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ORIGINAL ARTICLE

Clinical Outcome and Characteristics of Turkish Breast Cancer Patients who had SARS-Cov-2 Infection

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OBJECTIVE

COVID-19 pandemic has placed an unprecedented burden on health-care system. Patients with cancer are reported to have a higher risk of infection and a more complicated COVID-19 course. Breast cancer (BC) is the most common cancer in women in Turkey. We report clinical outcomes and characteristics of patients with COVID-19 who were on treatment for BC at our center.

METHODS

We reviewed medical records of BC patients who had COVID-19 between July 2020 and 2021 at our center. We recorded pathological, clinical, treatment characteristics, and the clinical outcome of COVID-19 infection.

RESULTS

A total 82 BC patients had COVID-19 between July 2020 and 2021. All patients were female, with a median age of 49 (43-64 years). 85% of all patients had early and 14.6% of them had advanced stage BC. COVID-19 had a mild clinical course in 73%, hospitalization was required in 27% of patients. Twenty-five patients who required hospitalization were discharged and three patients died due to COVID-19. All of the patients who died from COVID-19 had metastatic BC (p=0.002). Metastatic disease (p=0.002) and chemotherapy within 7 days of COVID-19 diagnosis (p=0.024) have been associated with increased mortality.

CONCLUSION

Majority of BC patients with COVID-19 have a mild course, patients with risk factors that increase mortality should be followed more carefully.

Keywords: Advanced breast cancer; breast; cancer; chemotherapy; COVID-19, pandemic, tumor.

INTRODUCTION

Since December 2019, approximately 409 million patients have been diagnosed with COVID-19.[1] The first case in Turkey was reported on March 11 and the first death due to COVID-19 occurred on March 15, 2020.[2] Nationwide restrictions and lockdown started in April 2020. Turkish health system never overwhelmed due to waves of COVID 19 partly because of the high number of intensive care units (ICU) in the world. Rarity of hospices or nursing homes, long legacy of contact tracing, universal healthcare and lockdown

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policy were the main reasons for low fatality rate (REF). Vaccination against COVID-19 has started in February 2021 initially with inactivated vaccine and then mRNA base vaccine. The first peak of COVID-19 was in the last week of the April and the second peak occurred in September 2020.

It has been reported that cancer patients have worse prognosis during this pandemic.[3] In addition, patients with cancer were more likely to have severe disease and poor prognosis due to anti-tumor treatments, especially hematological malignancies, lung cancer, and metastatic cancers. Among all COVID-19 cases, patients with cancer had a 11.4-28.6% mortality rate and most of these studies included all solid tumors.[4-11] In articles including only breast cancer (BC) patients, the mortality rate in patients has been reported to be approximately 7%.[7-9]

Most of the patients with COVID-19 present with complaints including fever, fatigue, anosmia, cough, shortness of breath, myalgia, headache, nasal congestion, and sore throat; however, some patients may remain asymptomatic.[5] Asymptomatic presentation is reported to be in the range of 17.9-30.8%.[6,7] Asian ethnicity, recent cancer diagnosis, hematological malignancies, male sex, age over 60 years, and elevated C-reactive protein levels were reported to be associated with increased mortality in cancer patients.[8-11]

MATERIALS AND METHODS

We conducted a retrospective cohort study of patients who had COVID-19 and were on treatment for BC at our medical oncology Breast Health Center between July 2020 and July 2021. This period covers second peak of COVID-19 in Istanbul when the delta variant was the dominant variant in Istanbul. Clinical, pathological, and treatment characteristics of patients with BC were recorded from electronic medical records. The onset of symptoms, method of diagnosis, relation with most recent anti-cancer therapy, and the severity of clinical course are collected.

Statistical Analysis

SPSS-22 program was used in statistical analysis. Data were presented as mean±standard deviation, number of individuals, and percent. We analyzed patient characteristics with descriptive statistics. Student's t-test was used to compare the two normally distributed quantitative data groups, and the Mann-Whitney U test was utilized to compare two non-normally distributed data groups. The qualitative data were compared with Pearson's Chi-square test and Fisher's exact test. Statistical significance level was set at $p<0.05$.

RESULTS

Approximately 5000-6000 patients with BC had their treatments at our center annually. We identified 82 patients who had COVID-19 while on therapy for BC from July 2020 to 2021. Clinical and pathological characteristics of patients are shown in (Table 1). All patients were female, with a median age of 49 (43-64 years). Majority of patients 85% (n=70) had early-stage and 15% (n=12) had advanced BC. 67% (n=55) patients had hormone receptor-positive/HER-2 negative, 21% (n=17) had HER-2 positive, and 12% (n=10) had triple-negative BC. Less than half of the patients had comorbidities. Most common comorbid diseases were hypothyroidism (19%, n=13), rheumatological diseases (7%, n=5), and hypertension (6%, n=5). 63% (n=52) of patients were on endocrine therapy (ET) when they had COVID-19 diagnosis. Among patients who were on chemotherapy/targeted therapy (n=16) at the time of COVID-19 diagnosis, the time from last chemotherapy/targeted therapy was <7 days in 10% (n=8) of patients. All patients who were on chemotherapy and/or targeted therapy had treatment delays up to 2 weeks during COVID-19 infection. COVID-19 diagnosis was confirmed with Polymerase chain reaction (PCR) test in 86% (n=71), with rapid antibody test in 7% (n=6), and chest computed tomography in 7% (n=6) of patients. 56% (n=46) of the patients had COVID-19 diagnosis at the emergency department, 17% (n=14) were diagnosed at the pandemic outpatient clinic, 5% (n=4) were diagnosed in the oncology ward, and 22% (n=18) had diagnosis at home by national contact-tracing teams who work 7/24. Clinical course of COVID-19 was mild in 73% (n=60) and 27% (n=22) of the patients required hospitalization.

Nineteen out of 22 hospitalized patients discharged with recovery (with a negative PCR test) and three patients died due to due to COVID-19 and all of them were heavily pretreated patients for metastatic BC.

Most common symptom was fever (Table 2) for all patients. The symptomatology differed somewhat between patients with a mild versus severe COVID-19 course. Patients with a mild course had more myalgia, fatigue, anosmia, headache, and 15% of them were asymptomatic compared to those with severe clinical courses. Metastatic stage (p=0.002) and shorter time (<7 days) since last chemotherapy (p=0.024) had significant impact on mortality due to COVID-19 in univari-

Table 1 Demographic and clinical characteristics of breast cancer patients with COVID-19

Characteristics	All patients n=82		Early-stage breast cancer (Stage I-III) n=70		Metastatic breast cancer (Stage IV) n=12	
	n	%	n	%	n	%
Age	49	26-84	49	26-84	42	38-78
Number of patients	82	100	70	85.4	12	14.6
Smoking						
Yes	8	9.7	6	8.6	2	6.7
No	59	71.9	51	72.9	8	66.7
Used to	15	18.2	13	18.6	2	16.7
Comorbidities						
Hypertension	4	5.7	4	5.7	0	0
Diabetes	2	2.9	2	2.9	0	0
Chronic cardiovascular disease	1	1.2	1	1.4	0	0
Hypothyroidism	13	15.8	13	18.6	0	0
Past TBC	2	2.4	2	2.9	0	0
Obesity	2	2.4	2	2.9	0	0
Chronic lung disease	2	2.4	2	2.9	0	0
Rheumatological disease	5	6	5	7.1	0	0
Cirrhosis	1	1.2	0	0	1	8.3
Other cancers	5	6	3	4.3	2	16.7
Subtype						
HR (+)	55	67.1	51	7.9	4	33.3
Her-2 (+)	17	20.7	11	15.7	6	50
TN	10	12.2	8	11.4	2	16.7
Time from last therapy						
<7 days from ET	52	63	49	70	3	50
<7 days from CT	8	9.7	2	2.9	6	50
<7 days from targeted therapy	8	9.7	5	7.1	3	25
Anticancer therapy within 1 month	8	9.7	5	7.1	3	35
Anticancer therapy more than 1 month	9	10.9	9	1.2	0	0
Disease severity						
Mild	60	73.1	54	77.1	6	50
Sever	22	26.8	16	4.9	6	50
Hospitalized	19	23	16	22.8	3	25
ICU	3	3.6	0	0	3	25
Clinical outcomes						
Discharge	19	30.4	16	4.9	3	25
Death	3	3.6	0	0	3	25
Test type						
Fast antibody test	6	7.3	5	7.1	1	8.3
RT-PCR (nasal swab)	71	86.5	60	85.7	11	91.7
Thorax CT	5	6	5	7.1	0	0
Test center						
ED	46	56	40	57.1	6	50
Fever clinic	14	17	13	18.6	1	8.3
Oncology clinic	4	4.8	1	1.4	3	25
Home health services	18	21.9	16	22.9	2	16.7

TBC: Tuberculosis; HR: Hormone receptor; HER-2: Human epidermal growth factor receptor 2; TN: Triple negative; ET: Endocrine therapy; CT: Chemotherapy; CT: Computed tomography; ICU: Intensive care units; RT-PCR: Reverse transcription polymerase chain reaction; ED: Emergency department

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Table 2 Type and frequency of symptoms due to COVID-19

Symptoms	Mild disease		Severe disease	
	n	%	n	%
Fever	26	43	14	63.6
Cough	7	11.7	7	31.8
Shortness of breath	0	0	4	18.2
Myalgia	25	41.7	4	18.2
Fatigue	24	40	0	0
Anosmia	20	33.3	3	13.6
Headache	15	25	0	0
Nasal congestion	1	1.7	0	0
Sore throat	2	3.3	0	0
Nausea	2	3.3	0	0
Asymptomatic	9	15	0	0

Table 3 Impact of clinical factors on mortality due to COVID 19 (univariate analysis)

Parameters	n=82	%	p
Age			
<50 years-old	44	53.4	
>50 years-old	38	46.3	0.594
Stage			
I-III	70	85.4	
IV	12	14.6	0.002
Number of symptoms			
1-2	43	52.4	0.549
3-4	29	35.4	0.243
Time from last therapy			
<7 days from CT	8	9.8	0.024
<7 days from ET	52	63.4	0.046
<7 days from targeted therapy	8	9.8	0.268

Chi-square test. CT: Chemotherapy; ET: Endocrine therapy

ate analysis (Table 3). Mortality due to COVID-19 was not affected by age, number of symptoms, time since last chemotherapy/targeted therapy in multivariate analyses.

DISCUSSION

Patients with cancer are inevitably affected by worldwide spread of COVID-19 since 2019. All countries adopted site/region-specific management strategies and changed their pattern of care during pandemic. Over time, we had more information on how different COVID-19 variants affected cancer patients. Retrospective data shed some light on how COVID-19's clinical course and potential risk factors for mortality in cancer patients.

Clinical outcomes and characteristics of BC patients with COVID-19 have been reported firstly from China and then from other countries in the world (Table 4). A multicenter retrospective study aimed to identify risk factors associated with COVID-19 in 45 BC patients with laboratory-confirmed diagnosis from seven hospitals in Hubei China. They collected data related to outcome of COVID-19 in BC patients till April 15, 2020. The median age of the patients was 62, all were female, 89% had a positive PCR test, and 27% had a severe clinical course. Five patients were >75 years old, 60% had comorbid diseases and hypertension was the most common comorbidity (31%). Three patients (6.7%) had metastatic disease. Twenty-three patients (51.5%) were on anti-cancer therapy (systemic and local) and 33% were receiving anti-cancer treatment within 1 week of COVID 19 diagnosis. The most common symptom was fever. Four patients required ICU, 3 (6.7%) patients died, all had a severe clinical course. Age >75 years old, ECOG score were associated with disease severity in univariate analysis. The impact of chemotherapy within 7 days of diagnosis was significant both in univariate and multivariate analyses.[12] Another retrospective study reported clinical, characteristics and outcomes of 35 BC patients with COVID-19 infection in the period between January and May 2020 from 5 hospitals in Wuhan.[13] All patients had laboratory-confirmed COVID-19 diagnosis by PCR or antibody test. In their study, 55 COVID-19 patients without cancer and 81 patients with cancer (non-BC) were also included as control groups. The median age was 56, the stage of BC (early vs. metastatic) was not reported and 11% patients had a severe COVID-19 clinical course. Twenty-four patients were symptomatic, cough was the most common symptom (72.7%), and fever was present in 6 patients (54.5%). All patients were female, more than one third of the patients had comorbidities and hypothyroidism was the most common comorbidity (15.8%). None of the patients required ICU admission and all patients were alive at the time of the analysis. Patients with other types of cancer were more likely to develop severe/critical disease and the mortality was 9.9% among them. The number male patients were higher (0 vs. 38) in the group with other types of cancer. Symptomatic infection was more common in patients without cancer and there was no difference in disease severity and mortality between BC and non-cancer patients. All COVID 19 patients without cancer were alive at the time of follow-up date. Age,

Table 4 Studies reporting the outcome of COVID-19 in breast cancer patients

Study	Kalinsky et al.	Zhang et al.	Vuagnat et al.	Wei et al.	Isıklar et al.
Number of patients	27	35	76	45	82
Period	March-April 2020	January-May 2020	March-April 2020	January-March 2020	July 2020-2021
Median age of patients, n (%)	56 (32-87)	56 (42-62)	58 (48-68)	62 (54-70)	49 (26-84)
Stage					
Early	22	NR	22	42	70
Metastatic	5	NR	37	3	12
Number of patients who, n (%) were on CT during COVID-19	14 (52)	6 (17.1)	8 (36)	4 (8.9)	8 (9.8)
Factors associated with mortality due to COVID-19	Male	NR	Hypertension age >70	Age >75 ECOG score CT <7 days	Metastatic disease Shorter time (<7 days) since last CT
Mortality rate	1/27	0/35	4/59	3/45	3/82
Method of COVID-19 diagnosis					
RT-PCR	22	35	59	40	71
Symptoms	4		17		
CT scan	1		41		5
Ab+CT scan				5	
Fast Ag test					6

NR: Not reported; CT: Computed tomography; ECOG: Eastern Cooperative Oncology Group; RT: Radiotherapy; PCR: Polymerase chain reaction; Ab: Antibody; Ag: Antigen

comorbidities, and abnormal chest computed tomography findings were significantly associated with disease severity in the univariate analysis in BC patients. Age retained its significant impact on disease severity also in the multivariate analysis.[13]

Two other reports from United States and Europe were published following these two reports from China. BC patients with COVID-19 infection were extracted from a prospective COVID-19 registry at Institute Curie Hospital from Paris. Seventy-six patients were identified from March to April 2020. Among 76 patients, 41 had RNA positive test, 18 had radiology-based. And 17 had symptom-based COVID-19 diagnosis. The median age was 58 (48-68), 17% were older than 70 years of age. Fever (46%) and cough (37%) were the most common symptoms. The most common morbidity was hypertension and two-thirds of the patients had metastatic disease. Twenty-eight out of 59 patients (47%) needed hospitalization, four patients required ICU, 45 out of 59 patients recovered. There was limited follow-up for ten patients at the time of data extraction from the registry. Four patients among 59 patients (6.7%) died, 3 of them had positive RNA tests and one patient had only diagnostic chest computed tomography findings. One of the patients, who died of COVID-19 infection, had triple negative early-stage BC and comorbidities including diabetes mellitus, hypertension, cardiomyopathy, and rheumatoid arthritis. Mortality was higher in the RNA-positive group at 9.7% (4/41). Age >70 years and hypertension were associated with the severity of infection. Authors concluded that risk factors for severe COVID 19 were similar to the general population and the mortality was not higher in BC patients. They also added that the actual number of COVID 19 patients might be higher due to potential under-declaration of the infection at the outpatient setting. Kalinsky et al. reported outcomes of 27 BC patients with COVID-19 in the period between March and April 2020 from New York. In their retrospective cohort, median age of BC patients was 56.5 and 19 patients were male. Five patients (19%) had metastatic disease, seven patients required hospitalization, none of them required ICU, and one 87 years-old male patients had died due to COVID-19 (who also had coronary artery disease and hypertension). The last received therapy before COVID19 was chemotherapy in 52% of the patients, the most common symptom was cough (70%), followed by fever (52%) and shortness of breath (52%). The most common comorbidity was hypertension (22%).[14,15]

The median age of patients was 49 in our study, younger than the patients reported from China, France, and United States. Only three patients were older than 75 years. Most common symptom was fever followed by myalgia and fatigue similar to other reports. The

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most common comorbidity was also hypertension in line with other reports. We reported the number of COVID19 infected BC patients between July 2020 and 2021. The total number of infected patients within 1 year period can be considered low in comparison to other reports (Table 4). Other studies reported the outcome of infected BC patients within 2-5 months of pandemic. Our study covered the period between the end of first peak and the whole second peak of COVID 19 in Istanbul. Almost all of the patients were not vaccinated since elderly patients and healthcare staff were prioritized and vaccinated first in April 2021.

The number of patients with metastatic BC was low (15%, n=12) and most patients had COVID-19 while they were on adjuvant ET (63%, n=52). Patients who were on chemotherapy or targeted therapy followed the pandemic isolation and hygienic precautions very strictly, thus fewer of them had COVID-19 infection. All of these factors might have an impact on our low mortality rate. Nevertheless, heavily pretreated metastatic BC patients who needed hospitalization for their scheduled chemotherapy or targeted therapy had a severe clinical course and all three of them died due to COVID-19. Older age, comorbidities, and hypertension were not associated with increased mortality in contrary to other studies. Our study has the highest number of BC patients with laboratory-based COVID 19 diagnosis. It is important to note that our study did not have a control group of COVID-19 infected patients without cancer or patients with cancer other than BC. Thus, it was not informative about the course of COVID 19 for other types of cancer. Of note, its retrospective nature, absence of laboratory and radiological follow-up data are the other limitations of our study.

COVID-19 pandemic is still ongoing and all of us including patients with cancer are still at risk. Patients with BC will be at more risk of getting this infection like many other cancer patients till pandemic is over. Any contact history, suspicious clinical symptom, or sign should be promptly evaluated since COVID infection might lead to death especially in hospitalized heavily treated patients with metastatic BC who are on chemotherapy or targeted treatments.

CONCLUSION

In this cohort study of patients with BC, most patients had a mild COVID-19 course. Advanced disease and chemotherapy within 7 days of diagnosis were the two risk factors for increased mortality.

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Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Institutional Review Board at Acibadem Altunizade Hospital (no: 2021-20/08, date: 14/10/2021).

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