood Cancer. 2020;67(7):e28397.
31. Kahn AR, Schwalm CM, Wolfson JA, et al. COVID-19 in Children with Cancer. Curr Oncol Rep. 2022;24(3):295-302.
32. Patel NA. Pediatric COVID-19: Systematic review of the literature. Am J Otolaryngol. 2020;41(5):102573.
33. Meena J, Yadav J, Saini L, et al. Clinical Features and Outcome of SARS-CoV-2 Infection in Children: A Systematic Review and Meta-analysis. Indian Pediatr. 2020;57(9):820-826.

34. Gallo Marin B, Aghagoli G, Lavine K, et al. Predictors of COVID-19 severity: a literature review. Rev Med Virol. 2021;31(1):1-10.
35. Badal S, Bajgain KT, Badal S, et al. Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: a systematic review and meta-analysis. J Clin Virol. 2021;135:104715.
36. Kara AA, Böncüoğlu E, Kıymet E, et al. Evaluation of predictors of severe-moderate COVID-19 infections at children: A review of 292 children. J Med Virol. 2021;93(12):6634-6640.
37. Nooh HA, Abdellateif MS, Refaat L, et al. The role of inflammatory indices in the outcome of COVID-19 cancer patients. Med Oncol. 2021;39(1):6.
38. Amicucci M, Mastronuzzi A, Ciaralli I, et al. The Management of Children with Cancer during the COVID-19 Pandemic: A Rapid Review. J Clin Med. 2020;9(11):3756.
39. Minotti C, Tirelli F, Barbieri E, et al. How is immunosuppressive status affecting children and adults in SARS-CoV-2 infection? A systematic review. J Infect. 2020;81(1):e61-e66.
40. Arous R, Djillali IS, Rouis NO, et al. High mortality of COVID-19 in children with cancer in a single center in Algiers, Algeria. Pediatr Blood Cancer. 2021;68(6):e28898.
41. Hrusak O, Kalina T, Wolf J, et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment. Eur J Cancer. 2020;132:11-16.
42. Hammad M, Shalaby L, Sidhom I, et al. Management and Outcome of Coronavirus Disease 2019 (COVID-19) in Pediatric Cancer Patients: A Single Centre Experience from a Developing Country. Clin Lymphoma Myeloma Leuk. 2021;21(11):e853-e864.
43. Orf K, Rogosic S, Dexter D, et al. Remdesivir during induction chemotherapy for newly diagnosed paediatric acute lymphoblastic leukaemia with concomitant SARS-CoV-2 infection. Br J Haematol. 2020;190(5):e274-e276.
44. Hashemieh M. Preventive Strategies for Cancer Patients during COVID-19 Pandemic: A Review. Int J Pediatr. 2021;9(2):12981-12987.
45. Ferrari A, Zecca M, Rizzari C, et al. Children with cancer in the time of COVID-19: An 8-week report from the six pediatric onco-hematology centers in Lombardia, Italy. Pediatr Blood Cancer. 2020;67(8):e28410.
46. André N, Rouger-Gaudichon J, Brethon B, et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: High risk of severe forms? Pediatr Blood Cancer. 2020;67(7):e28392.
47. Dorantes-Acosta E, Avila-Montiel D, Klünder-Klünder M, et al. Survival and complications in pediatric patients with cancer and COVID-19: a meta-analysis. Front Oncol. 2021;10:608282.
48. Mukkada S, Bhakta N, Chantada GL, et al. Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study. Lancet Oncol. 2021;22(10):1416-1426.
49. Faranoush P, Jahandideh A, Nekouian R, et al. Evaluation of the in vitro and in vivo effect of liposomal doxorubicin along with oncolytic Newcastle disease virus on 4T1 cell line: Animal preclinical research. Vet Med Sci. 2023;9(3):1426-1437.