JOURNAL OF CORONA VIRUS

Characteristics of COVID-19 in Pediatric Patients with Malignancy in Sulaymaniyah Governorate, Kurdistan Region of Iraq

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Article Information

Article Type: Research Article
Journal Type: Open Access
Volume: 1 Issue: 1
Manuscript ID: JCV-v1-1115
Publisher: Science World Publishing

Received Date: 01 March 2020
Accepted Date: 23 March 2021
Published Date: 31 March 2021

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Citation:
Al odda BKA (2021).
Characteristics of COVID-19 in Pediatric Patients with Malignancy in Sulaymaniyah Governorate, Kurdistan Region of Iraq. J Corona Virus. 1(1); 1-7

Authors' contributions:
Basil Kadhim Abdallah Al odda has been involved in clinical diagnostic evaluations and management.

Keywords:
COVID-19; Pediatric; Hematological malignancy; Solid tumor; Iraq

Abbreviation:
COVID-19: Coronavirus disease 2019**;** SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; TT-PCR: Real time polymerase chain reaction; SPSS: Statistical package for social sciences; IgM: Immunoglobulin M; IgG: Immunoglobulin G; CRP: C-reactive protein; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; C.T. scan: Computerized Tomography scan; MicroL: Micolitter

ABSTRACT

BACKGROUND: A recent human's pandemic of respiratory disease caused by a novel (new) coronavirus that rapidly spreads in the community and may causing life threating complications. All those exposed to it is at risk of becoming infected and getting COVID-19. Cancer Patients may be more likely at risk to getting the infection and developing life threating morbidity and even death as those cancer patients may have weakened immunity either because of the cancer treatment or direct effect of the disease.

OBJECTIVE: To obtain local data on the pattern of children and adolescent with cancer on treatment who have been infected with SARS-CoV-2 in our community and compare it with that of noncancerous patients.

PATIENTS AND METHODS: A prospective study conducted on 54 pediatric patients with cancer during their treatment with chemotherapy that developed RT-PCR approved COVID-19 in Sulaymaniyah Governorate-Kurdistan region of Iraq from April 2020 to October 2020 were carried out to analyze the demographic features and their clinical manifestation. Data analyzed using SPSS software; version 13 and P-value obtained by Chi-square test.

RESULTS: The median age at diagnosis was about 7 and peak age incidence occurred in adolescent between 13-17 years old with slightly female predominance. There was no correlation between gender and severity; patients with hematological malignancies seem to have more severe COVID-19 manifestation than solid tumor.

CONCLUSION: Overall morbidity and mortality from COVID-19 in cancer patients is seem to be similar to noncancerous patients.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19), the respiratory illness responsible for the COVID-19 pandemic [1, 2].

SARS-CoV-2 is a member of the family Coronaviridae and orders Nidovirales, is an enveloped and positive-sense single-stranded RNA (+ssRNA) virus[3].

The incidence of SARS-CoV-2 infection is seen most often in adult male patients with the median age of the patients was between 34 and 59 years [4,5], SARS-CoV-2 is also more likely to infect people with chronic comorbidities such as cardiovascular and cerebrovascular diseases and diabetes [6]. The highest proportion of severe cases occurs in adult's ≥60 years of age, and in those with certain underlying conditions, such as cardiovascular and cerebrovascular diseases and diabetes [4, 5]. Severe manifestations maybe also associated with coinfections of bacteria and fungi [6].

Fewer COVID-19 cases have been reported in children less than 15 years [5, 7, 8]. In a study of 425 COVID-19 patients in Wuhan, published on January 29, there were no cases in children under 15 years of age [9], Nevertheless, 28 pediatric patients have been reported by January 2020. The clinical features of infected pediatric patients vary, but most have had mild symptoms with no fever or pneumonia, and have a good prognosis [10]. Another study found that although a child had radiological ground-glass lung opacities, the patient was asymptomatic [9]. In summary, children might be less likely to be infected or, if infected, present milder manifestations than adults; therefore, it is possible that their parents will not seek out treatment leading to underestimates of COVID-19 incidence in this age group.

Patients with hematological or solid malignancy may be more likely at risk to getting the infection and developing life threating morbidity and even death as those cancer patients may have weakened immunity either because of the cancer treatment or direct effect of the disease.

Still there is a doubt regarding the potential effects and severity of COVID-19 on patient with active malignancy receiving chemotherapy specially young children and adolescents, and the major question regarding wither to continue or stopping the ongoing chemotherapy for those patients, so we did this study trying to answering this important questions.

PATIENTS AND METHODS

A prospective study of 54 patients with hematological malignancies and solid tumors in Hiwa cancer center, Sulaymaniyah province, Kurdistan region of Iraq, over a period of six months from April 2020 to October 2020 were carried out to analyze the demographic features, clinical presentations and consequences of SARS-CoV-2 in Pediatric cancer patients on chemotherapy.

Diagnosis of SARS-CoV-2 was based on detection of viral antigen on Real Time polymerase chain reaction (RT-PCR) in nasopharyngeal swab.

Inclusion criteria included all pediatric patients with any hematological and solid malignancies on chemotherapy, both gender, under the age of 18 years with full recorded data diagnosed with SARS-CoV-2 by RT-PCR from the nasopharyngeal swab. Exclusion criteria included all patients with negative RT-PCR for SARS-CoV-2 in the nasopharyngeal swab and patients who were diagnosed as COVID-19 on the bases of positive serology (SARS-CoV-2 IgG and/or IgM) or radiological findings without RT-PCR for SARS-CoV-2, patients who were not on chemotherapy and patients with additional comorbidity as metabolic or cardiac disease.

All included patients underwent detailed clinical history including co-morbid conditions; measurement of vital signs, Oxygen saturation (SpO2) evaluated for the severity of the disease specially the respiratory symptoms.

Then they have full hematological (Complete blood count and Blood Film), and biochemical investigations (liver adrenals functions, CRP, Lactate dehydrogenase and ferritin level, D-dimer, serum electrolyte and blood culture), radiological examination (chest X-ray and Computerized tomography of chest), SARS-CoV-2 RT-PCR from the nasopharyngeal swab.

The disease severity was categorized according to "Diagnosis and Treatment Protocol for 2019-nCoV" [11,12] into three classes; mild to moderate (mild symptoms up to mild pneumonia); Severe (dyspnea, hypoxia, or more than 50% lung involvement on imaging); and critical (respiratory failure, shock, or multiorgan system dysfunction), also in our study classified the patients according to the cheat radiological findings into normal and abnormal which included any abnormalities (bilateral, peripheral, ill-defined and ground-glass opacification, consolidation, pleural effusion and

lung collapsed) any chest X-ray or chest CT scan , then the patients treated according to the local guideline mostly by antibiotic and supportive care.

The study was approved by the study was approved by the Review Ethical Committee of Hiwa Hospital. Data were entered into Excel sheet and then transferred to SPSS-Descriptive analysis; Data analyzed using Statistical package for social sciences (SPSS) software; version 13 and P-value obtained by Chi-square test, P value less than 0.05 considered as significant.

RESULTS

sample of 54 of pediatric patients with different types of hematological malignancies and solid tumors with mean age of 10.2years (standard deviation is 11.6), minimum age was 2.1 years, maximum age was 17 years (range of 14.9 years) with median age of 7 years. Most cases of COVID-19 occurred in adolescents aged 13 to 17 years (37.4%) followed by those in children 9 to 12(27.77%). Table 1 shows the age distribution of our patients (Table 1).

Table 1: Age distribution

Age	Frequency	%
1-4	8	14.81
5-8	11	20.37
9-12	15	27.77
13-17	20	37.4

Girls was little bit more common than boy as 55.55% (30)of the patients were female and (24) 44.45% were male with male to female ratio of 0.8:1. Figure 1 shows the gender distribution for our patients (Figure 1).

As showed in figure 2, the majority of our pediatric patients with COVID-19 were initially diagnosed as acute lymphoblastic leukemia and the minority with lymphoma, 27 (50%) patients had acute lymphoblastic leukemia (ALL), 12 (22.22%) with Solid tumor, and 9(16.66%) were with acute myeloid leukemia (AML), and only 6(11.11%) patients were with lymphoma (Figure 2).

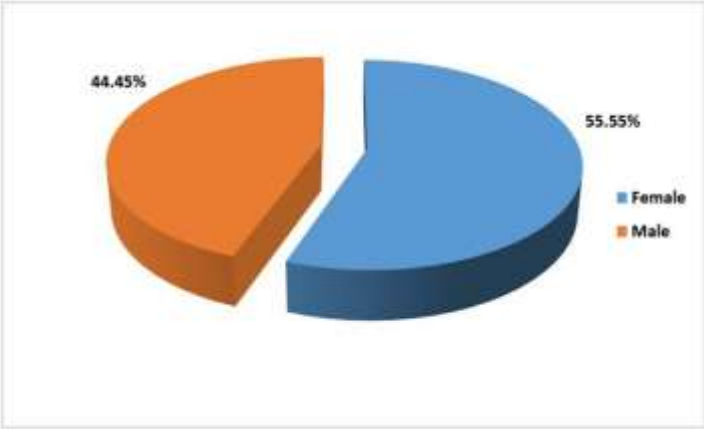

Figure 1: Gender distribution

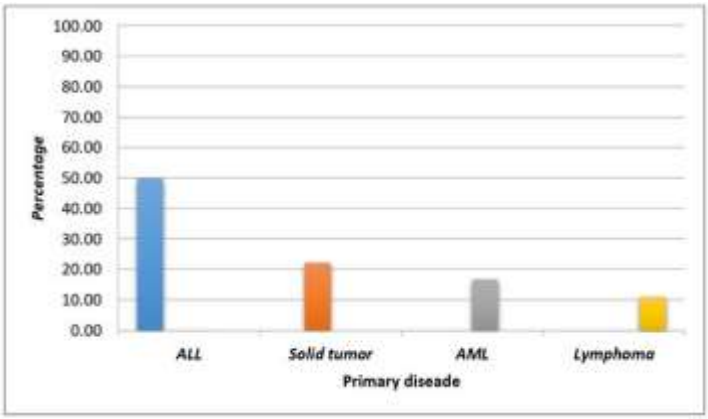

Figure 2: Distribution of primary diagnosis

The most Common presenting symptom was fever with core body temperature ranging from 37.8 to 40.2 °C in 39(72.22%) patients, followed by cough in 23(42.6%) , sneezing in 10(18.52%) patients, respiratory distress in 5(9.26%), nausea/vomiting in 4 (7.41%) and diarrhea in 2(3.7%). Table 2 shows the frequency and percentage of COVID-19 clinical manifestations (Table 2).

Regarding COVID-19 severity as shown in figure 3, 45(83.33%) with mild to moderate severity, 7(12.96%) patients with severe manifestations, and just 2(3.7%) patients were critical. Our study shows no mortality among our patients (Figure 3).

Table 2: Frequency and percentage of COVID-19 clinical manifestations

Clinical Manifestation	Frequency	percentage
Fever	39	72.22
Cough	23	42.6
Sneezing	10	18.52
Respiratory Distress	5	9.26
Nausea and vomiting	4	7.41
Diarrhea	2	3.7

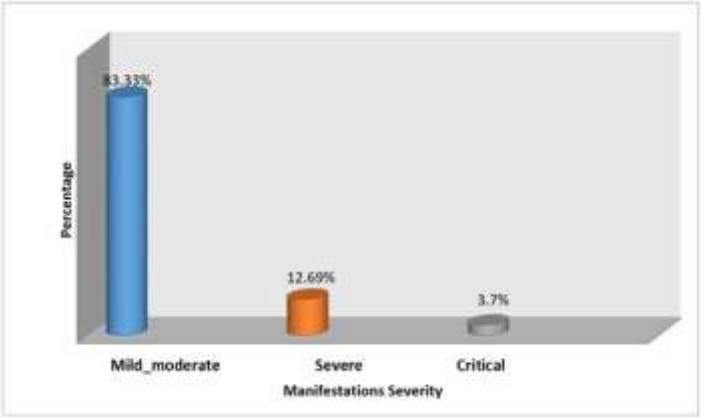

Figure 3: The disease severity distribution categorized according to "Diagnosis and Treatment Protocol for 2019-nCoV" [12, 13]

Chemotherapy related neutropenia (defined as an absolute neutrophil count (ANC) of less than 1500 per microliter (1500/microL) were observed in 38(70.37%) patients and 16(29.63%) without chemotherapy induced neutropenia. Figure 4 shows the distribution of chemotherapy induced neutropenia (Figure 4).

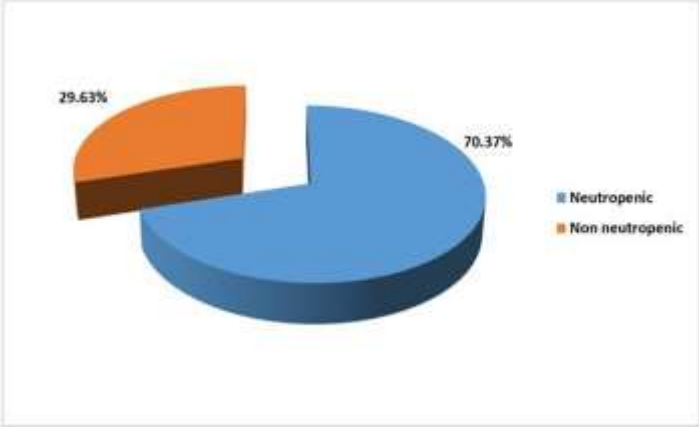

Figure 4: Chemotherapy induced neutropenia distribution

Chest radiology (as shown in figure 5) was normal in 43(79.62%) patients and abnormal in 11(20.37%) patients, Abnormal Chest radiology defined as bilateral, peripheral, ill-defined and ground-glass opacification, consolidation, pleural effusion and lung collapsed) any chest X-ray or chest CT scan (Figure 5).

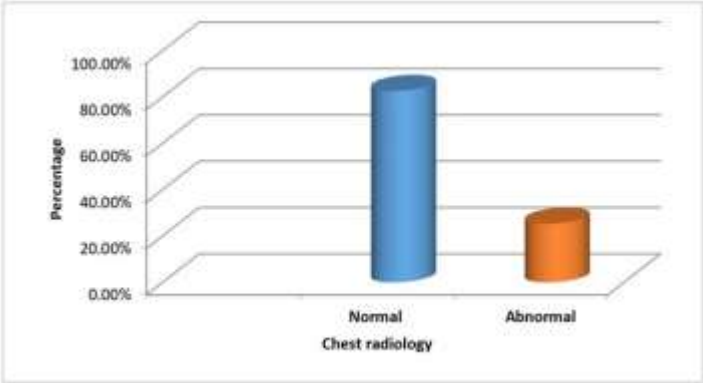

Figure 5: Chest radiological finding distribution.

Our study showed that the majority of our pediatrics cancer patients with severe and critical manifestations fall in 13-17 years age group, from them 60% with severe and 10% with critical disease severity, while all patients between (1-4 and 5-8years) were categorized as mild to moderate disease severity. Table 3 shows age group to disease severity relation (Chi-square test P- value = 0.04432409) (Table 3).

Relation between age groups and radiological finding on the chest showed that all younger age groups (1-4 and 5-8) years had normal chest radiology, while in older age groups (9-12) years and (13-17) years; abnormal chest radiology were observed in 4(25%) and 7(46.66%) respectively as showed in table 4 (Chi-square test P-value =0.005881) (Table 4).

Table 3: Age group correlation to disease severity (P-value = 0.04432409)

Age groups/year	Disease severity						Total
	Mild-moderate		Severe		Critical		
	No.	%	No.	%	No.	%	
1-4	8	100	0	0	0	0	8
5-8	11	100	0	0	0	0	11
9-12	14	93.33	1	6.66	0	0	15
13-17	12	60	6	30	2	10	20
Total	45	83.33	7	12.96	2	3.07	54

Table 4: Age group to chest radiological finding relation (P-value =0.005881)

Age groups/year	Chest Radiological Finding*				Total
	Normal		Abnormal		
	No.	%	No.	%	
1-4	10	100	0	0	10
5-8	13	100	0	0	13
9-12	12	75	4	25	16
13-17	8	53.33	7	46.66	15
Total	43	79.62	11	20.37	54

∗ defined as bilateral, peripheral, ill-defined and ground-glass opacification, consolidation, pleural effusion and lung collapsed) any chest X-ray or chest CT scan.

As showed in table 5, most of both boys and girls had Mild–moderate COVID-19 disease severity with 20(83.33%) of the male patients and 25(83.33%) of female patients had mild to moderate disease, just one (4.17%) of male patients had and one (3.33%) of female patients were had critical disease course (Table 5).

Regarding the initial diagnoses relation to the COVID-19 disease severity, both of our patients with Critical manifestations had acute leukemia, one (11.11%) with AML and other one (3.7%) with ALL, None of the patients with solid tumor or lymphoma had critical manifestations.

Table 5: Gender and COVID-19 severity correlation (Chi-square test P-value =0.984057)

Gender	COVID-19 severity						Total
	Mild-moderate		Severe		Critical		
	No.	%	No.	%	No.	%	
Male	20	83.3	3	12.5	1	4.17	24
Female	25	83.3	4	13.3	1	3.33	30
Total	45	83.3	7	12.96	2	3.70	54

Severe disease was just observed in hematological diseases, with 5(18.52%) patients with ALL, one (16.66) with initial diagnosis of lymphoma, and one (11.11%) patient had diagnosed as AML.

All patients with solid malignancy had just mild to moderate symptoms; no one from them had severe or critical disease severity. Initial malignancy diagnosis in relation to COVID-19 severity is shown in table 6 (Chi-square test P-value = 0.567222) (Table 6).

Table 6: Initial malignancy diagnosis in relation to COVID-19 severity (Chi-square test P-value = 0.567222)

Initial Disease Diagnoses	COVID-19 severity						Total
	Mild-moderate		Severe		Critical		
	No.	%	No.	%	No.	%	
ALL	21	77.78	5	18.52	1	3.7	27
AML	7	77.78	1	11.11	1	11.11	9
Lymphoma	5	83.33	1	16.66	0	0	6
Solid malignancy	12	100	0	0	0	0	12
Total	45	83.3	7	12.96	2	3.70	54

Comparing neutropenic and non neutropenic patients with the disease severity Table 7 (Chi-square test P-value = 0.045579), all patients with severe and critical disease were occurred in neutropenic patients with prevalence of (18.52%) severe and (3.7%) with critical symptoms. All non neutropenic patients were had just mild to moderate disease severity (Table 7).

Table 7: Neutropenia to COVID-19 severity correlation (P-value = 0.045579)

Neutropenia*	COVID-19 severity						Total
	Mild-moderate		Severe		Critical		
	No.	%	No.	%	No.	%	
Present	29	77.78	7	18.52	2	3.7	38
None	16	100	0	11.11	0	11.11	16
Total	34	3.4	7	46.3	2	50.3	54

∗defined as an absolute neutrophil count (ANC) of less than 1500 per microliter (1500/microL).

Also the vast majority of patients presented with abnormal radiological features had neutropenia, which occurred in 10(26.32%) of neutropenic patients in compares to 1(6.25%) of patients without neutropenia. Table 8 shows the correlation between the presence and absence of neutropenia with the chest radiological findings (Table 8).

Table 8: Neutropenia in relation to chest radiological findings (Chi-square test P-value = 0.000120)

Neutropenia	**Chest Radiological Finding***				**Total**
	Normal		Abnormal		
	No.	%	No.	%	
Present	28	73.68	10	26.32	38
None	15	93.75	1	6.25	16
Total	43	79.63	11	20.37	54

5. Discussion

Pediatric and adolescent cancer continues to be the leading cause of death in children younger than 17 years old, Infections still important cause of mortality and morbidity among pediatric patients with cancer, a recent human's pandemic of respiratory disease caused by a new coronavirus that rapidly spreads in the community and may causing life threating complications. The virus has been named SARS-CoV-2, and the disease it causes has been named coronavirus disease 2019, which is abbreviated COVID-19.

In this Prospective study conducted on 54 pediatric Patients with cancer who developed COVID-19 in Sulaymaniyah province of Kurdistan/ Iraq, we tried to study the demographic feature of pediatric cancer with COVID-19 in addition to find any correlation between type of cancer and degree of neutropenia with the severity of COVID-19.

We found that median age at time of diagnosis of COVID-19 in cancer patients is 7 years (range interval between 2.1-17 years) which is similar to the result of a retrospective Chinese study of 2143 children younger than 18 years with confirmed or suspected COVID-19 in which the median age was 7 years [11].

In our study most cases of COVID-19 occurred in adolescents aged 13 to 17 years (37.4) followed by those in children 9 to 12(27.77%). This result was similar to a result done in Italia which included non-cancer pediatric patients and showed that that most cases of COVID-19 occurred in adolescents aged 13 to 17 years (40.1%), followed by those in children 7 to 12years (28.9%) [13].

Slightly more of the cases occurred in girls (55.55%) than in boys (44.45%) with Male to female ratio of 0.8:1, but the difference was not statistically significant.

The majority of our pediatric patients with COVID-19 were initially diagnosed as hematological malignancies including acute leukemia (ALL and AML), and less cases was reported in solid tumors, possible explanation for this finding may related to either that the majority of pediatrics cancer cases are Hematological malignancy specially ALL, or due to effect of hematological cancer on T-lymphocyte function when compared with solid tumors.

The most Common presenting symptom was fever with core body temperature ranging from 37.8 to 40.2 °C in (72.22%) of the studied cases, followed by cough in (42.6%) of patients the result was similar to study done between January 15, 2020, and March 15, 2020, in mainland China [14]. But on other hand fever as presenting feature in our study (72.22%) was more prevalent than that reported by Systematic and Meta-Analysis Medline database was searched between December 1st 2019 and April 6th 2020 which were studied 1124 patients (with or without comorbidity as immunosuppression) younger than 18 years old in which fever was the presenting feature in (47.5%) of patients1[15], possible explanation for this difference is that febrile neutropenia was the reason to evaluated the patients for COVID-19 in our study.

We also observed that the majority of our patients 45(83.33%) with mild to moderate severity which was similar to the systemic meta-analysis done by Tiago H. de Souza MD, PhD, et al [15] in which (36.3%) were mild, (46.0%) were moderate collective-

ly (82.3). but when we compare the same meta-analysis [15] with our study we found that we had more prevalent (12.96%) patients with severe, and 2(3.7%) patients with critical manifestations. Our study shows no mortality among our patients in compares with (2.1%) severe, and (1.2%) are critical in Tiago H. de Souza MD, PhD, et al [15]; this difference may be due to that there were neither asymptomatic nor infant under the age of 2 years (as it was not reported in our study), or possible effect of immunosuppression by the disease or chemotherapy.

We observed no mortality among our 54 patients and this was comparable to the overall death rate from covid-19 that has been estimated at 0.66% and declining to 0.0016% in children aged 9 and under [16].

Less prevalence of abnormal chest radiological finding (20.37%) was observed in our patients compared to multicenter study done by Pablo Caro-Dominguez, et al. [17], this study was done on ninety-one non oncological children were included (49 males; median age: 6.1 years, interquartile range: 1.0 to 13.0 years, range: 9 days-17 years). which showed that just 10% of them were normal and all others (90%) were abnormal.

Our study found a significant statistical correlation (P value=0.04432409) between age and disease severity with the majority of our pediatrics cancer patients with severe and critical manifestations fall in 13-17 years age group, from them 60% with severe and 10% with critical disease severity, while all patients between (1-4 and 5-8years) were categorized as mild to moderate disease severity, this observation is similar to what was reported by (Leung et al., 2004a) [18] in which younger children comparatively had shown milder disease as compared to the 12 years of age and adolescents. It was reported that adolescent somehow resembled the clinical and radiological findings as adults and showed decline in their conditions as well.

There was also significant relation between age groups and abnormal radiological finding (P-value =0.005881), all younger age groups (1-4 and 5-8) years had normal chest radiology, while in older age groups (9-12) years and (13-17) years; abnormal chest radiology were observed in 4(25%) and 7(46.66%) respectively.

No statistical significant correlation between gender and disease severity was observed in this current study unlikely to the result in) Jie Qian, Lin Zhao, Run-Ze Ye, et al) [19] which stated that (Interestingly, females might be more prone to get the disease but are less likely to have a poor or fatal outcome).

All patients with solid malignancy in our study had mild to moderate symptoms, all the severe and critical severity had hematological malignancy especially acute lymphoblastic leukemia in which (18.52%) had severe and (3.7%) had critical disease severity, and this finding was statically not significant (P-value = 0.567222), however it may be clinical significant due to small sample size.

We found significant statistical correlation (P-value = 0.045579) between the presence and absence of neutropenia and COVID disease severity, all patients with severe and critical disease were occurred in neutropenic patients with prevalence of (18.52%) severe and (3.7%) with critical symptoms. All non neutropenic patients were had just mild to moderate disease severity with no one from them had severe or critical COVID disease severity.

Lastly the vast majority of patients presented with abnormal radiological features had neutropenia, which occurred in 10(26.32%) of neutropenic patients in compares to 1(6.25%) of patients without neutropenia, this difference was statically significant (P-value = 0.000120)

CONCLUSION

In conclusion our pediatric cancer patients with COVID-19 neither had significant increasing in morbidity nor did mortality compare with others non-cancerous pediatric patients. More severe disease tends to occur in young adolescent rather than young children with hematological malignancies namely acute leukemia are at a particular risk for severe disease, However we found no increasing mortality neither in adolescent nor hematological malignancies when compared with the non-cancerous pediatric COVID-19 cases.

In addition to the fact that pediatric malignancies is highly curable when compared to adult cancers, accordingly it is seem to be more satisfactory to continue on chemotherapy during this SARS-CoV-2 pandemic for pediatric patients without COVID-19 or even in a patient who proved with COVID-19 who is asymptomatic or even mild symptoms especially during low dose maintenance chemotherapy, however this needs a further larger study and the decision of chemotherapy should be individualized for each patient and with strict cautions and follow up.

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