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Research Article

Course and Consequences of COVID-19 Infection in Cancer Patients: Single-Center Experience

Gokhan Karakaya,[1] Sevki Peduk,[2] Gokhan Tazegul[3]

[1]Department of Medical Oncology, Mardin State Hospital, Mardin, Turkey
[2]Department of Surgical Oncology, Mardin State Hospital, Mardin, Turkey
[3]Department of Internal Medicine, Ankara Polatlı Duatepe State Hospital, Ankara, Turkey

Abstract

Objectives: Herein, we aimed to contribute to the literature on our single-center experience of the course and consequence of COVID-19 infection on cancer patients, presenting the demographic characteristics, clinical course, mortality rates, and the laboratory parameters of cancer patients infected with COVID-19.

Methods: Demographic and clinical characteristics, non-cancerous comorbid diseases, treatment modalities for cancer and COVID-19 infection, laboratory tests including blood counts and serum biochemistry, inflammatory markers, and thoracic CT scans were evaluated.

Results: A total of thirty-eight patients infected with COVID-19 confirmed with a positive nasopharyngeal swab polymerase chain reaction (PCR) were identified, and their data were included in the final analysis. The mortality rate due to COVID-19 infection was 26.3%. All deaths were observed in metastatic patients. The neutrophil-to-lymphocyte ratio (NLR) was higher in cancer patients with COVID-19 mortality (p=0.0003). C-reactive protein (CRP) and d-dimer values were higher in cancer patients who died due to COVID-19 as well (p=0.04 and 0.018, respectively). Of cancer patients infected with COVID-19, 57.9% had delays in cancer treatment and 73.7% had delays in follow-up appointments. The median delay time was 25 days (range: 7-63 days). Cancer progression was observed in 7.9% of patients due to delays in follow-up appointments caused by COVID-19 infection.

Conclusion: Both COVID-19 and cancer are severe life-threatening diseases, and mortality rates are much higher in cancer patients. Metastatic disease and increased inflammatory markers are associated with COVID-19 associated mortality in cancer patients. Additionally, COVID-19 infection results in delays in treatment and follow-up of cancer patients. This also resulted in disease progression. Further studies are needed to identify the best treatment modalities for the at-risk cancer patient population and reduce delays in treatment and follow-up of cancer patients infected with COVID-19.

Keywords: Cancer, Coronavirus disease-2019, COVID-19, mortality, respiratory syndrome, symptoms

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COVID-19 infection, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), quickly became a global crisis. The World Health Organization considered COVID-19 infection a pandemic shortly after the first case was seen in Wuhan, China, in December 2019 (WHO).[1,2]

The disease course of individuals infected with SARS-CoV-2 is very diverse. Most people appear to have only mild symptoms or no symptoms but actively carry and spread the virus. However, it has been shown that severe symptoms occur in some individuals, and clinical condi-

Address for correspondence: Gokhan Karakaya, MD. Mardin Devlet Hastanesi Tıbbi Onkoloji Anabilim Dalı, Mardin, Turkey
Phone: +90 544 884 61 87 **E-mail:** g.karakaya87@gmail.com

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tions such as respiratory failure, cytokine release syndrome, and multiple organ failure develop. COVID-19 infection has been shown to have a high risk of morbidity and mortality, including elderly patients, patients of male gender (compared to women), and patients with comorbidities such as hypertension, chronic lung disease, diabetes, and cancer.[3]

Patients with cancer are thought to have a worse prognosis and a higher risk of infection, considering that most cancer patients are of advanced age, that they often have comorbid diseases and immunosuppression caused by the cancer treatments.[4] It is of great importance to be able to determine the risk factors, clinical course, and the effect of COVID-19 infection on the prognosis of cancer in this specific patient population and to reveal its results considering the rapid spread of COVID-19 infection and its results and the prevalence of cancer in the world.

Herein, we aimed to contribute to the literature on our single-center experience of the course and consequence of COVID-19 infection on cancer patients, presenting the demographic characteristics, clinical course, mortality rates, and the laboratory parameters of cancer patients infected with COVID-19.

Methods

Patient Population

Permission was obtained from Mardin State Hospital and Republic Of Turkey Ministry Of Health management for the use of patient data. This study was conducted according to the ethical principles of the Declaration of Helsinki. The data of patients followed up by the Medical Oncology Clinic of [censored] State Hospital and diagnosed with cancer were retrospectively analyzed. All adult patients (≥18 years of age) diagnosed with malignant tumors according to histopathological diagnosis were included in the study among patients diagnosed with COVID-19 infection between March and December 2020. Patients with benign tumors were excluded. Overall, there were forty-two patients with COVID-19 infection. Four patients with clinical findings and computerized thoracic tomography (CT) results suggesting COVID-19 infection with a negative nasopharyngeal swab polymerase chain reaction (PCR) were excluded from the study. A total of thirty-eight patients infected with COVID-19 confirmed with a positive nasopharyngeal swab polymerase chain reaction (PCR) were identified, and their data were included in the final analysis.

Demographic and clinical characteristics, non-cancerous comorbid diseases, treatment modalities for cancer and COVID-19 infection, laboratory tests including blood counts and serum biochemistry, inflammatory markers, and thoracic CT scans were evaluated. Thoracic CT results were classified as "typical for COVID-19 infection", "other atypical findings," or "normal." The previous cancer treatments and data on COVID-19 infection diagnosis, follow-up, treatment, and hospitalization were accessed from patient files and the Republic of Turkey Ministry of Health Public Health Management System (HSYS). The severity of COVID-19 infection was determined using the CURB-65 score (confusion, blood urea >42,8 mg/dl, respiratory rate >30/min, blood pressure <90/60 mm Hg, age >65). Those with a CURB 65 score of zero and one were evaluated as mild, two as moderate, three as severe, and 4-5 as very severe. Patients who have received cancer treatment within four weeks of being diagnosed with COVID-19 infection were defined as "actively treated cancer patients." Patients who died within four weeks of being diagnosed with COVID-19 were considered COVID-19 infection-related deaths. Treatments for COVID-19 infection, including hydroxychloroquine (HCQ), favipiravir, and other therapies, were analyzed. Admission to the intensive care unit (ICU) and hospitalization status and length of stay were recorded. We also recorded whether the patients had any delays and length of delays for follow-up appointments or cancer treatments due to COVID-19 infection.

Statistical Analysis

SPSS for Windows version 23.0 was used for data analysis. Continuous variables are expressed as median (minimum-maximum), and categorical data are expressed as values and percentages. Chi-square tests and Fisher's exact test were used for categorical data, and Mann-Whitney-U tests were used for continuous variables in inter-group comparisons. The statistical significance limit was accepted as $p<0.05$ for all statistical tests.

Results

Thirty-eight cancer patients with confirmed COVID-19 infection by PCR tests were included in the final analysis. The mean age of the patients was 58 years (range: 37-78), and 55.3% of the patients were female. The most common types of cancer were breast cancer (42.1%), gastrointestinal (stomach, colon, pancreas) cancers (18.4%), prostate cancer (10.5%), gynecological cancers (10.5%), lung cancer (7.9%), and other cancers (10.5%). 55.3% of the patients had a comorbid disease, and 34.3% had multiple (two or more) comorbidities. The most common comorbidity was chronic obstructive pulmonary disease (COPD), which was found in 10.5% of the patients. 60.5% of the patients had metastatic disease, and 39.5% had local or locally advanced disease. 81.6% of the patients received active cancer treatment:

34.2% received cytotoxic chemotherapy, 7.9% received targeted biological agent only, 23.7% received combination (cytotoxic and biological agent), and 15.6% received hormonal treatment. 18.4% were being followed up in remission. There were no patients receiving immunotherapy.

The most common symptoms of COVID-19 infection in cancer patients were weakness and myalgia in 36.8% and shortness of breath in 28.9% of the patients. 13.2% of the patients presented with multiple (two or more) symptoms. Thoracic CT results revealed typical findings for COVID-19 in 63.2% and atypical results in 21.1% of the patients. The remaining 15.8% had normal CT results. 18.4% of the patients were asymptomatic, 39.5% had mild, 15.8% had moderate, 13.5% had severe, and 13.5% had very severe COVID-19 infection, according to the CURB-65 score. 63.2% of all patients required hospitalization for COVID-19 infection, and 21.1% of patients required hospitalization in the intensive care unit. 21.1% of all patients received favipiravir, 28.9% received HCQ, 36.8% received hydroxychloroquine and favipiravir, 13.2% received favipiravir, hydroxychloroquine and broad-spectrum antibiotics. 44.7% of the patients received systemic corticosteroids, and 63.2% of the patients received anticoagulant therapy.

Out of thirty-eight patients, twenty-eight (73.7%) survived, and ten (26.3%) died due to COVID-19 infection. The mortality rate due to COVID-19 infection was 26.3%. All deaths were observed in metastatic patients. Mortality was 0% in the local or locally advanced cancer patients and 43.4% in metastatic patients (p=0.0002, chi-square test, Figure 1). The mortality rate of hospitalization (37.5% vs. 7.1%) and intensive care hospitalization (75% vs. 13%) was higher as well (p=0.04 and p=0.002, respectively, chi-square test). Mortality rates due to COVID-19 were higher in patients with higher CURB-65 scores (4-5) (80% vs. 22%) (p=0.02, chi-square test). Mortality rates were similar between other subgroups (Table 1).

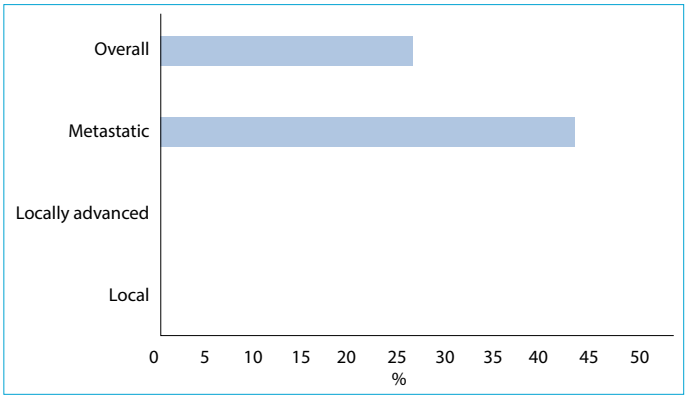

Figure 1. Mortality rates in cancer patients infected with COVID-19.

Table 1. Comparison of demographic characteristics of surviving cancer patients and patients who died due to COVID-19 infection.

	Alive, n (%)	Dead, n (%)	p
Age	57 (37-78)	62 (46-74)	0.66
Gender			
Female	18 (64.3)	3 (30)	
Male	10 (35.7)	7 (70)	0.06
Comorbidities			
No	12 (42.9)	5 (50)	
Yes	16 (57.1)	5 (50)	0.72
Diabetes	1 (3.6)	1 (10)	
Hypertension	1 (3.6)	1 (10)	
COPD	3 (10.7)	1 (10)	
Multiple	11 (39.3)	2 (20)	
Cancer type			
Lung	2 (7.1)	1 (10)	
Breast	14 (50)	2 (20)	
GI	6 (21.4)	1 (10)	
Prostate	2 (7.1)	2 (20)	
Gynecological	3 (10.7)	1 (10)	
Others	1 (3.6)	3 (30)	0.09
Stage			
Local	6 (21.4)	0 (0)	
Locally advanced	9 (32.1)	0 (0)	
Metastatic	13 (46.4)	10 (100)	0.002
Treatment status			
Active treatment	22 (78.6)	9 (90)	
Follow-up	6 (21.4)	1 (10)	0.39
Treatments			
Cytotoxic	8 (28.6)	5 (50)	
Targeted	3 (10.7)	0 (0)	
Combination (Cytotoxic and targeted)	6 (21.4)	3 (30)	
Hormonal treatment	7 (25)	1 (10)	
None or others	4 (14.3)	1 (10)	0.22

COPD: Chronic obstructive pulmonary disease; GI: Gastrointestinal.

Leukocyte and neutrophil values were higher in patients who died due to COVID-19 infection than those who survived (p=0.04 and 0.01, respectively, Mann-Whitney-U test). The neutrophil-to-lymphocyte ratio (NLR) was higher in cancer patients with COVID-19 mortality as well (p=0.0003, Mann-Whitney-U test). C-reactive protein (CRP) and d-dimer values were higher in cancer patients who died due to COVID-19 as well (p=0.04 and 0.018, respectively, Mann-Whitney-U test). Other laboratory parameters were similar between patients who died and survived (Table 2).

We also recorded whether the patients had any delays and length of delays for follow-up appointments or cancer treatments due to COVID-19 infection. 57.9% of cancer patients infected with COVID-19 had delays of a median of 25

Table 2. Comparison of laboratory parameters of surviving cancer patients and patients who died due to COVID-19 infection.

Parameter	Alive	Dead	p
Leukocyte (×103/μL)	5.26 (1.83-1.77)	7.42 (2.36-18.85)	0.04
Neutrophil (×103/μL)	3.62 (0.79-7.86)	5.53 (1.73-18.01)	0.01
Lymphocyte (×103/μL)	0.99 (0.34-3.29)	0.82 (0.25-2.45)	0.2
Neutrophil lymphocyte ratio	2.79 (0.81-13)	6.72 (1.16-72.04)	0.003
Albumin (g/dL)	4.15 (2.1-4.6)	3.5 (2.5-4.6)	0.06
Lactate dehydrogenase (U/L)	270 (109-504)	319 (195-1114)	0.18
C-reactive protein (mg/L)	17.25 (2.1-109)	86.5 (1.4-363)	0.04
D-dimer (μg/L)	513 (153-5530)	2710 (217-5480)	0.018
Ferritin (ng/L)	180 (28-1650)	434 (64-1704)	0.116

days (range: 7-62 days) in cancer treatment appointments. Additionally, 73.7% of the patients infected with COVID-19 had delays in follow-up appointments. The median control delay time was 25 days (range: 7-63 days). Cancer progression was observed in 7.9% of patients due to delays in follow-up appointments caused by COVID-19 infection.

Discussion

In this study, we aimed to report our single-center experience of COVID-19 infection on cancer patients. The 4-week mortality rate due to COVID-19 was 26.3% in these patients receiving cancer treatment in our center. There were several factors associated with COVID-19 mortality. The mortality rate was higher in patients requiring hospitalization and intensive care. All mortalities were reported in metastatic patients. Leukocytosis, neutrophilia, higher CRP, D-dimer, and NLR were associated with increased mortality. A higher CURB-65 score at hospital admission was also associated with increased mortality. Other factors such as cancer type, active treatment, comorbidities, gender and age, treatment for COVID-19 factors for cancer did not affect mortality rates. These results suggest that metastatic disease and high inflammatory markers are associated with COVID-19 mortality in cancer patients. Notably, a high proportion of cancer patients with COVID-19 had significant delays in treatment and follow-up appointments due to infection. Cancer progression was also observed in 7.9% of patients due to these delays. These results suggest a negative impact on the prognosis of cancer due to the COVID-19 infection of the patients.

Our study reported that the hospitalization rate was 63%, and the intensive care unit hospitalization rate was 21%. These results were much higher than those in the Chinese, MSKCC, and UKCMMP studies, but the mortality rates were similar.[5-7] The mortality rate of COVID-19 has been 4.4% worldwide since the onset of the pandemic.[8] Previous studies have shown that COVID-19-related mortality rates are higher in cancer patients compared to non-cancer counterparts. The mortality rate was 28.6% in cancer patients in China's first study.[5] In another study conducted by the Memorial Sloan Kettering Cancer Center, the mortality rate was 12%.[6] Lee et al.[7] reported a 28% mortality rate in patients with metastatic cancer and cancer treatment in the UKCCMP study. Giannakoulis et al. showed a nearly three-fold increase in mortality in cancer patients compared to non-cancer patients (13.5% vs. 5.1%).[9] The overall mortality rate due to COVID-19 determined by the Ministry of Health in Turkey in October 2020 was 2.67%.[10] In Turkey, a multicenter national study reported the mortality rate of COVID-19 infection with solid tumors as 5.1%, which is twice than the overall mortality rate.[11] Our reported mortality rate due to COVID-19 infection was 26.3%, relatively higher than previously published Turkish data. This difference may be due to several factors: (i) difference in sociocultural and socioeconomic levels of the region, (ii) rural localization of most of our patients, and (iii) a higher rate of metastatic patients in our study. The higher hospitalization rates may confirm this finding and suggest that our patients were symptomatic and may have admitted to the hospital late due to being located in rural areas.

Mortality rates in patients receiving active cancer treatment were similar to patients who did not receive treatment in our study. Additionally, there was no difference between cytotoxic, hormonal, or targeted treatment recipients in terms of death rates. These results are also supported by other large cohorts, including the Turkish cohort as well.[4,7,11,12] Therefore, it may not be appropriate to postpone or discontinue treatment due to the concern of COVID-19 infection in such a fatal disease, given the rates of cancer-related mortality. This is also supported by the fact that patients infected with COVID-19 are already under the risk of disease progression.

We observed that higher neutrophil, leukocyte, NLR, CRP, and d-dimer values were associated with higher mortality

rates. The association of an increase in inflammatory markers such as leukocytosis, neutrophilia, and elevated CRP with mortality is also supported by other studies in the literature.[5,13,14] However, d-dimer and inflammatory markers may increase due to cancer itself as well. Although increased NLR was associated with increased mortality risk in our study, there are conflicting results in the literature related to NLR. Prospective studies are needed to determine the prognostic significance of NLR and other markers in this instance.

Herein, we have also demonstrated that cancer patients infected with COVID-19 had significant delays in cancer treatment and follow-up appointments. Cancer progression was observed in 7.9% of patients due to delays in follow-up appointments caused by COVID-19 infections. Controversially, Akagunduz et al.[15] also demonstrated that 64% of the patients had a high coronaphobia score and 59% were noncompliant, as assessed by COVID-19 Phobia Scale (C19P-S). They have also demonstrated greater coronaphobia was associated with noncompliance with follow-up and treatment in cancer patients. Therefore, both being infected with COVID-19 and having coronaphobia negatively affects follow-up and treatment processes of cancer patients during COVID- 19 pandemic.

Our study's most important limitations were the retrospective and single-center nature of the study; hence, only a small number of patients could be included. The fact that we could not reach all laboratory results of the patients and included only PCR positive patients is also among our study's limitations. However, our study results were similar to the results of studies conducted with large patient populations in the literature. Besides, we examined whether COVID-19 infection was delayed in the treatment and control times of cancer patients in our study, and there are no extensive studies in the literature on this subject.

Conclusion

We presented the effect of COVID-19 on the clinical, demographic, laboratory parameters, and mortality rates of cancer patients who had COVID-19 infection and the treatment and control processes of cancer in our study. Both COVID-19 and cancer are severe life-threatening diseases, and mortality rates are much higher in cancer patients. Additionally, COVID-19 infection results in delays in treatment and follow-up of cancer patients. Well-planned, prospective observational studies are urgently needed to (i) identify the best treatment modalities in this specific patient group and (ii) to determine long-term results such as progression and response status of primary tumors and cancer-related mortality in patients infected with COVID-19.

Disclosures

Ethics Committee Approval: Work permission and data use permission was received from the republic of Turkey Ministry of Health and Mardin State Hospital Department on 02.04.2021, The Ethics Committee was not appliced because it is a retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – G.K.; Design – G.K.; Data collection &/or processing – S.P., G.K.; Analysis and/or interpretation – G.K., G.T.; Literature search – G.K.; Writing – G.K., G.T.; Critical review – S.P., G.K.

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