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RESEARCH ARTICLE

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The demographic characteristics, prognosis, and relationship with cancer subtypes of hospitalized COVID-19 patients with malignancy: A single-center experience

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Abstract

Undoubtedly, cancer patients have suffered the most from the COVID-19 pandemic process. However, cancer is a heterogeneous disease, and each patient has responded differently to COVID-19. We aimed to describe the clinical characteristics and outcomes of patients with cancer and COVID-19. We retrospectively reviewed 45 cancer patients hospitalized in the Cerrahpaşa Medical Faculty COVID-19 department from March 23 to October 23, 2020. We analyzed the demographic characteristics, symptoms, laboratory findings, treatment, prognosis, and cancer subtypes of patients and mortality who were hospitalized for COVID-19. Between March 23 and October 23, 2020, 45 hospitalized cancer patients who had laboratory-confirmed COVID-19 infection were included, with a median age of 60 years (range: 23–92). Patients were divided into two groups a survivor and a non-survivor. Symptoms, demographic information, comorbidities, treatments for COVID-19, and laboratory findings of the two groups were evaluated separately. Two parameters were found, which showed a significant difference between non-survivors and survivors displaying a disadvantage for COPD and low platelet count ($p = 0.044$–0.038). The mortality rate of all patients was 66%. The presence of comorbidities such as COPD and low platelet count in cancer patients with COVID-19 infection may draw the attention of physicians.

KEYWORDS

cancer patients, COVID-19, SARS-CoV-2

1 | INTRODUCTION

COVID-19 was first detected in December 2019 in Wuhan city of China. It affected the whole world quickly and turned into a pandemic, and it has caused severe acute respiratory syndrome and death in some patients. As of January 30, 2021, 101,561, 219 cases have been confirmed worldwide with 2,196,944 deaths.[1]

Patients with comorbidities such as hypertension, diabetes, chronic lung disease, immunosuppression, and cancer have increased mortality with COVID-19.[2] Patients with cancer have been reported to require high intensive care unit levels and have an increased risk

of death.[3] However, cancer consists of a heterogeneous group with many subtypes and stages. Therefore, the cancer subtype and stage are essential determinants of COVID-19 prognosis.[4] There was no doubt that terminal cancer patients would suffer the most significant damage from the pandemic process.

We collected and analyzed data from patients with cancer and COVID-19 hospitalized at Cerrahpaşa Medical Faculty in Istanbul, Turkey. We aimed to describe the clinical features and outcomes of patients with cancer diagnosed with COVID-19 and hospitalized and identified the risk factors associated with in-hospital mortality.

2 | METHODS

We retrospectively reviewed 45 cancer patients hospitalized in the Cerrahpaşa Medical Faculty COVID-19 department from March 23 to October 23, 2020. We analyzed the demographic characteristics, prognosis, and cancer subtypes of patients who were hospitalized for COVID-19.

The diagnosis COVID 19 was made based on WHO criteria and confirmed by reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swab specimens.

The inclusion criteria were based on pathological diagnosis of a malignant tumor and laboratory confirmation of COVID-19 infection. The patients included were followed up in our medical oncology department. Patients were included in the study regardless of the hospital stay. Cancer patients diagnosed with COVID-19 but not hospitalized were not included in the study. Patients who could not be found to be RT-PCR positive and who could not be reached in the medical oncology follow-up file were omitted (Figure 1). There was no sample size determination, and all patients meeting the inclusion criteria were recruited. The cut-off date for our study was November 1, 2020.

Ethics approval was obtained from Istanbul University Cerrahpaşa-Cerrahpaşa Medical Faculty, Turkey, at the beginning of the study. We also received an approval letter from the Ministry of Health of Turkey.

We obtained information about demographic data, clinical manifestations, cancer subtypes, laboratory findings, chest computed tomography (CT) examinations, treatment, and outcomes of all enrolled patients from the hospital database.

The SPSS (Statistical Package for the Social Sciences) for the 22.0 Windows program was used for statistical analyses. Student's *t*-test and Mann–Whitney *U* test were used for intergroup comparison of regular and not normally distributed data for quantitative analyses of the data. Differentiation in demographic and clinical characteristics, laboratory findings, and COVID-19 symptoms between living and deceased patients were analyzed by Chi-Square and Fisher's exact tests. Multivariate Cox proportional hazards models were used to analyze the prognostic impact of clinical parameters.

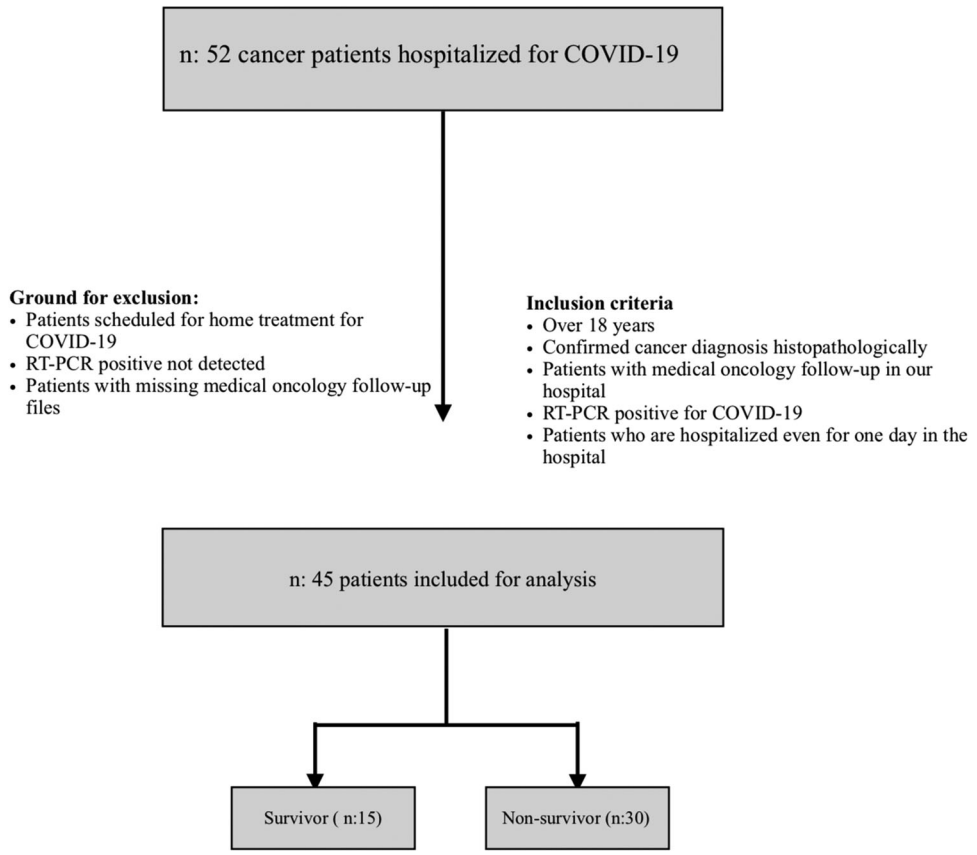

FIGURE 1 Flow diagram of patient inclusion and exclusion

The Kaplan–Meier log-rank test was used for survival analysis. Results were evaluated within a 95% confidence interval and at a significance level of $p < 0.05$.

3 | RESULTS

Fifty-two patients with active cancer hospitalized in the Cerrahpaşa Medical Faculty COVID-19 departments with documented SARS-CoV-2 infection were registered in the hospital database from March 11, 2020. Seven patients were excluded from the study because their documentation on cancer treatments was missing. The median age of the remaining 45 patients was 60 years. Twenty-three (51%) of 45 patients were men, and the median age was 66 years. Twenty-two (49%) of 45 patients were women, and the median age was 54 years. There was no difference in survival between men and women ($p = 0.67$). Six (%13) of the patients were actively smoking. Only 1 out of the smoker patients survived COVID-19 infection. Most of the patients had metastatic disease ($n = 38$, 85%). Two patients had stage 2 cancer, and both survived. Seventeen (77%) of women had stage 4 disease and this rate was 83% ($n = 19$) in male patients. Nevertheless, only 26% of patients ($n = 10$) with stage 4 survived. Seven (70%) of stage 4 surviving patients were men and 3 (30%) of them were women.

The most frequent cancer subtype was lung cancer ($n = 12$, 26%). According to cancer subtypes, the distribution of patients is shown in Table 1. Twenty-two patients (48%) were receiving treatment actively for the last 4 weeks when COVID-19 was diagnosed. One of them was receiving immunotherapy (nivolumab), and one was receiving tyrosine kinase inhibitor (sunitinib), and the remaining 20 patients had received cytotoxic chemotherapy in the last 4 weeks. Although 15 patients had an active cytotoxic treatment plan, their chemotherapy was interrupted in the last 4 weeks, and they could not receive it. The remaining eight (28%) patients were not receiving oncological treatment, and two (4%) of them were being followed up without treatment because they had stage 2 disease. Six (13%) of them were terminal cancer patients and were receiving palliative care.

Fatigue and dyspnea were the most common symptoms, followed by fever and cough. More than half of the patients had comorbidities, including chronic obstructive pulmonary disease, diabetes, hypertension, coronary heart disease, and asthma (Table 2). No significant differences in all comorbidities except COPD were observed between survivors and non-survivors. The mortality rate was significantly higher in hospitalized cancer patients with COPD ($p = 0.044$).

Laboratory findings of all patients at the first diagnosis are given in Table 3. Radiological findings are thorax CT at the time of initial diagnosis. Thoracic CT of 12 (27%) patients was not compatible with COVID-19. A total of 33 (73%) patients with available radiological data showed unilateral/bilateral inflammatory infiltration or ground-glass opacities. There was no significant difference in radiological findings between survivors and non-survivors. Compared with survivors and non-survivors, no significant differences were detected in all laboratory results except thrombocytopenia. We found a significantly lower platelet count between non-survivors and survivors, displaying a disadvantage for COPD and low platelet count ($p = 0.038$).

Of the 45 patients included, $n = 30$ (63%) received hydroxychloroquine, $n = 25$ (53%) received azithromycin, $n = 26$ (58%) received oseltamivir, $n = 33$ (73%) received favipiravir, and $n = 5$ (11%) patients received tocilizumab. Corticosteroids were given to 25 (53%) patients. Therapeutic plasma exchange treatment was not used for any patients. Noninvasive mechanical ventilation was applied to $n = 5$ (11%), and invasive ventilation was applied to $n = 23$ (51%) of 45 patients. Compared with survivors and non-survivors, it was observed that the treatments were not significantly different from the two groups. The median length of stay in the hospitalization days for the 45 patients was 14 (minimum 1 day, maximum 76 days). Intensive care unit was necessary for 26 (58%) patients and the median length of stay in the intensive care unit was 11 days (minimum 1 day – maximum 70 days).

TABLE 1 Cancer subtypes of hospitalized cancer patients

Cancer type	*N*	Percantage (%)
Lung cancer	**13**	**28.8**
Adenocarcinoma	5	11
Squamous carcinoma	4	8
Small cell carcinoma	2	4
NOS	2	4
Gastrointestinal cancer	**14**	**31**
Colorectal carcinoma	6	13.3
Ampulla Vateri carcinoma	1	2
Pancreas carcinoma	1	2
Stomach carcinoma	5	11
Esophagus carcinoma	1	2
Breast cancer	4	8
Gynecological cancer	**4**	**8**
Ovarian carcinoma	3	6.6
Cervical carcinoma	1	2
Urogenital cancer	**5**	**11**
Renal cell carcinoma	2	4
Bladder carcinoma	1	2
Prostate carcinoma	2	4
Others	**5**	**11**
Mesothelioma	2	4
Carcinoma of unknown primary	1	2
Sarcoma	1	2
Thyroid carcinoma	1	2

TABLE 2 Demographics and baseline characteristics of hospitalized patients

	All patients (n = 45)	Survivor (n = 15)	Non-survivors (n = 30)	p
Age years[a]	60.3 ± 15.65	61.8 ± 15.6	59.6 ± 15.9	0.65[b]
≤40	5 (11%)	1 (7%)	4 (13%)	0.77[c]
41–60	17 (38%)	5 (33%)	12 (40%)	
61–80	19 (42%)	7 (47%)	12 (40%)	
≥80	4 (9%)	2 (13%)	2 (7%)	
Sex				
Female	22 (49%)	8 (53%)	14 (47%)	0.67[c]
Male	23 (51%)	7 (47%)	16 (50%)	
Symptoms				
Fatigue	40 (89%)	12 (80%)	28 (93%)	0.31[c]
Dyspnea	39 (87%)	12 (80%)	27 (90%)	0.38[c]
Fever	34 (75%)	12 (80%)	22 (73%)	0.72[c]
Cough	19 (42%)	3 (20%)	16 (53%)	0.03[c]
Headache	12 (27%)	7 (47%)	5 (17%)	0.07[c]
Myalgia	13 (29%)	4 (27%)	9 (30%)	1.00[c]
Arthralgia	3 (7%)	2 (13%)	1 (3%)	0.25[c]
Comorbidities				
Hypertension	11 (24%)	6 (40%)	5 (17%)	0.14[c]
Diabetes	9 (20%)	4 (27%)	5 (17%)	0.45[c]
COPD	15 (33%)	2 (13%)	13 (43%)	0.04[c]
Coronary heart disease	8 (19%)	4 (27%)	4 (14%)	0.41[c]
Chronic kidney disease	3 (6%)	2 (13%)	1 (3%)	0.25[c]
Asthma	3 (6%)	1 (7%)	2 (7%)	1.00[c]

[a]Parametric variables.
[b]Student t-test.
[c]Chi-square test.

4 | DISCUSSION

Patients with cancer are a fragile population in the COVID-19 pandemic.[5] They are at high risk of infection and have higher severe morbidity and increased mortality once diagnosed with COVID-19.[6] We know that some studies describe the clinical features, outcomes, and risk factors for mortality in patients with cancer and diagnosed with COVID-19.[7] However, studies on cancer patients hospitalized for COVID-19 are limited. This article aimed to explain the demographic characteristics, symptoms, prognosis, treatments, and relationship with cancer subtypes of hospitalized cancer patients by comparing them with surviving and non-surviving patients. Cancer patients diagnosed with COVID-19 and hospitalized on March 11, 2020, were included in this study. Patients with symptoms necessitating follow-up in the hospital were hospitalized considering risk factors. Previous studies have found several risk factors for severe illness related to COVID-19 and mortality. Wu et al.[8] found that older age and more comorbidities were associated with a higher risk of severe pneumonia and mortality in patients infected with COVID-19. Older age was not a risk factor for mortality in our study. This condition could be because of evaluating elderly patients mostly (median age 60 years). Regarding underlying diseases, 67% of patients in our study had at least one comorbid disease. We found that COPD was associated with a higher risk of mortality. The mortality rate in patients diagnosed with COPD was 87%. The mortality rate in patients diagnosed with COPD was statistically significant compared to survived and non-survived (p = 0.044).

The majority of patients have presented with fever and cough in many studies on COVID-19 but different from our study, dyspnea and fatigue were the most common clinical manifestations among patients with COVID-19.[9] We found unilateral or unifocal/bilateral lung lesions in 73% of patients with available records. This rate was higher than that of the general population. In the study of Wu et al.,[10] bilateral lung involvement in the general population was 59%, unifocal involvement was 7% and multifocal lung involvement was 69%. In this data set, the proportion of cancer patients was only 2%.[10]

There is no difference in survival between men and women in our study, but Yang et al.[11] found men were at a higher risk of mortality than women among COVID-19 patients. Many studies are showing that mortality is higher in male patients. In our study, there was no statistically significant difference in survival between men and women (p = 0.67). However, when the survival rates of stage 4 patients were examined, it was seen that this rate was higher in male patients. Ten of the stage 4 cancer patients survived and 7 (70%) of them were men. Although the stage 4 cancer rate in males is 83%, it has not created a disadvantage for survival when compared to women.

In our study, 22 patients (48%) were receiving active treatment when COVID-19 was diagnosed. Moreover, almost all of them were on cytotoxic chemotherapy and had been treated in the last 4 weeks. We found that cytotoxic chemotherapy within 4 weeks before symptom onset was associated with an increased risk of mortality. The mortality rate was 90% in the group that received cytotoxic chemotherapy in the last 4 weeks and 40% in the group that did not. Nevertheless, Jacoba et al. did not detect an increase in mortality in patients receiving this treatment in their cohort. Jacoba et al. found that chemotherapy could decrease the inflammation associated with higher mortality in COVID-19 as an unexpected outcome.[12] Although molecular-targeted therapy rarely impairs patients' immunity, we had one patient who received tyrosine kinase inhibitors and severe bilateral pneumonia developed in this patient. Besides this, bilateral lung fibrosis developed in one patient who received immunotherapy. Both of these patients did not survive. Due to the small number of patients in our study who received

TABLE 3 Laboratory findings of hospitalized cancer patients with COVID-19

	All patients ($n = 45$)	Survivors ($n = 15$)	Non-survivors ($n = 30$)	p
Laboratory finding				
White blood cells, ×10 cells per L[a]				
Median	7000 (4400–12 350)	6600 (4200–8600)	7500 (4425–13 000)	0.35[b]
≤4	10	3	7	0.27[c]
4–10	23	10	13	
≥10	12	2	10	
Neutrophils, ×10 cells per L[a]				
Median	4800 (3000–9350)	4500 (3200–7200)	4950 (2950–11 000)	0.50[b]
≤2	9 (20%)	3 (20%)	6 (20%)	1[c]
Lymphocytes, ×10 cells per L[d]				
Mean	871.11 ± 408.77	960 ± 311.2	826 ± 447.9	0.30[e]
≤1	28 (62%)	10	18	0.66[c]
Platelets, ×10 cells per L*				
Mean	195 ± 125.19	192.8 ± 81.2	196.3 ± 143.4	0.93[e]
≤100	12	1	11	0.038[c]
Mean hemoglobin, g/L[d]	9.89 ± 2.01	10.9 ± 2.2	9.4 ± 1.7	0.019[e]
≤8	8 (18%)	1 (7%)	7 (23%)	0.23[c]
Neutrophil to lymphocyte ratio ≥ 4	30 (67%)	9 (60%)	21 (70%)	0.5[c]
Mean albumin, g/L[d]	2.98 ± 0.44	3.23 ± 0.41	2.86 ± 0.40	0.005[e]
Lactate dehydrogenase ≥ 245 U/L	32 (71%)	10 (67%)	22(73%)	0.73[c]
Creatine kinase ≥ 185 U/L	11 (24%)	3 (20%)	8 (27%)	0.76[c]
D-dimer ≥ 0.5 mg/L	43 (96%)	13 (87%)	30 (100%)	0.10[c]
Mean C-reactive protein, mg/L[d]	137.97 ± 91.58	85 ± 68	164 ± 91	0.006[e]

[a]Non-parametric variables; median and interquartile range (lower quartile – upper quartile).
[b]Mann–Whitney *U* test.
[c]Chi-square test.
[d]Parametric variables.
[e]Student *t*-test.

immunotherapy and tyrosine kinase inhibitor before the onset of COVID-19, we could not analyze the effect of immunotherapy and tyrosine kinase inhibitor on patient outcomes.

There was no significant difference in the laboratory findings except for thrombocytopenia. Platelet count was significantly lower in the group that could not survive compared to survivors ($p = 0.038$). Platelets are critical immune cells, which play an essential role in hemostasis, coagulation, inflammatory response, and tumor biology.[13,14] Talla et al. showed that severe infections and immune-related factors cause secondary thrombocytopenia characterized by rapid platelet decline.[14] There are two hypotheses regarding thrombocytopenia in patients with COVID-19: The first is that coronaviruses were directly leading to hematopoietic inhibition.[15] The second is that the lung may be one of the organs in which mature megakaryocytes release platelets. Thrombocytopenia may be associated with lung damage in COVID-19 patients.[16] In our study, 27% of the patients had thrombocytopenia. This rate was found to be similar to those in studies on COVID-19 and the platelet relationship.[17]

COVID-19 vaccine studies are giving good results. However, treatment options are limited including antiviral treatment, antibiotics, steroids, and immune-modulator drugs. In our study compared with survivors and non-survivors, it was observed that the treatments were not significantly different from the two groups. John et al. found that tocilizumab was not adequate for preventing intubation or death in moderately ill hospitalized patients with COVID-19.[18] These results were similar to those of our study. In our study, approximately 11% of the patients received tocilizumab, and we found that 80% of the patients who received tocilizumab did not survive.

Our patients had a high mortality rate, with 66% deaths. When evaluated in two groups such as lung cancer and nonpulmonary cancers, no significant overall survival was found between them. The subgroup analysis was examined in more detail and divided into six groups (lung, gastrointestinal, breast, urogenital and gynecological, and other malignancies). There was no significant difference in survival between the six subgroups. The sample could not show a normal distribution due to the small number of patients.

In the study of Lennard et al., cancer subgroup analysis was performed. Unlike our study, hematology patients were also included. A significantly high mortality rate was observed in patients diagnosed with leukemia.[19] However, no difference in survival was found between the groups in the subgroup analysis performed among those with solid tumors. This was similar to our study findings.

Our study had some limitations; the number of hospitalized cases was low. The sample size was too small to derive any firm conclusions. Additionally, we did not compare the characteristics, outcomes, and treatment strategies of patients with cancer against a control group of non-solid tumors.

In conclusion, cancer patients hospitalized for COVID-19 require special attention as they are a fragile population with a much higher case-fatality rate than the general population. Having a comorbidity that causes lung damage, such as COPD, and having a low platelet count in the laboratory are two indicators that might help us to identify patients with cancer at high risk of fatal outcomes.

AUTHOR CONTRIBUTIONS

Fuat H. Demirelli, Ezgi Değerli, and Sümeyra Derin conceived and designed the study. Şahin Bedir, Gülin Alkan, and Nihan Şentürk Öztaş collected samples and ran experiments. Nilay Şengül Samancı and Emir Çelik performed data acquisition and collection. Ezgi Değerli, Kerem Oruç, and Sümeyra Derin did data analysis. Ezgi Değerli, Nilay Şengül Samancı, Kerem Oruç, Şahin Bedir, Emir Çelik, and Nihan Şentürk Öztaş interpreted the data. Ezgi Değerli prepared the first draft. Nebi Serkan Demirci, Gülin Alkan, Şahin Bedir, Ezgi Değerli, and Fuat H. Demirelli critically revised the manuscript for important intellectual content. All authors have approved the final article.

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