JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Coronavirus Pandemic

Changing characteristics of cancer patients during the COVID-19 pandemic

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Abstract

Introduction: Cancer patients are more sensitive to infections, and, compared to other patients, may have more serious outcomes. Thus, cancer patients are a high-risk group in the COVID-19 pandemic. The aim of this study was to evaluate how cancer patients are affected by COVID-19 infection; the prevalence, and factors affecting mortality.

Methodology: This single-centre, retrospective study included cancer patients under follow-up treatment at our hospital with a laboratory-confirmed diagnosis of COVID-19. Demographic and clinical data were obtained from electronic medical records. The effects of tumour subtype and patient demographic data on COVID-19 prevalence and mortality were analyzed using univariate and multivariate models.

Results: Evaluation was made of 217 cancer patients, comprising 140 (64.5%) males and 77 (35.5%) females with a mean age of 62.05 ± 12.95 years. Mortality was seen in 84 (38.7%) patients. Disease grade, chemotherapy within the last 3 months and CT findings were determined to be related to mortality. In logistic regression analysis, the most important factors affecting survival were determined to be severe lung involvement ($p < 0.001$) and hematological malignancy.

Conclusions: It is clear that cancer patients are at greater risk from COVID-19 infection than individuals without a malignant disease. The results showed that cancer patients with different tumour types had different levels of sensitivity to COVID-19. It is clear that with ongoing viral mutations, the duration of the pandemic is unknown. Therefore, the continuation of cancer screening and cancer treatments should not be interrupted.

Key words: COVID-19, malignant diseases, mortality.

J Infect Dev Ctries 2022; 16(3):453-461. doi:10.3855/jidc.15155

(Received 10 April 2021 – Accepted 14 December 2021)

Introduction

The new coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus first emerged in the city of Wuhan in the province of Hubei, China, in December 2019 [1]. Corona viruses are membranous single-stranded RNA (ribonucleic acid) viruses of the Coronaviridiae family, which are known as "corona viruses" because of the crown-like projections on the outer surface. Angiotensin converting enzyme 2 (ACE2) is used as the receptor binding motif (RBM). The virus enters host cells after contact with these specific ACE2 receptors through endocytosis or membrane fusion. The viral genome must be expressed for the replication of the virus that has entered the host cell [2,3].

Following the first reported case, the number of cases worldwide exceeded 100,000 within 3 months, and in March 2020, the World Health Organisation (WHO) declared COVID-19 as a global pandemic [4]. The first case in Turkey was recorded on 11 March 2020. The first wave of the pandemic in Turkey lasted until the end of May. A second wave started in October with an increasing number of cases and continued until February 2021 [5]. The global COVID-19-related mortality rate since 1 February 2021 has been reported as 2.16%, although in Turkey this rate is 1.05% [6]. Differences can be seen between the mortality rates of different countries according to the available resources, geography, literacy rates, population, and political factors [7].

A study conducted in the United Kingdom during the second wave of the pandemic showed that the mortality rate of patients infected with the Variant of Concern (VOC)-202012/01 mutated virus was approximately 2-fold higher than that of patients infected with the previous variant [8]. In Turkey, the VOC-202012/01 mutation analysis started at the end of December 2020, and the first mutated viruses were determined on January 1; the number of patients infected with these mutations continued to increase rapidly after that period [9].

COVID-19 is highly infectious and can have a long incubation period before the emergence of symptoms such as fever, cough, shortness of breath, and diarrhea. While some patients may be asymptomatic, in others, COVID-19 may cause multiple organ failure involving the lungs, heart, and liver [10,11]. Epidemiological and clinical evidence has shown that COVID-19 has a more severe course in the elderly, in males, and in patients with comorbidities such as hypertension, diabetes, and malignant diseases [12-19].

Previous studies have reported that cancer patients constitute a population at high risk of severe COVID-19. The mortality rate of cancer patients diagnosed with COVID-19 has been found to be in the range of 12.4-33.3% in studies conducted in different centres [12,13,19-22]. Factors such as immunosuppressive treatments, advanced age, presence of comorbidities, metastatic cancer, and lung involvement (primary lung cancer or metastasis of cancer in the lungs) are among the reasons for a more severe course of COVID-19 in cancer patients [23-26]. It has also been reported that COVID-19-related mortality varies according to the type of malignant disease [27].

The aim of this retrospective study, conducted in the largest pandemic centre in Istanbul, was to evaluate how cancer patients were affected by COVID-19 infection in the second wave of the pandemic in Turkey and to investigate the clinical course and factors affecting mortality.

Methodology

Study design and participants

Our hospital is the largest (1000 bed) pandemic centre in Istanbul, designated to only accept COVID-19 patients following the first wave of the pandemic. The study included cancer patients diagnosed with COVID-19 who were followed up and treated in our hospital between 15 March-15 May 2020 (first wave) and 1 October 2020-1 February 2021(second wave). All the patients included had a positive result in reverse transcription polymerase chain reaction (RT-PCR) analysis of nasopharyngeal and oropharyngeal smear samples. All the samples taken for genomic RNA isolation were transferred to Biospeedy transfer tubes (BIOEKSEN, Istanbul, Turkey) containing 2 mL of nucleic acid preservative and transported to the laboratory at 2-8 °C. All samples were handled at biosafety level-3 (BSL-3) with full personal protective equipment. An isolation device (QIAGEN, Dusseldorf, Germany) was used for RNA extraction.

Approval for this study was granted by the Ethics Committee of Bakirkoy Sadi Konuk Training and Research Hospital and the National Ethics Committee (decision no: 2021/123-01.03.2021). All procedures were applied in compliance with the Helsinki Declaration and its later revisions.

Data Collection

Demographic information, medical history, clinical characteristics, and thorax computed tomography (CT) images of all the patients were obtained retrospectively from the electronic medical records system. COVID-19-related death is defined by the WHO as death of a case with RT-PCR-confirmed COVID-19 infection when there is no alternative cause of death [28]. The WHO criteria were accepted for the mortality rates in this study.

Radiological methods

The major CT demonstrations were described using the international standard nomenclature defined by the Fleischner Society glossary, using terms including ground-glass opacity (GGO), crazy-paving pattern, and consolidation. The cases were divided into 3 groups as mild involvement (< 25% involvement), moderate involvement (26–74% involvement) and severe involvement (> 75% involvement).

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM Statistical Package for the Social Sciences (SPSS) version 18.0 software. Descriptive statistical methods were used in the evaluations (mean ± standard deviation (SD), median, minimum and maximum values, number, and percentage). Conformity of quantitative data to normal distribution was assessed with the Kolmogorov-Smirnov test, the Shapiro-Wilk test, and graphic methods. The Student's *t*-test was applied in the comparison of two groups of quantitative data showing normal distribution and the Mann Whitney U-test was used for data not showing normal distribution. The Pearson Chi-square test was used for the comparison of

qualitative data. Logistic regression analysis using the Enter method was performed to compare the effect of independent variables on dependent variables. A value of $p < 0.05$ was accepted as statistically significant.

Results

The clinical and demographic data were retrospectively recorded for 282 patients with a diagnosis of cancer who were admitted to our hospital for COVID-19 treatment between 15 March-15 May 2020 (first wave) and 1 October 2020-1 February 2021 (second wave). During the first and second period, 14769 patients were hospitalized because of a diagnosis of COVID-19, and of these treated patients, 1.9% had cancer.

The demographic and clinical characteristics of the first and second wave cancer patients are shown in Table 1.

The mean age of the patients was 62.06 ± 12.42 years and 63.4% (n = 179) were male. There was no statistically significant difference in mortality rates between the genders ($p < 0.05$).

The leading malignant disease type in the patient population with COVID-19 infection was gastrointestinal system cancer (n = 77, 27.3%), followed by lung cancer (n = 48, 17%). Patients with gastrointestinal system cancer and lung cancer comprised 57.9% of the solid organ tumour deaths and those with hematological malignancy constituted 23.2% of all deaths. In the comparisons made according

Table 1. Demographic and clinical characteristics, and mortality status of patients with malignant diseases.

	Survivors (n = 183)	Non-survivors (n = 99)	*p*	OR (CI 95%)
Sex			0,181[a]	
Male (%)	111 (60.7)	68 (68.7)		
Female (%)	72 (39.3)	31 (31.3)		
Age (mean ± SD)	62.71 ± 12.05	60.84 ± 13.06	0.229[b]	
(median)	31-97 (64)	18-91 (63)		
Cancer class			0.074[a]	
Gastrointestinal (%)	51 (27.9)	26 (26.3)		
Lung (%)	30 (16.4)	18 (18.2)		
Genitourinary (%)	31 (16.9)	12 (12.1)		
Breast (%)	25 (13.7)	7 (7.1)		
Others (%)	26 (14.2)	13 (13.1)		
Hematological (%)	20 (10.9)	23 (23.2)		
Cancer type			0.005[a**]	0.405 (0.210-0.783)
Hematological Cancer (%)	20 (10.9)	23 (23.2)		
Non-hematological Cancer (%)	163 (89.1)	76 (76.8)		
Tumor stage (Non-hematological cancer)			0.001[a**]	2.846 (1.717-4.716)
Stage I-III (%)	117 (63.9)	38 (38.4)		
Stage IV (%)	66 (36.1)	61 (61.6)		
Chemotherapy received within the last 3 months			0.005[a**]	2.042 (1.243-3.357)
No (%)	117 (63.9)	46 (46.5)		
Yes (%)	66 (36.1)	53 (53.5)		
Admission to Intensive Care Unit			0.001[a**]	50.827 (24.255-106.510)
Present (%)	14 (7.7)	80 (80.8)		
Absent (%)	169 (92.3)	19 (19.2)		
Comorbidities				
Diabetes mellitus (%)	51 (27.9)	30 (30.3)	0.666[a]	
Hypertension (%)	57 (31.1)	45 (45.5)	0.017[a**]	1.842 (1.112-3.050)
Chronic obstructive pulmonary disease (%)	30 (16.4)	21 (21.2)	0.316[a]	
Coronary artery disease (%)	10 (5.5)	7 (7.1)	0.589[a]	
Chronic kidney disease (%)	12 (6.6)	6 (6.1)	0.871[a]	
Cerebrovascular disease (%)	8 (4.4)	6 (6.1)	0.533[a]	
Length of stay in hospital (days-median)	1-80 (10)	1-64 (14)	0.087[c]	
Pneumonia severity			0.001[a**]	
None (%)	9 (4.9)	0		
Mild (%)	119 (65)	20 (20.2)		
Moderate (%)	44 (24.1)	29 (29.3)		
Severe (%)	11 (6)	50 (50.3)		

[a] Chi-square test; [b]Student's t-test; [c] Mann Whitney U-test; ** A *p*-value of less than 0.05 is accepted as being statistically significant.

to malignant disease type, the mortality rate of patients with solid organ malignant disease was determined to be approximately 3-fold higher than that of the patients with hematological malignancy ($p = 0.005$). The other malignant disease types and mortality rates are shown in Table 1.

The 119 (42.2%) patients who had received chemotherapy within the last 3 months had approximately 2-fold increased mortality ($p = 0.005$). Tumor stage-IV (non-hematological cancer) increased the mortality rate 2.8-fold ($p = 0.001$).

The most common comorbidity in the cancer patients was hypertension at 36.2%, followed by diabetes mellitus at 28.7%. When comparisons were made according to the presence of comorbidities, a higher rate of hypertension was determined in the patients with mortality ($p = 0.017$).

Thorax involvement seen on CT images was classified as mild, moderate, and severe. Severe pneumonia was seen in 50.3% of the patients who developed mortality. Increased severity of pneumonia was associated with mortality ($p = 0.001$). Of the patients with mortality, 80.8% were patients who were followed up in the Intensive Care Unit (ICU).

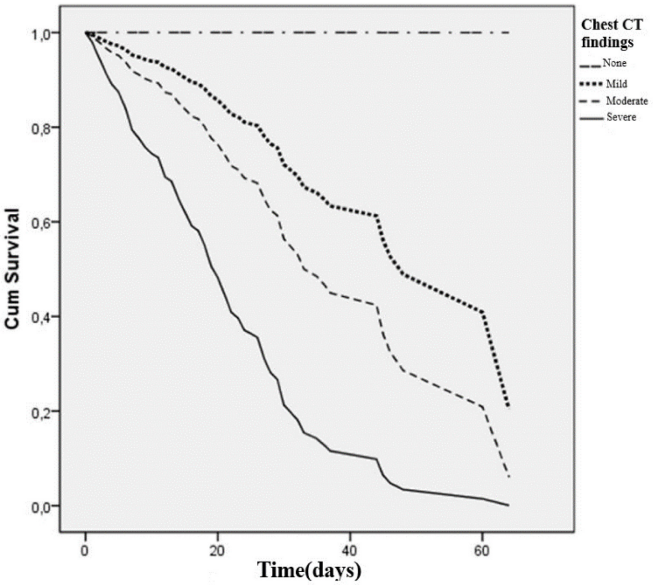
In the multivariate analysis, the most important factors affecting mortality were determined to be lung involvement (moderate-severe) ($p < 0.001$), hematological malignancy ($p = 0.01$, cancer), tumor stage ($p < 0.001$) and admission to ICU ($p < 0.001$) (Table 2).

When the length of stay in hospital and mortality rate were examined according to the severity of pneumonia, mortality was not observed in patients without pneumonia, and it was observed that as the severity of pneumonia increased, mortality was more frequent and occurred more rapidly (Figure 1).

The data of 1511 patients without cancer in the second wave were examined retrospectively. The comparisons of the demographic and clinical data of patients with and without cancer are shown in Table 2.

The rate of comorbid diseases such as hypertension, chronic obstructive pulmonary disease, and coronary artery disease was significantly greater in patients without cancer compared to those with cancer ($p < 0.05$). The severity of pneumonia on admission was determined to be more severe in patients without cancer ($p = 0.001$). The rate of admission to ICU was determined to be significantly higher in patients with cancer ($p = 0.001$). The mortality rate of patients without malignant disease was 8.76%, and this rate was approximately 4-fold higher at 38.8% in cancer patients.

Figure 1. The survival rates according to chest CT findings.



The comparisons of the demographic and clinical data of the cancer patients in the first and second waves are shown in Table 3. No statistically significant difference was determined between the age, gender, and types of cancer in the second wave of the pandemic ($p > 0.05$). In the tumour grading, stage IV was determined at a significantly higher rate in cancer patients in the second wave ($p = 0.001$). The rate of chemotherapy received in the previous 3 months was higher during the second wave, but the difference was not statistically significant ($p > 0.05$).

Table 2. Logistic regression analysis of the factors with an effect on mortality.

	p	OR	95% C.I.	
			Lower	Upper
Hematological-Non-hematological cancer	0.010**	0.151	0.036	0.638
Tumor stage	< 0.001**	7.024	2.498	19.749
Chemotherapy use (< 3 months)	0.689	0.831	0.335	2.061
CT findings (mild-moderate-severe)	< 0.001**	31.261	9.138	106.943
Hypertension	0.338	1.551	0.632	3.807
Admission to Intensive Care Unit	< 0.001**	49.667	18.865	130.810

** A *p*-value of less than 0.05 is accepted as being statistically significant.

Table 3. Differences in the characteristics of patients with malignant diseases in the first and second waves of the pandemic.

	First wave of the pandemic (n=66)	Second wave of the pandemic (n=216)	*p*
Gender			
Male (%)	40 (60.6)	139 (64.35)	0.580[a]
Female (%)	26 (39.4)	77 (35.65)	
Age Mean	62.09 ± 10.5	62.05 ± 12.98	0.982[a]
Median	32-81 (62)	18-97 (64)	
Cancer class			0.402[a]
Gastrointestinal (%)	19 (28.8)	58 (26.8)	
Lung (%)	7 (10.6)	41 (19)	
Genitourinary (%)	12 (18.2)	31 (14.3)	
Breast (%)	11 (16.7)	21 (9.7)	
Others (%)	8 (12.1)	31 (14.4)	
Hematological (%)	9 (13.6)	34 (15.7)	
Tumor stage (Non-hematological cancer)			0.001[a**]
Stage I-III (%)	51 (77.3)	104 (48.1)	
Stage IV (%)	15 (22.7)	112 (51.9)	
Chemotherapy received within the last 3 months			0.063[a]
No (%)	44 (66.7)	119 (55.1)	
Yes (%)	22 (33.3)	97 (44.9)	
Comorbidites			
Diabetes mellitus (%)	24 (36.4)	57 (26.4%)	0.117[a]
Hypertension (%)	31 (47)	71 (32.9%)	0.037[a**]
Chronic obstructive pulmonary disease (%)	17 (25.8)	34 (15.74%)	0.064[a]
Coronary artery disease (%)	2 (3)	15 (6.9)	0.242[a]
Chronic kidney disease (%)	7 (10.6)	11 (5.1%)	0.109[a]
Cerebrovascular disease (%)	5 (7.6)	9 (4.2%)	0.264[a]
Hospital length of stay, median (days)	1-39 (9)	1-80 (11)	0.044[c**]
Pneumonia severity (%)			0.371[a]
Mild	35 (55.6)	104 (49.5)	
Moderate	18 (28.6)	55 (26.2)	
Severe	10 (15.9)	51 (24.3)	
Admission to Intensive Care Unit	16 (24.2)	78 (36.1%)	0.073[a]
Mortality	15 (22.7)	84 (38.9%)	0.016 [a**]

[a] Chi-square test, [b]Student's t-test [c] Mann Whitney U-test; ** A *p*-value of less than 0.05 is accepted as being statistically significant.

Table 4. Clinical and demographic characteristics of the non-malignant and malignant groups.

	Second wave of non-malignant diseases (n=1511)	Second wave of malignant diseases (n=216)	*p*
Sex			
Male (%)	879 (58.17%)	139 (64.35)	0.080[a]
Female (%)	632 (41.83%)	77 (35.65)	
Age Mean	60.12 ± 14.73	62.05 ± 12.98	0.890[b]
Median	21-103 (63)	18-97 (64)	
Comorbidites			
Diabetes mellitus (%)	503 (33.28%)	58 (26.85%)	0.058[a]
Hypertension (%)	726 (48.04%)	72 (33.33%)	0.001[a**]
Chronic obstructive pulmonary disease (%)	62 (4.1%)	34 (15.74%)	0.001[a**]
Coronary artery disease (%)	217 (14.36%)	16 (7.41)	0.005[a**]
Chronic kidney disease (%)	67 (4.43%)	11 (5.09%)	0.662[a]
Cerebrovascular disease (%)	53 (3.5%)	9 (4.16%)	0.626[a]
Hospital length of stay, median (day)	1-48 (7)	1-80 (11)	0.062[c]
Pneumonia severity (%)			0.001[a**]
Mild	335 (22.1%)	104 (48.14%)	
Moderate	727 (47.92%)	55 (26.19%)	
Severe	455 (29.98%)	51 (23.61%)	
Admission to Intensive Care Unit	164 (10.81%)	78 (36.11%)	0.001[a**]
Mortality	133 (8.76%)	84 (38.88%)	0.001[a**]

[a] Chi-square test, [b]Student's t-test, [c]Mann Whitney U-test; ** A *p*-value of less than 0.05 is accepted as being statistically significant.

Among the comorbidities affecting mortality, hypertension was determined to be significantly high in the first wave ($p = 0.037$), and no significant difference was determined in the other comorbidities ($p > 0.05$). The mortality rate was 22.7% in the first wave and increased significantly to 38.9% in the second wave ($p = 0.016$).

Discussion

The results of this study of COVID-19-related deaths of cancer patients showed a mortality rate of 35.1% during the first and second waves of the pandemic. The mortality rate was seen to be highest in patients with hematological malignancy and lung cancer. In other studies, the mortality rate of cancer patients has been reported as 33.3% by Garassino *et al.* [13], 33.1% by Melo *et al.* [22], 28% by Mehta *et al.* [14], 20% by Tian *et al.* [29], 24% by Luo *et al.* [30], 15% by Barlesi *et al.* [21], and 12.4% by Fernandes *et al.* [20]. Considering the variations in the populations examined and differences in viral strains, no conclusion can be drawn from the differences between studies.

In the current study population, the mortality rate was seen to be 2.5-fold greater in hematological malignancies than in solid tumours, and this rate was 2-fold greater than the rate reported in the study by Fernandes *et al.* [20], and 1.5-fold greater than that of Lee *et al*. [27]. The reason for the high mortality rate of patients with hematological malignancy was thought to be immunosuppression associated with intense treatment with myelosuppression.

Among the cancer patients with solid tumours, those with lung involvement (primary lung cancer or cancer metastasis of the lungs) have less defence against COVID-19, and several studies have reported mortality to be greater in these patients, similar to the findings of the current study [12,21,22,30-33].

In patients with lung cancer, reduced lung function can contribute to worse outcomes. In addition, whatever the disease stage, abnormal ACE2 expression is seen in lung carcinoma compared to normal tissues and this renders this patient population more defenceless against COVID-19 [32,34].

Consistent with the findings of the current study, other studies have determined no significant difference in the mortality rates of those who had recently received chemotherapy [16,19,35,36]. However, some studies have reported that having received chemotherapy is associated with an increased risk of mortality [13,21,23,27].

In the current study, no significant difference was determined in the mortality rates of patients who had received chemotherapy in the previous 3 months. The reason that there was no increase in mortality was due to the fact that in accordance with recommendations, chemotherapy doses were reduced during the pandemic to avoid potential myelosuppression, and prophylactic G-CSF (granulocyte colony stimulating factor) was applied after chemotherapy to suitable patients [37,38]. These changes were probably started in a rational way during an acute period of the pandemic, with little evidence to support them. Since there is insufficient evidence, there have been very few studies defining the individual risk for cancer patients taking the primary tumour subtype, age, and gender into consideration.

It is thought that low-dose chemotherapy administered to reduce immunosuppression in patients could cause an increase in cancer grades. In the light of this information, although low-dose chemotherapy aims to reduce the severity of COVID-19 by preventing immunosuppression, there is an increase in mortality because of the involvement of the whole system as a result of the progression of the malignant disease. Moreover, at the onset of the pandemic during the first wave, there was a temporary halt to screening services and reduced access to cancer facilities, and therefore, insufficient diagnosis and treatment may have caused progression of clinical stage in patients.

The higher mortality rates in geriatric patients with COVID-19 may be due to their less effective immune response [39,40]. Previous studies of cancer patients have associated advanced age with mortality [20,22,27,41], but in the current study no significant difference was determined.

Studies which have examined gender have reported higher mortality rates in male cancer patients [15,25]. In the current study, although mortality was higher in males, as reported in previous studies [14,20,22], no statistically significant difference was observed between the genders in respect of COVID-19-related mortality. Sex hormones are believed to play an important role in the immune response, and oestrogen is known to have an immune strengthening effect. However, there is a need for further studies to evaluate the interactions of COVID-19 and androgens [42].

Thoracic involvement on CT was seen to be related to disease severity in the current study patients, and mortality has been previously reported to be higher in those with severe involvement on CT [19,32,43]. Since almost all of the current study patients presented with pneumonia, thoracic involvement on CT was very important in the prediction of disease severity and general survival. The criteria for hospital admission in Turkey [44] are that patients with a poor prognostic

measurement in blood tests or severe pneumonia should be admitted and treated. The high mortality rate of patients with hematological malignancy and lung involvement determined as a result of this study suggests that these patients would be suitable for in-patient follow-up and treatment.

Patients with cancer have a higher mortality rate than patients without cancer [15,23,45,46]. Patients without cancer have more comorbidities, although mortality is higher in cancer patients.

Conclusions

In conclusion, three main strategies should be implemented for the management of cancer patients during the COVID-19 pandemic.

The first of these is that COVID-19 vaccination follow-up is important in cancer patients. Although it is thought that the efficacy of the vaccine may be reduced in some viral mutations, it is largely unknown how cancer patients will ultimately respond to these types of preventative measures.

The second strategy is that personal protective measures must be taken by healthcare personnel and cancer patients to prevent cross-infection, and a PCR sample for surveillance purposes must be taken from every patient admitted to a clinic or starting chemotherapy. The emergence of SARS-CoV-2 requires unprecedented interventions to control the spread of infection and protect the most vulnerable in society. There has been an increase in infection-sensitive cancer patients and the use of antibiotics in ICU in particular. Despite the focus on hand hygiene, the COVID-19 pandemic has caused a relaxation in antimicrobial management policies. Continuous efforts must be made against the threat of long-term global antimicrobial resistance on the antimicrobial resistance rates of the adverse outcomes of these changes [47].

Thirdly, although delaying adjuvant chemotherapy, reducing the dose, and administration in combination with oral agents aim to reduce patient visits to hospital, it is clear that the oncology community may be facing an unknown threat for many years as the duration of the pandemic is unknown with ongoing viral mutations. Therefore, careful selection of patients is required for the continuation of cancer screening; and cancer treatments not to be interrupted, although they can be admininistered in combination with oral agents.

This study has some limitations. The study was conducted in a single centre, and the laboratory and mutation analysis data of the patients were not included. In addition, since the patient group included many types of malignant disease, it was difficult to interpret and analyze a certain type of malignant disease due to the low number of patients.

Authors' Contributions

RK, GSE, KKY and DT were responsible for the study concept, design and statistical analysis. RK, GSE, IKA were responsible for the literature search, analysis and interpretation of data and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RK, GSE, KKY, IKA, MB and DT were responsible for the data acquisition. RK, GSE, KKY and DT were responsible for critical revision of the manuscript for important intellectual content. RK, GSE, KKY, IKA, MB and DT were responsible for drafting the manuscript.

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Conflict of interests: No conflict of interests is declared.