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Original Article

COVID-19 in Children with Cancer: A Retrospective Study

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Abstract

Background: The emerging COVID-19 is less common in children than adults and has fewer symptoms. However, there are more concerns about the severity of symptoms in patients' kids undergoing chemotherapy. This study aimed to investigate COVID-19 infection in pediatric cancer patients.

Methods: This was a retrospective study of 302 patients with COVID-19 infection confirmed by RT-PCR test and aged ≤18, referred to a multi-specialized pediatric hospital, Ahvaz-Iran, from 2020-2021. Children were divided into two groups: malignant (n = 31) and non-malignant (n = 271).

Results: The median age of the patient was 7 years. 73.7 % of the patients were male. The most common symptom was cough (47.36%). On admission, leucopenia was recorded in 63.15% of malignancy patients. The Outcomes death was %0.7 and %3.2 in the malignancy and Controls groups, respectively. There was a statistically significant reduction between the malignancy and Controls group (P=0.02). Also, in terms of myalgia, the group of children with malignancy showed a lower percentage than the control group or non-cancerous children (P=0.04). Laboratory data showed that leukopenia, CRP, and ferritin levels caused by COVID-19 disease in children with malignancy were not significantly different from healthy children (p> 0.05).

Conclusion: COVID-19 mortality in children with malignancy is significantly lower than in non-cancerous children. Further studies are needed to understand the course of COVID-19 infection in children with cancer.

Keywords: Cancer; Children; COVID-19; Malignancy; Mortality

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Introduction

The emerging COVID-19 (SARS-CoV-2) has spread rapidly worldwide since the first case was reported in Wuhan, China, in late December 2019 (1). In Iran, the first case was identified and reported in February 2020 (2). According to studies, the mortality rate from COVID-19 is between 1- 6% in the general population (3). COVID-19 can be present along a clinical spectrum from asymptomatic, mild symptoms such as cold-like, influenza-like (e.g., fever, malaise, and myalgia) to severe lower respiratory disease with dyspnea and pneumonia (4). COVID-19 complications are more common in the elderly than in children and young adults, especially in elderly patients with underlying diseases (5, 6). In addition to age, other risk factors such as weakened immune systems due to transplantation or malignancy have been reported in studies (1, 7, 8). Fortunately, the prevalence of COVID-19 disease in children without underlying disease was low, and COVID-19 in them was reported asymptomatic or with mild complications and rarely led to hospitalization (9). However, the reason for mild symptoms of COVID-19 is not clear. Cytokine storms have been implicated in the pathogenesis of severe forms of the disease in adults. Thus, one possible explanation may be a weaker immune response to SARS-CoV-2 in children than adults. Other hypotheses consider possible viral competition in the respiratory tract of young children and the expression of the angiotensin-converting enzyme receptor (10). The possibility that more severe disease is associated with immunosenescence, along with an increased risk of severe disease in adults with cancer, but a case report of a critically ill child who developed COVID-19 during myelosuppressive chemotherapy has raised the concern that COVID-19 among immunosuppressed children might be a much more severe illness than that seen in otherwise healthy children (5). In addition, it has been confirmed in a study that malignant children, especially those receiving systemic anti-cancer therapies, were more likely to die from COVID-19 (11). However, studies have reported fewer deaths from COVID-19 in children with malignancy, and they are not at higher risk for COVID-19 and, like other children, have experienced mild symptoms (5, 12). To the best of our knowledge, there are rare data, some of which are contradictory, about COVID-19 mortality and complications in children with malignancy. Therefore, this study aimed to describe the clinical and demographic characteristics and outcomes of COVID-19 in malignant and COVID-19 children.

Materials and Methods

Study Design

This retrospective study was conducted within A Medical Children Center, Ahvaz province in Khuzestan, Iran from March 2020 to March 2021. Three hundred and two children with a diagnosis of COVID-19 -19 confirmed by RT-PCR test were candidates. We included children with malignancy (n = 31) and no malignancy (controls, n = 271). The study was approved by the ethics committee of Ahvaz Jundishapur University of Medical Sciences with ethical code number IR.AJUMS.REC.1400.091.

Inclusion and Exclusion Criteria

Inclusion criteria included all patients with COVID-19 infection confirmed by RT-PCR test and aged ≤18, referred to a multi-specialized pediatric hospital. Patients with no definitive diagnosis of COVID-19 and patients with other viral infections were excluded

Data Collection

Data were collected and classified according to date of admission, discharge date, length of hospital stay, time of cancer diagnosis, type of malignancy, presenting symptoms, the severity of symptoms, laboratory values (CRP, leukopenia, ferritin), and delay or stop chemotherapy due to COVID-19 infection. All data were extracted from the health information system (HIS). In addition, demographic information, including patients' age, sex, weight, and body mass index (BMI), was also recorded.

Statistical Analysis

Data were analyzed using descriptive statistics (mean), the descriptive and analytical statistics were carried out by the R software. Kolmogorov–Smirnov and, Shapiro–Wilk tests were applied to test for evaluating the normal distribution of data. Independent samples t-tests were used to compare group mean differences. Chi-square tests assessed

variable associations for categorical data. Statistical significance was assessed at the 5% level.

Results

Among Three hundred and two patients included in this study, 73.7% of patients were male, and 26.3% were female. The means age was 7.83±4.91 and 7.61±4.33 years in the malignancy and Controls groups, respectively (P = 0.29). The mean weight in the malignancy and Control group was 27.11 ± 14.6 kg and 25.03 ±12.4 kg, respectively (P=0.18). There was no significant difference between the two groups regarding weight index (P = 0.35). Patient demographic data are shown in **Table 1**.

Considering the length of hospital stay (days) of the patient, the difference was not found to be significant between the two groups, and the length of hospital stay of the two groups was almost the same (P=0.23) (**Table 2**). The mean length of PICU admission was 2.63 ±0.9 and 2.56 ±1.2 years in the malignancy and Control groups, respectively (P = 0.29). The Outcomes Death was %0.7 and %3.2 in the malignancy and Controls groups, respectively. There was a statistically significant difference between the malignancy and Controls group (P=0.02). Regarding symptoms, according to **Table 2**, there was no significant difference between the two groups in most variables (P <0.05). However, regarding myalgia, the group of children with malignancy showed a lower percentage than the control group of non-cancerous children (P=0.04).

Out of 31 malignant children with COVID-19,

Table1. Demographic data in control and malignancy group.

Parameters		Malignancy Group (n=31)	Controls (n=271)	p-value
Sex	female	73.9%	71.6%	0.31
	male	26.1%	29.4%	
Age (year)		26.93 ±5.6	28.86 ±6.4	0.29
Weight(kg)		27.11 ± 14.6	12.4±25.03	0.18
BMI (kg/m^2)		16.47± 4.6	17.13± 4.3	0.35

Table 2. Parameters of study groups.

Parameters		Malignancy Group (n=31)	Controls (n=271)	p-value
length of hospital stays (days)		10.89± 2.6	10.43 ±1.4	0.23
Length of PICU admission (days)		2.63 ±0.9	2.56 ±1.2	0.61
Use an oxygen mask N (%)		16 (51.6%)	142 (52.3%)	0.38
Outcomes N (%)	Discharge	28 (90.0%)	230 (84.2%)	0.09
	Discharge with personal consent	2 (6.2%)	22 (8.8%)	0.21
	Death	1 (%3.2)	19 (%7.0)	0.02
	All	31 (%100)	271 (%100)	0.27
Signs and symptoms (%)	Cough	45.5%	49.8%	0.13
	fever	29.1%	28.5%	0.55
	vomiting	12.9%	11.3%	0.17
	abdominal pain	9.7%	6.9%	0.23
	respiratory distress	6.4%	7.7%	0.15
	myalgia	6.4%	13.9%	0.04
	diarrhea	6.4%	5.4%	0.27
	bone pain	6.4%	5.1%	0.19
	Shortness of breath	3.2%	4.4%	0.24
	Other symptoms	6.4%	8.7%	0.17

Leucopenia was detected in 63.15%. The average WBC was 3.8. Most children had high levels of C-reactive protein (66.6%) (**Table 3**). Laboratory data showed that leukopenia, CRP, and ferritin caused by COVID-19 disease in children with malignancy were not significantly different from non-malignant children (p> 0.05).

The clinical features of malignancy patients in this study were demonstrated in **Table 4**. 79.9% affected by COVID-19 had to delay receiving their anti-cancer treatments. Delays ranged from 12 to 30 days. The highest frequency was related to 14 days delay, which was observed in eight patients. Seven types of malignancy were identified in malignant children with COVID-19. The types of which are as follows: acute lymphoblastic leukemia (55.9%), acute myeloid leukemia (15.8%), Hodgkin's lymphoma, neuroblastoma, Ewing's sarcoma, and osteosarcoma (equally 5.3%). The time from diagnosis of malignancy varied from 2 days to 5 years. The average was 15 months.

Table 3. Laboratory findings.

Parameters	Malignancy Group (n=31)	Controls (n=271)	p-value
Leucopenia (cell/µL)	63.15%	65.62%	0.19
C-reactive protein (mg/l)	6.15± 19.7	7.15± 18.6	0.11
Ferritin (ng/mL)	134.34± 32.2	131.79± 29.2	0.38

Table 4. Clinical features of malignancy patients.

Parameters	N	%
Delay in receiving anti-cancer treatment		
• 0 Days	4	21.1%
• 12 Days	1	5.3%
• 14 Days	8	42.1%
• 17 Days	1	5.3%
• 25 Days	1	5.3%
• 30 Days	4	21.1%
Types of malignancy		
Acute lymphoblastic leukemia (ALL)	16	53.9%
Acute myeloid leukemia (AML)	5	15.8%
Hodgkin's lymphoma	2	6.4%
Neuroblastoma	2	6.4%
Ewing's sarcoma	2	6.4%
Osteo sarcoma	1	3.2%
Sarcoma	1	3.2%
Cancer therapy 1 month before the diagnosis of COVID-19	15	79.9%
Metastatic cancer	2	10.52%

Discussion

Lima et al. published the first reports of children being infected with COVID-19 and the risk of developing the disease. Their studies warned about the high risk of death from COVID-19 in patients with pediatric cancer (13). Considering the importance of children's health with cancer, the present study retrospectively recognizes the role of COVID-19 disease in cancer patients and its impact on the severity of COVID-19 and infant mortality. In our study, mortality in children with COVID-19 was significantly lower than in non-cancerous children. Also, the incidence of myalgia in children with cancer was lower than in non-cancer children. This suggests that, unlike many studies, children with cancer had lower

mortality rates than those with COVID-19. However, in most cases, no significant difference was observed between the two groups. Similar studies by Hrusa et al. on children with COVID-19 disease showed that the rate of morbidity and mortality in these children did not have a significant effect (5). Other parallel studies have also confirmed this finding (12). For example, a study in Poland found that the course of COVID-19 treatment in children with childhood cancer was intermittent but not associated with mortality and that there was no statistically significant difference between COVID-19 mortality in children with cancer and non-cancer in the short term (14). A meta-analysis study found that hematologic neoplasia or other solid tumors and COVID-19 were not risk factors in children with cancer (15). Many studies have shown reduced access to medical facilities for children with COVID-19. Parents have been less likely to go to medical centers for fear of exposing their children to the virus, and face-to-face visits for primary care have been reduced, which can affect the health of these patients (16, 17). Related to these concerns, the present study shows that the risk of mortality and morbidity in cancer patients was not significantly different from non-cancerous children, which could reduce concerns about children with cancer. Graetz et al. reported a reduction in the provision of health care to cancer patients. They found that during the COVID-19 pandemic, the decline in surgical care, shortage of blood products, interruption of radiotherapy, and interference with chemotherapy increased dramatically (18). Contrary to the present study, many studies have shown that children with cancer are highly vulnerable to the virus during an outbreak of COVID-19-disease. Children with malignancies are at higher risk of developing COVID-19 than children without cancer. These children show varying degrees of severity due to the primary disease as well as anti-tumor treatment of their immune system (19, 20). However, some research has shown that the severity of the disease plays a role in influencing the mortality rate of children with cancer. A study at Pediatric Cancer Research and Treatment Center in Iran (MAHAK) found that children with cancer are generally immunosuppressed and particularly vulnerable to COVID-19 infections in severe cases. They reported that COVID-19 symptoms were mild in fourteen patients, and three patients were asymptomatic. They stated that in mild cases, COVID-19 disease did not affect the mortality of children with cancer who were treated during the study period. However, death was observed in hospitalized children with cancer (21). This finding shows the importance of further investigation into children. An important reason for the vulnerability of patients with malignancy is the side effects of chemotherapy drugs. Although there are similar side effects to chemotherapy drugs, the type of chemical structure of the drug is effective in reducing and increasing the side effects. Many drugs cause less damage despite cytotoxicity, but some drugs, such as cyclophosphamide, have more negative effects on the health of cancer patients (22, 23). Despite the side effects of chemotherapy, our findings show that children with cancer had lower mortality rates than non-cancer children. A decreased immune response is a common finding in patients undergoing chemotherapy. In many cases, it causes various complications for patients with prolonged use; however, some drugs have been shown to reduce the immune response in these patients. One of the hypotheses for the present study is that immune response reduction in children with malignancy can prevent cytokine storms and lead to lower mortality (24- 26). In this regard, some findings have been reported on the positive effect of effective anti-cancer drugs on cytokines that inhibit cytokines and reduce tumorigenesis. Decreased cytokines have been reported to be associated with lower immune response. Innate immunity plays a lesser role in viral inflammation, with lymphocytes and the specific immune system playing the most critical role. Although a dedicated immune system specifically identifies the virus; but cytokines, chemokines, and other proteins involved in innate immunity non-specifically identify external factors. As a result, in COVID-19 disease, the activation of innate immunity is to the detriment of the patient (27, 28). Focusing on recognizing and evaluating the role of immune cell levels in these children can help solve this problem. The data show that about 140,000 people in Iran have been infected with the COVID-19, of which about 2 million were children. However, information on the age group of children with COVID-19 in Iran has not been recorded until January 25, 2022 (29),

and the need to review and record epidemic data can be important in further identifying this risk factor. Overall, the findings of this study reject cancer as a risk factor for mortality in children with cancer; but it is essential to pay attention to prevention strategies. Because although children have a milder course of COVID-19 infection than adults, their health is important to the family as a vulnerable population. One of the most effective ways to prevent COVID-19 is to minimize the risk of exposure as well as severe isolation.

One of the limitations of the study is the small sample size due to being a single-center study, which reduces the generalizability of the results.

Conclusion

Mortality in children with cancer who are suffering from COVID-19 was significantly lower than in non-cancer children. Also, the incidence of myalgia in children with cancer was lower than in non-cancer children; this shows that, unlike many studies, children with cancer were less vulnerable to COVID-19. However, despite vaccination, the risk of COVID-19 has been significantly reduced, but mutations in the virus are unpredictable and unpreventable to cause disease. Therefore, it is important to recommend that further studies of blood clotting factors in children with COVID-19 and cancer be reviewed. In addition, there are many unanswered questions in the management of children with cancer who are infected with COVID-19. Further studies are needed to understand the course of COVID-19 infection in children with cancer.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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