

Covid-19 Disease in Pediatric Cancer Patients: A Single Center Experience

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ABSTRACT: Children with cancer can have a severe disease when infected with respiratory viruses. In this study, we aimed to understand the clinical course and outcomes of SARS-CoV-2 infection in children with cancer. Data evaluated about laboratory-confirmed SARS-CoV-2 infections in sixty-three children (<18 years) with cancer between 01.06.2020 - 01.08.2021 were retrospectively reviewed. Data for demographics, oncological diagnosis, clinical course, and cancer therapy details were collected. Primary outcomes were disease severity and modification to cancer-directed therapy. The median (range) age was 7.6 ± 5.3 (0-18) years, and the most common underlying diagnosis was leukemia (74.6%). The most common symptom was fever (67.7%), and most patients had symptoms (70%). The mild disease was most common (60.3%). During Covid-19 infection, disease severity increased 23 times ($p=0.003$) in those with fever and 4.083 ($p=0.045$) in those with neutropenia. It was observed that the severity of the disease increased 2.589 times as CRP increased ($p<0.001$). However, few patients (9.5%) were admitted to the intensive care unit. Five patients died, but none of the deaths could be attributed to Covid-19 alone. Most patients did not experience chemotherapy treatment interruption (57%). When interruption did occur, this duration was 13.9 ± 14.3 (1.0-60.0) days. In this cohort of pediatric oncology patients, nearly 43% of patients who had Covid-19 were their chemotherapy interrupted. Future studies will only reveal the final effect of the pandemic on childhood cancer.

Keywords: Chemotherapy; Covid-19; immunosuppressive; pediatric oncology; SARS-CoV-2.

INTRODUCTION

The covid-19 disease is a viral respiratory tract disease caused by the coronavirus (SARS-CoV-2). It has a broad spectrum that can be asymptomatic or life-threatening due to causing severe hypoxia. Covid-19 rapidly became a global pandemic, reaching 479,254,266 confirmed cases worldwide on 25 March 2022 and causing 6,137,266 deaths¹. In Turkey, the death rate from Covid-19 was 2.7%, and 0.19% of all deaths were in childhood². Considering the general population, it has been reported that SARS-CoV-2 is seen more frequently in the adult age group, and children constitute only 2% of all Covid-19 cases³. Furthermore, in pediatric cases of Covid-19, more than half (55.4%) of cases are asymptomatic or have only mild symptoms, while

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severe Covid-19 disease affects 5.4%. This is in contrast to adult cases, where the severe disease is reported to affect 18.5% of cases⁴.

SARS-CoV-2, through its receptor, the so-called "spike protein", for human angiotensin-converting enzyme 2 (ACE2), can interact and invade host cells⁵. ACE2 has broad tissue expression, so that COVID-19 can cause significant effects related to many systems, including the cardiovascular and immune response, especially the respiratory system⁶⁻⁸. The low Covid-19 cases in children could be related to ACE2 receptor expression. The lesser severity of disease in children has been associated with lower expression of the ACE2 receptor and different inflammatory responses, with higher numbers of B and T regulatory cells, and thus a less inflammatory immune response⁹. Although pediatric patients are less affected by Covid-19 disease, there are few not studies on this issue in children with cancer^{10,11}.

Viral infections are generally associated with increased morbidity and mortality in immunosuppressed patients, such as those treated for cancer¹². It was observed that the risk of severe disease and death in adults with cancer with Covid-19 infection was higher than in the general population^{13,14}. While other coronaviruses may cause more severe disease with lower respiratory tract infection in immunosuppressed children^{3,15} the severity of Covid-19 infection seems milder in these children¹⁶. Moreover, delays in cancer treatment due to SARS-CoV-2 continue to raise concerns, so research is needed. This study was performed to assess the course of SARS-CoV-2 infection in children with hematological or oncological malignancies who have been actively treated with systemic therapy and its impact on the timing of cancer therapy.

MATERIALS AND METHODS

The files of the pediatric patients with cancer receiving treatment at the department of Pediatric Hematology and Oncology, Başakşehir Çam, and Sakura City Hospital, Istanbul, Turkey, between 01 June 2020 and 01 August 2021 were reviewed retrospectively. In the study period, approximately 160 new pediatric cancer diagnoses were made, and approximately 300 children were treated with chemotherapy. All hospitalized pediatric hematology and oncology center patients were routinely tested for SARS-CoV-2 at admission (since June 2020), those with a history of contact, and in cases of suspected COVID-19 (any time, at physician discretion). Possible patients whose diagnosis was not confirmed by PCR were excluded.

SARS-CoV-2 was detected by real-time quantitative PCR (RT-qPCR). Combined nasopharyngeal and oropharyngeal specimens from patients were collected by viral nucleic acid isolation swab and media (vNAT, Bio-speedy, Bioeksen, Istanbul, Turkey). These samples were transferred to the laboratory under cold chain conditions. Detection of the SARS-CoV-2 RNA was performed by one-step reverse transcription and real-time PCR targeting SARS-CoV-2-specific ORF1ab and N gene fragments using the SARS-CoV-2 Double Gene RT-qPCR kit (Bio-speedy, Bioeksen, Istanbul, Turkey) in the Department of Medical Virology. In addition, positive, negative, and internal controls (RNase P gene) were included in every run. RT-qPCR was performed on the Bio-Rad CFX96 Touch instrument (Hercules, CA, USA) using the following conditions: 52°C for 5 minutes and 95°C for 10 seconds, 40 cycles of amplification at 95°C for 1 second, and 55°C for 1 second. The cycle threshold (Ct) value is the number of cycles required for the target viral gene to cross the threshold. A Ct value below 38 was considered positive for SARS-CoV-2.

Patients were categorized into three groups according to their clinical, laboratory, and radiological properties: mild, moderate, and severe. The mild disease group consisted of patients who did not show Covid-19 symptoms or could be followed

as outpatients, even if they did. They were found to be positive while hospitalized and without interrupting chemotherapy treatment. The moderate disease group included patients who had symptoms requiring hospitalization (presence of fever, muscle/joint pains, cough, sore throat with one of the following findings: tachypnea (≥ 30 /minute) / SpO₂ level in room air $\leq 90\%$ / Disseminated pneumonia on chest X-ray or CT scan but who did not need intensive care). Severe disease, on the other hand (dyspnea and respiratory distress; respiratory rate ≥ 30 /min, PaO₂/FiO₂ < 300 , oxygen demand increased in monitoring, SpO₂ $< 90\%$ or PaO₂ < 70 mmHg despite 5 L/min oxygen therapy, hypotension (systolic blood pressure < 90 mmHg and normal systolic blood pressure of 40, decrease more than mmHg and mean arterial pressure < 65 mmHg, tachycardia > 100 /min, acute kidney injury, acute liver function test abnormalities, confusion, acute bleeding development of acute organ dysfunction such as diathesis, patients with immunosuppression, presence of skin disorders such as troponin elevation and arrhythmia, lactate > 2 mmol, capillary return disorder and cutis marmoratus) consisted of patients receiving treatment in the intensive care unit (ICU). The patient or parent/legal guardian provided written informed consent for the treatment and the analysis of clinical data. The study was approved by the University of Health Sciences Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (1245/2021) in 2021, following the Declaration of Helsinki.

The data were analyzed with IBM SPSS, version 23 (IBM Inc. Armonk, NY, USA). The conformity to the normal distribution was evaluated using the Shapiro-Wilk test. Data are presented as mean \pm standard deviation (SD) and median (minimum-maximum) for quantitative data and as frequency (percent) for categorical data. Chi-square and Fisher's Exact tests were used to compare categorical data according to the groups, and multiple comparisons of the rates were analyzed with the Bonferroni corrected Z test. Mann-Whitney U test was used to compare non-normally distributed data between paired groups. Binary logistic regression analysis was used to examine the risk factors affecting the severity of the disease. The level of significance was taken as $p < 0.050$. Risk factors affecting the severity of the disease were analyzed using binary logistic regression analysis as Univariate and Multivariate models.

RESULTS AND DISCUSSION

There were 300 pediatric patients receiving cancer treatment in our clinic between 01.06.2020 and 01.08.2021. Of these, 63 (21%) patients were diagnosed with Covid-19 and included in the study. The median age of the patients was 7.6 ± 5.3 (0-18) years, and there were more male (57.1%) than female patients (Table1).

The most frequent type of cancer among the patients with Covid-19 was leukemia (74.6%). The underlying diagnoses in the study cohort was acute lymphoblastic leukemia (61.9%); acute myeloblastic leukemia (9.6%); chronic myeloid leukemia (3.1%); lymphoma (6.4%); neuroblastoma (8%); Wilms tumor (3.1%); osteosarcoma (3.1%); Ewing's sarcoma (1.6%); rhabdomyosarcoma (1.6%); and Langerhans cell histiocytosis (1.6%) (Table1). Patients receiving intense immunosuppressive treatment as relapse/resistant cancer treatment (9.5%) constituted a minority group. One patient received an allo hematopoietic stem cell transplant (HSCT) more than one year earlier.

Fever was the most frequent presenting symptom of Covid-19 (67.7%). Other than fever, the other symptoms detected less frequently were: runny nose (9.5%); cough (9.5%); fatigue (15.9%); difficulty in breathing (4.8%); and diarrhea (4.8%). In the analysis of the severity of the disease, mild disease (60.3%) was the most frequent, followed by moderate disease (30.2%) and severe (9.5%) disease made up

the smallest category (Table 1). Of the 63 patients having PCR-confirmed Covid-19 infection, radiological evaluations were conducted for 31 patients (49.2%), and findings consistent with pneumonia were found in 12 (19%). Among the patients with positive Covid-19 PCR tests, the number of patients whose treatment was continued without interrupting chemotherapy (57.1%) was higher than those whose chemotherapy treatment had to be interrupted (42.9%). Reasons for interruption of treatment were: respiratory distress/pneumonia (26%); family request (14.8%) (mild disease); fever and development of neutropenia (48.1%); waiting for the Covid-19 tests to become negative because relapse treatment would be started (3.7%); and deterioration of the general status of the patient so that ICU admission was required (7.4%).

Table 1. Demographic Findings of the Patients

Patient Characteristics		%	
Age	7.6 ± 5.3		
Female	27 patients	42.9	
Male	36 patients	57.1	
Diagnosis		Patients Number	%
Acute Lymphoblastic Leukemia		39	61.9
Acute Myeloblastic Leukemia		6	9.6
Chronic Myeloid Leukemia		2	3.1
Lymphoma		4	6.4
Neuroblastoma		5	8
Osteosarcoma		2	3.1
Wilms		2	3.1
Ewing		1	1.6
Rhabdomyosarcoma		1	1.6
Langerhans cell histiocytosis		1	1.6
Symptoms		Patients Number	%
No presenting symptom		19	30.2
Fever		42	67.7
Runny nose		6	9.6
Cough		6	9.6
Fatigue		10	15.9
Difficulty in breathing		3	4.8
Diarrhea		3	4.8
Anosmia		2	3.2
Covid disease severity		Patients Number	%
Mild		38	60.3
Moderate		19	30.2
Severe		6	9.5
		Patients Number	%
Hospitalizations due to Covid		25	39.7
Intensive care unit admission		6	9.5
Death		5	7.9

Approximately one-third of the patients (39.7%) whose treatment was interrupted was hospitalized and treated for Covid-19; Six (9.5%) were put into the ICU, and five of these died while in the ICU (Table 1).

Table 2. Descriptive Statistics of Quantitative Data

	Patients Number	Mean \pm S. Deviation	Median (min. - max.)
Duration of chemotherapy interruption	27	13.9 \pm 14.3	10.0 (1.0 - 60.0)
Duration of stay in intensive care for those admitted	6	13.3 \pm 8.4	12.0 (1.0 - 25.0)
Duration of Covid positivity	63	22.7 \pm 23.0	15.0 (1.0 - 134.0)

For the patients whose chemotherapy treatment was interrupted, the mean period of interruption was 13.9 days, the mean duration of stay in the intensive care unit was 13.3 days, and the approximate duration of Covid positivity was 22.7 days (Table 2).

Table 3. Results of Comparison of Leukemia and Other Cancer

	Other Cancer Numbers	Leukemia Number	Total Patients Number	P
Hospitalization	5	18	25	0,613**
Interruption of chemotherapy	5	22	27	0,277**
Duration of stay in ICU	2	4	6	0,639*

*Fisher's Exact test, **Ki-kare test

Table 4. Results of Comparison of Relapsed Patients and Other Patients.

	Relapsed Patients n (%)	Other Cancer Patients n (%)	Total	p*
Total Patients	6	57	63	
Those hospitalized and treated for covid	3 (50)	20 (35.1)	23 (36.5)	0.666
Patients in intensive care for covid	4 (66.7)	2 (3.5)	6 (9.5)	<0.001
Chemotherapy interrupted	3 (50)	24 (42.1)	27 (42.8)	1.000

*Fisher's Exact test, frequency (percent)

No significant difference between hematological and solid tumors was found in terms of hospitalization, interruption of chemotherapy, and duration of stay in ICU (Table 3). While 66.7% of relapsed patients were admitted to the ICU, this rate was significantly lower (3.5%) in non-relapsed patients ($p < 0.001$). There was no statistically significant difference between the distributions of other variables according to the presence of relapse (Table 4).

Table 5. Results of Comparison According to the Severity of the Disease

		The not Hospitalized Patients (Mild) n (%)	The Hospitalized Patients (Moderate+ Severe) n (%)	Total n (%)	p
Patients number		38 (60.4)	25 (39.6)	63	
Relapsed/Other Patients	Relapsed Other	2 (5.3) 36 (94.7)	4 (16) 21 (84)	6 (9.5) 57 (90.5)	0.204*
Diagnosis group	Leukemia Other	27 (71.1) 11 (28.9)	20 (80) 5 (20)	47 (74.6) 16 (25.4)	0.425**
Gender	Female Male	17 (44.7) 21 (55.3)	10 (40) 15 (60)	27 (42.9) 36 (57.1)	0.710**
Chemotherapy interrupted	Yes No	10 (26.3) 28 (73.7)	17 (68) 8 (32)	27 (42.9) 36 (57.1)	0.001**
Deaths while having Covid- pneumonia	Yes No	0 (0) 38 (100)	5 (20) 20 (80)	5 (7.9) 58 (92.1)	0.008*
History of contact (before or after testing)	Yes No	19 (50) 19 (50)	2 (8) 23 (92)	21 (33.3) 42 (66.7)	0.001**
Had fever during Covid	Yes No	19 (50) 19 (50)	23 (95.8) 1 (4.2)	42 (67.7) 20 (32.3)	<0.001* *
Neutropenia	Yes No	24 (63.2) 14 (36.8)	21 (87.5) 3 (12.5)	45 (72.6) 17 (27.4)	0.036**
Imaging	Yes No	14 (36.8) 24 (63.2)	18 (72) 7 (28)	32 (50.8) 31 (49.2)	0.006**
Chest X- Ray	Yes No	11 (28.9) 27 (71.1)	16 (64) 9 (36)	27 (42.9) 36 (57.1)	0.006**
HRCT	Yes No	8 (21.1) 30 (78.9)	12 (48) 13 (52)	20 (31.7) 43 (68.3)	0.025**
Findings on the imaging	Yes No	13 (92.9) 1 (7.1)	6 (33.3) 12 (66.7)	19 (59.4) 13 (40.6)	0.001**
Presenting symptom	None	16 (42.1)	3 (12)	19 (30.2)	0.001**
	Fever	12 (31.6)	19 (76)	31 (49.2)	
	Runny nose	5 (13.2)	1 (4)	6 (9.5)	
	Cough	4 (10.5)	2 (8)	6 (9.5)	
	Fatigue	4 (10.5)	6 (24)	10 (15.9)	
	Dyspnea	1 (2.6)	2 (8)	3 (4.8)	
	Diarrhea	1 (2.6)	2 (8)	3 (4.8)	
	Anosmia	1 (2.6)	1 (4)	2 (3.2)	

*Fisher's Exact test, **Chi-square test, frequency (percent), Asx: Asymptomatic.

Significantly more patients with severe disease had to have an interruption to their chemotherapy compared to those with mild disease (68% vs. 26.3%; $p=0.001$), and 20% of those with the severe disease died in the ICU. Fifty percent of those with mild disease and 8% with severe disease had a history of contact ($p=0.001$) (Table 5).

Table 6. Comparison of Quantitative Data According to the Severity of the Disease

	The not Hospitalized Patients (Mild) Median (min. - max.)	The Hospitalized Patients (Moderate+Severe) Median (min. - max.)	p
Age	8.0 (1.0 - 18.0)	5.0 (2.0 - 17.0)	0.312
Days chemotherapy was interrupted	8.5 (5.0 - 60.0)	10.0 (1.0 - 60.0)	0.647
CRP	1.0 (1.0 - 5.0)	3.0 (1.0 - 5.0)	<0,001
Duration of covid positivity	14.0 (1.0 - 63.0)	16.0 (8.0 - 134.0)	0.261

*Mann-Whitney U test statistics

When stratified by disease severity, a statistically significant difference emerged between the findings of fever, neutropenia, CRP level, and the distribution of imaging tests during Covid. Significantly fewer patients with mild disease had fever than those with the severe disease during Covid infection (50% vs. 95.8%, respectively; $p<0.001$). Neutropenia was seen in 63.2% of those with mild disease and 87.5% with severe disease ($p=0.036$). Imaging was performed for 36.8% of those with mild and 72% with severe diseases ($p=0.006$) (Table 4). The CRP of those with the mild disease was $1,8 \pm 1,1$ (median=1), while those with severe disease had a CRP of $3,4 \pm 1,4$ (median=3) ($p<0.001$) (Table 6). There was no statistically significant difference between the distribution of other variables based on disease severity (Table 6).

Table 7. Examination of Risk Factors Affecting the Severity of the Disease

	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	P
Had fever during Covid	23 (2.815 - 187.949)	0.003	48.85 (1.335 - 1787.662)	0.034
Neutropenia	4.083 (1.03 - 16.192)	0.045	0.461 (0.016 - 13.397)	0.652
Age	0.933 (0.843 - 1.033)	0.184	0.798 (0.634 - 1.004)	0.054
CRP	2.589 (1.593 - 4.208)	<0.001	2.154 (0.926 - 5.007)	0.075
Duration of Covid positivity	1.018 (0.992 - 1.045)	0.182	1.039 (0.967 - 1.117)	0.297

Disease severity was 23 times ($p=0.003$) in patients with fever, 4.083 times ($p=0.045$) in patients with neutropenia, and 26 times more in those with imaging findings compatible with pneumonia ($p=0.005$). As CRP increased, disease severity increased 2.589 times ($p<0.001$). When the results of the multivariate model were examined, the severity of the disease was found to be 48.85 times higher in patients with fever ($p=0.034$). However, other variables were not found to be risk factors ($p>0.050$) (Table 7).

Covid-19 is a public health emergency of international importance to the World Health Organization¹⁷. With the worldwide spread, persistence, and variation of the

disease, the clinical course remains uncertain, especially in children¹⁶. This uncertainty raises many concerns about the care of immunosuppressed children diagnosed with cancer; delays in chemotherapy treatment and the unknown future effects of this on prognosis raise many question marks. The limited published data on this issue shows the need for comprehensive studies and highlights the importance of sharing clinical experiences with colleagues.

The median age of patients diagnosed with cancer was reported within the range of 6-10 years in different studies, and this was true of the presented cohort^{2,18-20}(Table1). The male dominance in the gender distribution of the general adult and pediatric population reported in the literature was also observed in our data^{16,21,22} (Table1).

In earlier studies, the underlying disease mainly was hematological malignancies^{19,20}. In a study conducted in 2020, it was reported that there is a statistically significant relationship between the underlying diagnosis and the severity of the Covid-19 disease²³. In our study, although the underlying disease was hematological malignancy in most cases, no significant correlation could be found between the severity of the Covid-19 disease and the underlying diagnosis (Table1,3). The underlying diagnosis was mostly hematological malignancies may be due to the higher incidence of these malignancies among childhood cancers. In our study, regardless of the underlying primary diagnosis, 66.7% of the relapsed patients were significantly more likely to be put into ICU after contracting Covid-19 than the other patients (Table 4).

The clinical spectrum of Covid-19 can range from asymptomatic to severe respiratory distress¹⁶. In the study of Kebudi et al., the proportion of asymptomatic patients was 47%². In our cohort, 30.2% were asymptomatic at presentation (Table1). It was reported that 32.5% of the pediatric cancer patients had no symptoms when they presented to the hospital, and a further 33.3% had mild symptoms²⁴.

Shekerdemian et al. reported that 72% of the cases presented with respiratory symptoms, 25% with other systemic symptoms, such as gastrointestinal and neurological symptoms²⁵. In a study where 98 pediatric patients diagnosed with cancer were analyzed, the most frequent symptoms were fever (82.2%), cough (61.6%), and respiratory distress (26%)²⁵. In our study, fever was present in more than two-thirds of symptomatic patients (67.7%) (Table1).

In our study, 50% of the patients with mild disease and 8% with moderate/severe disease had a history of contact (Table 5). This seems to be due to those tested only because they had contact, although they did not have any symptoms. In an early Turkish study, the presence of abnormal imaging findings was found to increase the severity of Covid-19 significantly². In our study, 36.8% of patients with mild disease and 72% of patients with moderate/severe disease had imaging, the imaging findings consistent with Covid-19 were present in 7.1% of patients with mild disease and 66.7% of patients with moderate/severe disease (Table 5). The increased likelihood of severe disease in those to whom imaging was performed seems to be because imaging was performed in patients with symptoms of pneumonia. An increase in disease severity in patients who clinically have pneumonia is not unexpected.

A multicenter study in Turkey reported that 17.6% of the cases needed intensive care, and the mortality rate was 1.9%². Furthermore, it has been reported that 60% of the pediatric cancer patients hospitalized and receiving treatment for Covid-19 infection required ICU admission, which was significantly higher than that reported in pediatric patients without cancer². In our study, most patients had mild disease, but of the nearly 40% who were hospitalized, one-quarter needed ICU care

(Table 1). Of the six patients requiring ICU care, five died, all of whom were in relapse. Therefore, while the overall mortality rate in this study was 7.9% (5/63), we suggest that no death was attributable to Covid-19 disease alone (Table 1). However, Covid-19 may have contributed significantly to the acceleration of death. For this reason, in our study, COVID-19 disease was not correlated with increased mortality, except for children who were already at high risk of death from their malignancies. The limitations of the study are its retrospective nature and relatively small cohort.

CONCLUSION

In this cohort of pediatric oncology patients, all of whom contracted SARS-COV-2 infection, and the resulting Covid-19 tended to be mild (60.4%). In our cohort, nearly 43% of patients who had Covid-19 were their chemotherapy interrupted. It is unclear how interrupted chemotherapy treatment will affect the prognosis. This question will require more evidence from extensive prospective studies to be answered satisfactorily. Furthermore, the death rate in this study was low, and mortality was not due to Covid-19 alone in any patient who died.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest concerning this article's research, authorship, and publication.

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