




## Breast Cancer Survivors and COVID-19: Prevalence and Risk of Severe Disease in a Screening Study

Vahid Zangouri<sup>1,2</sup>, Aliyeh Ranjbar<sup>1</sup>, Farhad Homapour<sup>1,2</sup>, Mahdihyeh Sadat Seyyedy<sup>1</sup>, Shakila Gooya<sup>1</sup>, Mohammad Yasin Karami<sup>1,2\*</sup> , Elham Halimi<sup>1</sup>

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### Abstract

**Background:** Determining the risk of severe course coronavirus disease 2019 (COVID-19) and its related factors in survivors of common cancers such as breast cancer is important. This study has been designed to evaluate the prevalence of COVID-19 infection in breast cancer survivors and also estimate the risk of severe disease in this population.

**Methods:** Out of 6134 patients in the Shiraz Breast Cancer Registry (SBCR), A total of 292 patients who elapsed less than a year from their breast cancer diagnosis were excluded. We called 5842 patients. Finally, 4135 breast cancer survivors who agreed to cooperate were screened for COVID-19 symptoms by a symptom-based questionnaire in November 2020. COVID-19 in symptomatic participants was confirmed by a polymerase chain reaction (PCR) test. The clinical and paraclinical data of the COVID-19 course were collected for patients with a positive PCR test.

**Results:** A total of 247 (5.9%) participants had at least reported one of the COVID-19 symptoms. Also, 17% of symptomatic participants had a positive PCR test; 83.7% had mild disease, 9.5% moderate, and 16.7% had severe conditions. Chronic cardiovascular disease, hypertension, and diabetes were related to an increased risk of severe illness ( $P = 0.018$ ,  $P = 0.018$ ,  $P = 0.002$ ).

**Conclusion:** This study suggests that breast cancer intermediate and longtime survivors without other underlying diseases are considered at low risk for developing severe/critical COVID-19.

**Keywords:** Coronavirus disease 2019, Breast Cancer Survivors, Outcomes

**Conflicts of Interest:** None declared

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### Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the newest member of the coronavirus family in late 2019 following several cases of pneumonia of unknown cause in China (1). Within a short time, the virus spread dramatically and was officially declared a pandemic by the World Health Organization on March 11, 2020 (2).

By June 2022, >500 million cases of coronavirus disease 2019 (COVID-19) have been reported, subsequently resulting in > 6 million deaths worldwide (3).

SARS-CoV-2 can cause a range of clinical features

from asymptomatic infection to acute respiratory distress syndrome and multiorgan dysfunction. A significant percentage of cases of COVID-19 infection are asymptomatic or mild. Approximately, 20% of COVID-19 infections develop severe disease requiring hospitalization, and it leads to a critical condition such as respiratory failure or shock in 5% of patients (4-6).

Some factors—such as older age, male sex, hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and chronic renal disease—are related to increasing the risk for a severe course of COVID-19.

**Corresponding author:** Dr Mohammad Yasin Karami, [karamiy@sums.ac.ir](mailto:karamiy@sums.ac.ir)

<sup>1</sup> Breast Diseases Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>2</sup> Surgical Oncology Division, General Surgery Department, Shiraz University of Medical Sciences, Shiraz, Iran

#### ↑What is “already known” in this topic:

COVID-19 is related to poor prognosis and increased risk to develop a severe course in patients with cancer.

#### →What this article adds:

This study suggests that breast cancer intermediate and longtime survivors without other underlying diseases are considered at low risk for developing severe/critical COVID-19.

Also, COVID-19 is related to poor prognosis and increased risk to develop a severe course in patients with cancer (7-9). The mortality rate among cancer patients increased to 5.6% compared with 2.3% in noncancer patients (10). Studies showed that patients under current treatment for cancer and short-term cancer survivors have a high risk of severe disease (11, 12); nonetheless, this is less known for medium- to long-term cancer survivors.

Breast cancer is one of the high-prevalence cancers (13). It is the most frequent cancer among Chinese COVID-19 patients (14). Breast cancer systemic treatments are associated with effects such as an increased risk of heart disease and a weakened immune system that can increase the risk of severe course COVID-19 infection in breast cancer survivors (15, 16). Chemotherapy-associated immune parameter changes remain a year or more after the end of treatment (15, 17). Breast cancer is curable in an early stage with a large number of medium- to long-term survivors. The overall 5-year survival of breast cancer is about 80% (18-20). Concerns about the increased risk of infection can have a significant impact on their quality of life and an increase in psychological problems such as depression (21, 22).

The first mass vaccination program against COVID-19 started in December 2020. Vaccination has been effective in reducing the incidence of COVID-19 and its mortality (23, 24). However, the efficacy of COVID-19 vaccines was hampered by viral mutations, resulting in an increased rate of infection and mortality (25-29). The virus may be infectious even after the third dose of the vaccine (30).

Considering the high number of breast cancer survivors, it is important to determine the severity of COVID-19 and its related factors in this group. Our study aimed to investigate the prevalence and risk of severe course COVID-19 in breast cancer survivors.

## Methods

### Study Population

This study was conducted using data from the Shiraz Breast Cancer Registry (SBCR) (18). The registry includes patient-related data on socioeconomic status, baseline characteristics, patients' and family clinical history, physical examination, imaging, disease course, and prognosis from 6134 patients who were diagnosed with breast cancer. The inclusion criteria were breast cancer survivors aged 18 to 90 years who elapsed at least a year from their breast cancer diagnosis. The exclusion criteria were presenting active malignancy, receiving chemotherapy in the last year, or having any malignancy except breast cancer.

### Data Collection

Age, history of previous disease, stage of breast cancer, the time elapsed since diagnosis, surgery, and receiving the last dose of chemotherapy of 6134 breast cancer survivors were extracted from SBCR records. A total of 292 patients who elapsed less than a year from their breast cancer diagnosis were excluded. We called 5842 patients. Finally, 4135 patients who agreed to cooperate were screened in November 2020 by a symptom-based ques-

tionnaire.

This questionnaire evaluated patients with symptoms of fever, fatigue, and severe muscle pain, anorexia, headache, dizziness, cough, sputum secretion, sore throat, runny nose, abdominal pain, nausea, vomiting, and diarrhea in the last 2 weeks. Patients who had symptoms were referred to medical centers for COVID-19 PCR testing. Data on medical interventions during hospitalization or home isolation, including oxygen saturation percentage, severity of illness, chest computed tomography scan or radiographic report, length of stay, and use of ventilators (nasal cannula, O<sub>2</sub> mask, mechanical ventilation), and medications were collected for COVID-19 PCR positive patients using a data grading form. The severity of the disease was determined by clinical criteria used in previous studies (19, 20). Patients with mild signs or symptoms without signs of pneumonia in imaging were considered to have mild illness. Patients present with fever, respiratory tract symptoms, and imaging in favor of pneumonia were considered as having moderate illness. A patient was considered as having severe illness if they met any of the following: (1) respiratory distress; respiratory rate of  $\geq 30$  beats per minute; (2) SpO<sub>2</sub>  $\leq 93\%$  at resting; and (3) arterial PaO<sub>2</sub>/FiO<sub>2</sub>  $\leq 300$  mmHg. A patient was considered as having a critical condition if they met any of the following: (1) respiratory failure; needing mechanical ventilation; (2) shock; and (3) combined with other organ failures, requiring intensive care.

### Data Analysis

In this study, mean and standard deviation, frequency, and frequency and percentage were used. To compare data between the 2 groups, the chi-square test or the Fisher exact test was used. Comparison of quantitative variables, such as age and tumor size, were performed by a t test. SPSS 22 was used at an alpha level of 0.05 and a power of 80%.

## Results

This study included 5842 breast cancer survivors who had at least elapsed a year since the last dose of chemotherapy. The mean age of participants was  $48.92 \pm 11.3$  years (min-max: 21-92 years). On average,  $7.49 \pm 4.4$  years (min-max: 2-33) have passed since their breast cancer diagnosis. At least 1223 patients had an underlying medical condition associated with an increased risk of severe COVID-19 illness. Demographic and clinical characteristics are demonstrated in Table 1.

A total of 4135 patients participated in this study. A total of 5.9% (n = 247) of participants who reported at least one of the COVID-19 checklist symptoms, were referred to related centers for the COVID-19 PCR test. The result of 17% (n = 42) of COVID-19 PCR tests was positive and 83% (n = 205) of PCR tests were negative. The mean age and standard deviation of positive COVID-19 PCR test patients were  $54.5 \pm 12.7$  (min-max: 34-81). Heart diseases, hypertension, and diabetes with a prevalence of 14.3% (n = 6), 14.3% (n = 6), and 16.7% (n = 7) were the most common comorbidity.

**Table 1.** Demographic and Baseline Clinical Characteristics

Characteristic	Overall (N = 5842)
Gender	
Male	30 (0.5%)
Female	5537 (95.2%)
Missing	247 (4.2%)
Comorbidity	
Chronic Cardiovascular Disease	231 (3.5%)
Hypertension	1307 (19.6%)
Diabetes	905 (13.6%)
Chronic Pulmonary Disease	41 (0.6%)
Autoimmune Disease	2 (0.003%)
Two or More Comorbidities	1263 (19%)
Duration since diagnosis	
1-2 Years	281 (4.8%)
2-5 Years	2097 (35.9%)
5-10 Years	2234 (38.2%)
10-20 Years	1141 (19.5%)
>20 Years	89 (1.5%)
Missing	0 (0%)
Breast Cancer Stage	
I	559 (9.6%)
II	1636 (28%)
III	1210 (20.7%)
IV	53 (0.9%)
Missing	2384 (40.8%)
Breast Cancer Subtypes	
Luminal A	3192 (54.6%)
Luminal B	888 (15.2%)
HER2type	453 (7.4%)
TNBC	519 (86.2%)
Missing	808 (13.8%)

toms, were reported in 52.4% (n = 22), 50% (n = 21), and 47.6% (n = 20). Gastrointestinal symptoms were seen in 21.4% (n = 9) and dyspnea was reported in 35.7% (n = 15) of patients.

According to clinical classification, 73.8% (n = 31) of cases had mild, 9.5% (n = 4) moderate, and 16.7% (n = 7) severe COVID-19. The mean age in mild to moderate cases ( $53.7 \pm 11.6$ ) was significantly lower than the average age in the severe and critical groups ( $58.7 \pm 17.8$ ) ( $P = 0.026$ ). None of the patients was in critical condition. Chronic cardiovascular disease, hypertension, and diabetes were related to an increased risk of severe illness ( $P = 0.018$ ,  $P = 0.018$ ,  $P = 0.002$ ). Dyspnea was significantly more common in critically ill patients ( $P = 0.031$ ). Details of demographic, baseline clinical characteristics, and clinical features of COVID-19-infected breast cancer survivors are demonstrated in [Table 2](#).

## Discussion

The present study was the first study to investigate the prevalence and severity of COVID-19 in breast cancer survivors specifically. The clinical characteristics of 42 breast cancer survivors who had positive COVID-19 PCR tests were described. According to the results, consistent

**Table 2.** Demographic, Baseline Clinical Characteristics and Clinical Features of COVID-19-Infected Breast Cancer Survivors

Characteristic	Mild-Moderate (N=34)	Sever-Critical (N=7)	P-value
Gender			
Male	1 (2.9%)	0 (0%)	0.651
Female	34 (97.1%)	7 (100%)	
Comorbidity			
Chronic cardiovascular disease	3 (8.6%)	3 (42.9%)	0.018
Hypertension	3 (8.6%)	3 (42.9)	0.018
Diabetes	3 (8.6)	4 (57.1%)	0.002
Chronic pulmonary disease	0 (0%)	0 (0%)	
Autoimmune disease	1 (2.9%)	0 (0%)	
Two or more comorbidities	3 (8.6%)	4 (57.1%)	0.002
Breast Cancer Stage			
I	17 (48.6%)	4 (57.1%)	
II	14 (40%)	3 (42.9%)	0.638
III	4 (11.4%)	0 (0%)	
Breast Cancer Subtypes			
Luminal A	24 (72.7%)	4 (66.7%)	
Luminal B	4 (12.1%)	2 (33.3%)	0.490
HER2type	2 (6.1%)	0 (0%)	
TNBC	3 (9.1%)	0 (0%)	
Duration since diagnosis			
1-2 years since diagnosis	0 (0%)	0 (0%)	
2-5 years since diagnosis	10 (28.6%)	1 (14.3%)	0.433
>5 years since diagnosis	25 (71.4%)	6 (85.7%)	
BMI			
Underweight	0 (0%)	0 (0%)	
Normal	4 (12.9%)	4 (66.7%)	0.033
Overweight	18 (58.1%)	1 (16.7%)	
Obesity	8 (25.8%)	0 (0%)	
Lifestyle			
Smoking	5 (14.3%)	2 (28.6%)	0.355
Low Physical Activity	27 (77.1%)	5 (71.4%)	0.746
Symptoms			
Cough	16 (45.7%)	5 (71.4%)	0.214
Fever	16 (45.7%)	4 (57.1%)	0.58
Fatigue and Myalgia	22(62.9%)	4 (57.1%)	0.776
Dyspnea	10 (28.6%)	5 (71.4%)	0.031
GI Symptoms	7 (20.0%)	2 (28.6%)	0.614
Nasopharynx Symptoms	10 (28.6%)	2 (28.6%)	1
Headache	5 (14.3%)	3 (42.9%)	0.079
Anosmia	7 (20.0%)	0 (0%)	0.195
History of Close Contact with Covid-19 Patients			
Yes	17 (50%)	3 (42.9%)	0.782
No	17 (50%)	4 (57.1%)	

Myalgia, cough, and fever, as the most frequent symp-

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with the general population, breast cancer survivors presented similar clinical features such as cough, fever, and fatigue as the most common symptoms. Most breast cancer patients have mild symptoms and good short-term outcomes, and the risk of developing severe and critical conditions in breast cancer survivors is not high. Old age and underlying diseases like hypertension, diabetes, and chronic cardiovascular disease are the most relevant factors that increase the risk of severe COVID-19 disease.

Contrary to the results of our study, 2 studies conducted in Republic of Korea reported a high incidence of influenza-like illness among breast cancer survivors and survivors of childhood cancers (31, 32). A study by Carreira et al showed that non-hematologic cancer survivors may be at increased risk of severe illness from COVID-19 within 5 years of cancer diagnosis (33). In their study, the mean age of participants was 66.1 years, which is higher than in our study. Also, the prevalence of chronic respiratory disease and chronic cardiovascular disease was lower in our participants. Wei et al reported that 73.3% of breast cancer patients developed non-severe COVID-19. Also, they showed that age over 75 years, high Eastern Cooperative Oncology Group scores, and chemotherapy within 7 days before symptom onset could be risk factors for severe COVID-19 (34). According to the study by Kathuria-Prakash et al, older age and comorbidities were associated with poorer outcomes in COVID-19 patients. However, breast cancer treatment, including surgery, radiation therapy, systemic therapy, and endocrine therapy, was not linked to hospitalization (35).

Our study has several limitations. First, the duration of screening for COVID-19 was short. Second, the follow-up period of positive COVID-19 PCR patients was short. Third, we called our participants just once. Nonetheless, they may have contracted the disease within the next few days after our phone call. Fourth, our study lacked prognostic laboratory data for COVID-19. In general, our study showed that the risk of severe/critical COVID-19 in breast cancer survivors is low if they have no comorbidity and have not been under active treatment or postdiagnosis follow-up for 2 years.

Prospective long-time outcome clinical studies and more effort should be made to determine the outcomes of breast cancer survivors.

### Conclusion

This study suggests that intermediate and longtime breast cancer survivors without other underlying diseases are considered as low-risk for developing severe/critical COVID-19.

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### Conflict of Interests

The authors declare that they have no competing interests.

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