

What Has Changed in Patients Aged 65 and over Diagnosed with Breast Cancer during the COVID-19 Pandemic: A Single-Center Experience

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Keywords

Elderly · Breast cancer · Corona virus disease 19 · Pandemic · Treatment

Abstract

Introduction: The COVID-19 pandemic has a worldwide negative impact on healthcare systems. This study aims to determine how the diagnosis, clinicopathological features, and treatment approaches of patients with breast cancer (BC) diagnosed at ≥ 65 years old were affected during the pandemic. This survey has shown that patients, especially the elderly, had to postpone their BC health problems or delay their routine controls due to the risk of COVID-19 transmission, high mortality rates due to comorbidity, and restrictions. **Materials and Methods:** The medical records of 153 patients with BC diagnosed at ≥ 65 years old before (January–December 2019; group A, $n = 61$) and during (March 2020–May 2021; group B, $n = 92$) the COVID-19 pandemic were retrospectively analyzed. In addition, clinicopathological features of patients, including age, admission form, clinical stage, tumor (T) size-grade-histology-subtype, lymph node involvement, surgery type, and treatment protocols, were evaluated. **Results:** Patients mostly applied for screening purposes were included in group A and patients who frequently applied for diagnostic purposes due to their existing BC or other complaints were included in group B ($p = 0.009$). Group B patients had a higher clinical stage ($p = 0.026$) and had commonly larger ($p = 0.020$) and high-grade ($p = 0.001$) Ts. Thus, mastectomy and neoadjuvant systemic

therapy were more commonly performed in group B ($p = 0.041$ and $p = 0.005$). **Conclusion:** The survey showed significant changes in BC diagnosis and treatment protocols for patients diagnosed at ≥ 65 years old during the COVID-19 pandemic. Postponing screening and delaying treatment leads to more advanced BC stages in elderly patients.

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Introduction

The World Health Organization declared the COVID-19 pandemic as a public health emergency of international concern on 30 January 2020 [1]. The COVID-19 pandemic has emerged as an important health problem in the country in < 3 months. The severity of this pandemic puts great pressure on healthcare systems worldwide, and countries responded in different ways when reorganizing healthcare systems. This had repercussions on patients affected by other illnesses by reducing available facilities, personnel, hospital beds, and operating room capacity in many instances.

Initial epidemiological data showed that patients who were older and/or had comorbidities, notably cancer, were at a higher risk of developing severe COVID-19 infection [2]. In addition, concerns were raised in oncology regarding the risk of SARS-CoV-2 infections related to hospital visits and admissions for treatments and a possible additional risks related to surgery and chemotherapy-induced immunosuppression [3]. Consequently, vari-

ous recommendations and guidelines have been published, including managing breast cancer (BC). However, most recommendations are based on an expert's opinion rather than on scientific evidence.

BC is the most common cancer in women worldwide. Along with an increase in life expectancy, the incidence of BC is increasing in the aging population. While 80% of BC cases are diagnosed in patients ≥ 50 years old, 40% of all cases presented at >65 years old. Therefore, about three-fourth of the BC cases are estimated to be diagnosed in elderly women by 2025 [4].

A decrease in the admissions of patients ≥ 65 years old to health institutions for routine BC screening or due to existing complaints has been noted as a result of the increased burden on the healthcare system, the risk of disease transmission, and restrictions during the pandemic. Therefore, the current study aimed to evaluate the reason for admission, disease stage, tumor (T) characteristics, and treatment differences in patients ≥ 65 years old, who were diagnosed with BC before and during the COVID-19 pandemic in Turkey; this study was a single-center experience.

Materials and Methods

Study Population

A retrospective cohort study analysis was conducted on 153 patients ≥ 65 years old presenting with primary BC before (January–December 2019; group A, $n = 61$) and during (March 2020–May 2021; group B, $n = 92$) the COVID-19 pandemic. The patients were identified from the registry ($n = 411$) of the current study. Age was taken from the time of diagnosis. Patients were further characterized by hospital admission, clinical stage, T size, histologic grade, histopathologic type, molecular subtypes, lymph node (LN) status, surgery type, and medical treatment protocols.

Molecular Subtypes

Four different molecular subtypes of BC have been identified, including luminal A, luminal B, triple-negative (TN), and human epidermal growth factor receptor 2 (HER-2) overexpression based on the expression of estrogen receptor (ER), progesterone receptor (PR), HER-2, and Ki67, respectively. Luminal A is characterized as ER (+) and/or PR (+), HER-2 (-), and Ki67 $<14\%$. Moreover, luminal B is characterized as ER (+) and/or PR (+), HER-2 (-), and Ki67 $\geq 14\%$. The HER-2 overexpression subtype is characterized as ER (-), PR (-), and HER-2 (+). Furthermore, TN is characterized as ER (-), PR (-), and HER-2 (-) [5].

Statistical Analysis

The quantitative variables that are suitable for normal distribution were examined using the Kolmogorov-Smirnov test. A difference between independent groups in quantitative variables was examined using the *t* test or Mann-Whitney U test. The χ^2 analysis was used to examine whether qualitative variables are independent. Descriptive statistics of variables with normal distribution were presented as mean \pm standard deviation, and descriptive statistics of non-normally distributed quantitative variables were shown as median (25th–75th percentile). In addition, descriptive statistics of qualitative variables were expressed in frequency (in percentage). *p* values <0.05 were considered statistically significant.

Results

The analysis included 153 cases and the clinicopathological characteristics of patients are summarized in Table 1. Retrospectively analyzed for this study were 153 patients presenting with primary BC at ≥ 65 years old before (January–December 2019; group A, $n = 61$) and during (March 2020–May 2021; group B, $n = 92$) the COVID-19 pandemic.

The mean age (years) was 72.44 ± 7.21 and 73.62 ± 7.58 in groups A and B, respectively ($p = 0.339$). Of the cases, 147 (96%) female and 6 (3.9%) male patients were evaluated. Two (3.3%) and 4 (4.3%) patients in groups A and B, respectively, were males ($p = 1.000$). Admissions for diagnostic purposes were more frequent in group A (38; 62.3%) compared to group B (75; 81.5%), where patients applied for diagnostic purposes at a higher rate because of their existing complaints ($p = 0.009$).

Moreover, the clinicopathological characteristics and treatment protocols in patients were simultaneously evaluated. The clinical stages at the time of diagnosis of the patients were stages I, II, and III and IV in 32 (52.5%), 19 (31.1%), and 5 (8.2%) patients, respectively, in group A, and stages I, II, III, and IV in 29 (31.5%), 30 (32.6%), 20 (21.7%), and 13 (14.2%) patients, respectively, in group B ($p = 0.026$). T size was 20 (15–33) and 26 (20–40) mm in groups A and B, respectively ($p = 0.02$). When T histologic grade is evaluated, 3 (4.9%), 45 (73.7%), and 13 (21.3%) patients were grades 1, 2, and 3, respectively, in group A, and 3 (3.3%), 43 (46.7%), and 46 (50%) patients were grades 1, 2, and 3, respectively, in group B ($p = 0.001$). The detailed results for the histological diagnosis group were ductal (49; 80.3%), lobular (8; 13.1%), and mix and others (2; 3.2%) in group A, and ductal (69; 75%), lobular (15; 16.3%), mix (2; 2.1%), and others (6; 6.5%) in group B ($p = 0.722$). Molecular subtypes were luminal A, luminal B, and HER-2 and TN in 25 (41%), 32 (52.4%), and 2 (3.3%) patients, respectively, in group A, and luminal A, luminal B, HER-2, and TN in 36 (39.1%), 42 (45.7%), 5 (5.4%), and 9 (9.7%) patients, respectively, in group B ($p = 0.103$). In addition, the Ki67 proliferation index was 16 (11–26.5) and 20 (11.25–35) in groups A and B, respectively ($p = 0.127$). In groups A and B, 38 (62.3%) and 43 (46.7%) patients, respectively, had no axillary LN metastasis (pN0). Moreover, 23 (37.7%) and 49 (53.3%) patients in groups A and B, respectively, had axillary LN metastasis (pN+; $p = 0.059$).

When the surgical treatment applied was evaluated, 47 (77%) patients underwent a lumpectomy and 14 (23%) patients underwent a mastectomy, in group A. Moreover, 55 (59.8%) and 37 (40.2%) patients in group B underwent lumpectomy and mastectomy, respectively ($p = 0.041$). In axillary surgery, sentinel LN biopsy and axillary dissection AD) was performed in 41 (67.2%) and 20 (32.7%) pa-

Table 1. Descriptive statistics of variables

Variables	Group A, n (%)	Group B, n (%)	p value
N	61 (39.8)	92 (60.1)	
Age at diagnosis, years			
Mean \pm SD	72.44 \pm 7.21	73.62 \pm 7.58	0.339
Gender			
Male	2 (3.3)	4 (4.3)	1.000
Female	59 (96.7)	88 (95.7)	
Admission form			
Screening	23 (37.7)	17 (18.4)	0.009
Diagnosis	38 (62.3)	75 (81.5)	
AJCC stage			
I	32 (52.5)	29 (31.5)	0.026
II	19 (31.1)	30 (32.6)	
III	5 (8.2)	20 (21.7)	
IV	5 (8.2)	13 (14.2)	
T size (mm)	20.0 (15.0–33.0)	26.0 (20.0–40.0)	0.020
Histologic grade			
1	3 (4.9)	3 (3.3)	0.001
2	45 (73.7)	43 (46.7)	
3	13 (21.3)	46 (50.0)	
Histopathologic type			
Ductal	49 (80.3)	69 (75)	0.722
Lobular	8 (13.1)	15 (16.3)	
Mix	2 (3.2)	2 (2.1)	
Others*	2 (3.2)	6 (6.5)	
Molecular subtypes			
Luminal A	25 (41.0)	36 (39.1)	0.103
Luminal B	32 (52.4)	42 (45.7)	
HER-2 enriched	2 (3.3)	5 (5.4)	
TN	2 (3.3)	9 (9.7)	
Ki67, %			
Median 25–75 percentiles	16.0 (11.0–26.5)	20.0 (11.25–35.0)	0.127
LN status			
pN0	38 (62.3)	43 (46.7)	0.059
pN (+)	23 (37.7)	49 (53.3)	
Breast surgery			
Lumpectomy	47 (77.0)	55 (59.8)	0.041
Mastectomy	14 (23.0)	37 (40.2)	
Axillary surgery			
SLNB	41 (67.2)	48 (52.2)	0.077
AD	20 (32.7)	44 (47.8)	
Immediate reconstruction			
Yes	5 (8.2)	8 (8.7)	1.000
No	56 (91.8)	84 (91.3)	
Primer surgery	42 (68.9)	42 (45.6)	0.005
NST	19 (31.1)	50 (54.3)	
NAC	14 (22.9)	36 (39.1)	0.056
NET	5 (8.2)	14 (15.2)	0.299
Adjuvant therapy			
Chemotherapy	34 (55.7)	64 (70.3)	0.095
Hormonotherapy	53 (86.9)	63 (69.2)	0.021
RT			
Yes	38 (62.3)	62 (67.3)	0.669
No	23 (37.7)	30 (32.7)	

SD, standard deviation; AJCC, American joint committee on cancer; T, tumor; TN, triple-negative; pN, pathologic axillary lymph node; SLNB, sentinel lymph node biopsy; AD, axillary dissection; NST, neoadjuvant systemic therapy; NAC, neoadjuvant chemotherapy; NET, neoadjuvant endocrine therapy; RT, radiotherapy; LN, lymph node. * Including Papillary (n:5), medullary, apocrine, and mucinous (n:1).

tients, respectively, in group A. In group B, 48 (52.2%) and 44 (47.8%) patients underwent sentinel LN biopsy and AD, respectively ($p = 0.077$). In only a minority of patients, 5 (8.2%) and 8 (8.7%) immediate reconstructions in groups A and B were preferred ($p = 1.000$).

Neoadjuvant systemic therapy (NST) was preferred in 19 (31.1%) and 50 (54.3%) patients in groups A and B, respectively ($p = 0.005$). Five (8.2%) and 14 (15.2%) patients in groups A and B, respectively, preferred neoadjuvant endocrine therapy (NET; $p = 0.299$). Moreover, 34 (55.7%) and 53 (86.9%) patients in group A and 64 (70.3%) and 63 (69.2%) patients in group B underwent adjuvant chemotherapy ($p = 0.095$) and adjuvant hormone therapy ($p = 0.021$), respectively. Radiotherapy (RT) was applied to 38 (62.3%) and 62 (67.3%) patients in groups A and B, respectively ($p = 0.669$).

Discussion

The initial COVID-19 outbreak in Wuhan, China, in December 2019 had quick devastating global effects. The disease then went on to spread rapidly in other countries. Thus, the World Health Organization declared a “public health emergency of international concern” on 30 January 2020 and announced the disease as a pandemic on 11 March 2020 [6]. On the same date, the Republic of Turkey Ministry of Health announced the first case in Turkey. Consequently, various recommendations and guidelines have been published from the European Breast Cancer Research Association of Surgical Trialists, the American College of Surgeons, and the Senologic International Society including BC management during the pandemic. Similarly, in Turkey, under the leadership of the Turkish Federation of Breast Diseases Societies, guidelines containing the treatment management of patients diagnosed with BC during the COVID-19 pandemic process were rapidly created in line with the conditions and needs of the country [7]. Therefore, the treatments of patients diagnosed with BC since the first pandemic in Turkey were arranged in line with these guidelines. However, patients ≥ 65 years old postponed routine BC screening processes due to the increasing number of people infected with COVID-19, the burden on the healthcare system, restrictions, and the presence of comorbid conditions due to advanced age despite all these positive developments in Turkey. Moreover, patients also delayed applying to health institutions due to existing breast complaints.

BC is the most common cancer in women worldwide. Along with an increase in life expectancy, the incidence of BC is increasing in the aging population. Elderly women with BC are likely to be diagnosed with more advanced stages because they remain underrepresented in screen-

ing populations. Moreover, they are less likely to be aware of BC and more likely to delay reporting of complaints regarding breast lesions. Delays in the BC diagnosis process of patients ≥ 65 years old were inevitable due to the pandemic. Therefore, the diagnosis, clinicopathological features, and treatment approaches of patients with BC diagnosed at ≥ 65 years old were investigated before and during the pandemic.

In group A, the reasons for patients' admission to the breast clinic were diagnosis due to their existing breast complaints (38 patients, 62.3%) and diagnosis with BC after applying for routine screening (23 patients, 37.7%). In group B, applications for screening purposes decreased during the COVID-19 pandemic, and 17 (18.4%) patients were diagnosed with BC due to their application, while 75 (81.5%) patients were diagnosed after the application due to their existing complaints ($p = 0.009$). A great uncertainty regarding managing screening protocols for BC in the aging population is noted despite the increased BC burden in elderly patients [8, 9]. Adding the pandemic to this uncertainty causes delays in admission and diagnosis in patients in this age-group.

Of the patients, 5 (8.2%) were evaluated as stages III and IV in group A, and 20 (21.7%) and 13 (14.2%) as stage III and stage IV in group B, respectively ($p = 0.026$). Patients are diagnosed with more advanced BC as a natural consequence of the delay during the pandemic. Elderly patients with BC are likely to be diagnosed with more advanced stages. Similarly, in the current study, patients in group B commonly presented with a high stage than those in group A. This result revealed that patients ≥ 65 years old are diagnosed with more advanced stages and more common systemic metastatic BCs during the pandemic.

Elderly patients were also reported to have a higher incidence of greater T, axillary LN involvement, but lower T grades [10]. In the current study, T size was found to be 20 (15.0–33.0) and 26 (20.0–40.0) mm in groups A and B, respectively ($p = 0.020$), and histologic grade was higher in group B than in group A ($p = 0.001$). Axillary LN involvement in groups A and B were 23 (37.7%) and 49 (53.3%), respectively ($p = 0.059$). Thus, larger T presence in the breast, more frequent axillary LN metastasis, and higher T grades were detected in group B patients.

Mastectomy ($p = 0.041$) and AD ($p = 0.077$) were performed more frequently in patients in group B compared with patients in group A as an expected result of the larger T and more axillary LN metastases. Also, in line with the recommendations of the guidelines published during the COVID-19 pandemic, immediate reconstruction is preferred in only 8 (8.7%) patients in group B to reduce the risk of complications and shorten hospitalization. Moreover, immediate reconstruction was performed in 5 (8.2%) patients in group A, showing that patient preference plays an important role in the reconstruction deci-

sion in this age-group. Simultaneously, chronological age may be the main parameter affecting surgical choice [11].

No “one size fits all” approach to delivering BC care exists when the recommended medical treatment protocols during the COVID-19 pandemic were scrutinized. Major disparities in clinical practice underline the complex management of many different clinical and organizational situations and call for consensual evidence-based guidelines [12–15]. The management of new and old BC patients during the COVID-19 period should be personalized according to hospital resources and restrictions. Patients with TN/HER2+, T2N0-3M0, or T0-4N1-3M0 invasive BC should begin NST and have NET or neoadjuvant chemotherapy (NAC) for ER + stages I–III invasive BC. NET should be the first choice in old patients with ER + BC [16, 17]. In line with these guidelines, NST, NAC, and NET was preferred by 50 (54.3%; $p = 0.005$), 36 (39.1%), and 14 (15.2%) patients, respectively, in group B ($p = 0.056$ and $p = 0.299$). This increase in NST preference in group B is related to the frequent preference of NAC and NET in appropriate patients in line with the guidelines during the pandemic [18].

No significant difference between the groups was noted in terms of RT application practice ($p = 0.669$). Therefore, RT is assumed not to have systemic effects on the patient and thereby no increased risks related to COVID-19. However, although RT increases patients’ daily visits to the hospital and interactions with healthcare professionals and potentially other patients, it increases exposure risks. Thus, hypofractionation was considered protective by reducing the number of hospital visits [19].

Conclusion

The COVID-19 outbreak has dramatically affected all aspects of human life worldwide, including Turkey [20]. Thus, patients delay their routine checks for BC screening or postpone their admissions to health institutions due to existing complaints because of the restrictions that have had to be applied during the pandemic, the burden on healthcare institutions, the risk of transmission, and the

effect of other comorbid diseases, especially in the advanced age-group [21]. Consequently, when patients ≥ 65 years old, who were diagnosed with BC during the pandemic, were evaluated, they were diagnosed with a more advanced disease, were exposed to wider surgical procedures, and also needed a longer medical treatment period. Simultaneously, late diagnosis because of the lockdown and screening discontinuation may increase BC-related mortality [22–24]. BC should be treated without delay during the COVID-19 pandemic with the recommendations of the guidelines, especially in the ≥ 65 -year-old patient group, where the incidence of BC diagnosis and treatment process has increased.

Statement of Ethics

Ethical approval for this study (No: 2021-11/26) was provided by the ATADEK institutional Ethics Committee. Written informed consent was obtained from all patients for this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Aykut Soyder and Nilgün Göldoğan: collected the data and wrote the manuscript. Aysun Isıklar: analyzed the data. Erkin Arıbal and Aykut Soyder: designed the study. Gül Başaran: read and revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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