Impact of the COVID-19 Pandemic on Breast Cancer Stage at Diagnosis in a Tertiary Referral Cancer Center in Egypt

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Abstract:

Background: The COVID-19 pandemic caused cessation of breast screening programs in many cancer centers worldwide, and seeking medical care was delayed for many patients with suspected breast cancer. This study compared breast cancer stage at diagnosis and type of surgery performed in patients who presented to our institution before, during, and after the COVID-19 lockdown.

Methods: This retrospective study included medical records of all newly diagnosed breast cancer patients between January 2019 and December 2021 from the Beni-Suef University Registry. We compared patient characteristics between 3 cohorts: the pre-COVID-19 group (March 2019 – December 2019), the COVID-19 group (March 2020 – December 2020), and the post-COVID-19 group (March 2021 – December 2021).

Results: A total of 517 patients were identified among which 515 had complete staging data; 171 in pre-COVID-19 group, 145 in COVID-19 group, and 201 in post-COVID-19 group. The proportion of patients with stage 4 was higher during the COVID-19 pandemic (20.0%) compared with 10.5% pre-COVID-19 and 10.1% post-COVID-19 (p=0.003). Early-stage breast cancer (stage 0–IIB) was diagnosed more frequently in the pre-COVID-19 (55.0%) and post-COVID-19 (50.3%) groups compared with the COVID-19 (33.1%) group (p<0.001). Visceral metastases at diagnosis were present more frequently during the COVID-19 pandemic (10.3%) compared with pre-COVID-19 (6.4%) and post-COVID-19 (4.0%) (p=0.037). The median age, number of male patients, and proportion of patients who had mastectomy during COVID-19 pandemic did not differ from those in the pre-COVID-19 and post-COVID-19 periods.

Conclusions: More breast cancer patients presented with advanced stages and visceral metastases during the COVID-19 lockdown compared with the pre-lockdown period. Subsequently, these rates returned to pre-COVID-19 levels, most probably as a result of a successful vaccination campaign.

Keywords: Breast cancer; COVID-19; vaccination; staging; Egypt

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Background:

Breast cancer ranks first in incidence and second in mortality among all cancers in Egyptian females [1]. The mean age at diagnosis is 51 years old – much lower than that in developed countries [2]. Five-year survival rates are mostly obtained from single-center studies and range from 68% to 90.7% [3–5]. Early detection of breast cancer is associated with better survival and higher breast conservation rates [6,7]. As for estrogen receptor (ER)-positive disease, early detection frequently allows using less aggressive adjuvant treatment, particularly avoiding chemotherapy [8]. De-escalation of radical surgery to breast-conserving operations with less extensive axillary dissections is often feasible in patients with unifocal and even multifocal disease as it decreases post-operative morbidity and improves cosmetic results [9]. Successful de-escalation can be achieved if several steps are

followed, mainly early diagnosis and adherence to a multidisciplinary approach in the treatment of breast cancer [10].

In the past decade, many efforts have been made to encourage Egyptian women to attend breast screening campaigns and to seek medical advice as early as possible if a breast lump is detected. Previously published studies demonstrated that the breast self-examination rate among Egyptian females could be as low as 6% [11]. In the latest survey on the topic, 89.9% of women stated that mammography is useful in diagnosing small breast tumors, but half of them could not describe the procedure of obtaining a scan [12]. Due to low awareness together with the medical care accessibility issues, the mean time from breast cancer symptom development to diagnosis in our country was 4.4 months [13]. The Egyptian Government launched a program called The Egyptian Women's Health Initiative in 2019, allowing the residents aged 18 or more to undergo breast cancer screening, examination, and treatment free of charge. The initiative was reported to be successful with a decrease in the proportion of late stages (III-IV) at diagnosis from 58.5 to 29.5 percent [14]. However, most screening activities were suspended for 2020 due to the Coronavirus Disease 2019 (COVID-19) crisis.

In December 2019, a novel coronavirus SARS-CoV-2 emerged in Wuhan, Hubei Province, China. The infection spread rapidly, and numerous cases have been detected in many countries, posing a global health problem, and leading the World Health Organization to declare COVID-19 as a global pandemic in March 2020 [15–17]. Many health systems changed their workflow to shift health care workers to casualty departments and chest hospitals. This led to a reduction in the workforce in family medicine departments and screening units [18]. Among other diseases, cancer care suffered the most during the pandemic, with dramatic declines in admission rates [19].

Starting December 11, 2020, the Pfizer-BioNTech COVID-19 vaccine became available under the EUA for persons 16 years of age and older, with a subsequently approval by the FDA. In Egypt, the first disease case was registered in February 2020, and a mass immunization campaign started in March 2021, mostly using Sinopharm inactivated whole-virus vaccine and AstraZeneca and Sputnik V vector vaccines [20]. Many pharmaceutical companies have developed diverse vaccines against COVID-19, and the vaccines are now widely available, including in developing countries. COVID-19 vaccination has allowed people to gradually return to a normal lifestyle and medical procedures [21].

Several groups of authors from different countries have reported upstaging of breast cancer at diagnosis as a result of the COVID-19 pandemic, while some studies have shown no impact of lockdowns on the proportion of early diagnosed breast cancer cases [22]. It is still unknown whether COVID-19 had a negative effect on breast cancer staging at presentation in Egypt. Furthermore, it is unclear whether this effect has subsequently led to improved adherence to early detection and diagnosis procedures after the launch of a mass vaccination campaign and the relaxation of most COVID-19-associated restrictions in 2021.

Patients and Methods:

Patients' population

We retrospectively reviewed the clinical records of the Clinical Oncology Department, Beni-Suef University, to identify women diagnosed with breast cancer between March 2019 and December 2021. All types of treatment for breast cancer: surgery, medication, and radiation are performed in this clinic. The Department has the largest patient flow in Beni-Suef governorate in central Egypt, so most patients are referred here from the surrounding urban and rural areas, which allows to obtain a representative patient sample. During the lockdown, the Department did not restrict admission of patients, but the screening program was suspended. For those admitted, we did not modify the chemotherapy protocols compared with our routine practice.

Eligibility criteria included patients with histologically proven breast cancer (the sample obtained with either biopsy or surgery). The data was extracted for the International Statistical Classification of Diseases and Related Health Problems (ICD)-10 codes C50, malignant breast neoplasms, and D05.1, intraductal breast carcinoma in situ. Patients with lobular carcinoma in situ or other malignant tumors of the breast were not included.

Variables exported from the database included patient characteristics: sex, age, tumor characteristics: stage of the disease, biological subtype, and type of surgery performed (mastectomy vs breast-conserving). Date of the first hospital visit for breast mass was considered the date of diagnosis. Patients with multiple primaries and those with incomplete medical records were excluded.

Staging was done using the TNM system (7th edition). A tumor was considered ER- and progesterone receptor (PR)- positive if >1% of tumor cells showed expression at IHC. HER2 was considered positive if scored 3+ by IHC or scored 2+ by IHC but positive according to the fluorescence in situ hybridization (FISH) or silver in situ hybridization (SISH) analysis.

Ethical approval:

The ethical approval was obtained from the Ethical Committee, Faculty of Medicine, Beni-Suef University, Egypt (Approval No. FMBSUREC/06112022/Shaaban). The study was performed in accordance with the 2013 Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline.

Outcomes:

The patients were divided into 3 cohorts according to the time of the initial breast cancer diagnosis: the pre-COVID-19 group (March 2019 – December 2019), the COVID-19 group (March 2020 – December 2020), and the post-COVID-19 group (March 2021 – December

2021). Primary outcomes included differences in the staging ratio at diagnosis and the frequency of breast conservation between groups.

Statistical analysis:

Descriptive analysis (frequencies and percentages) was carried out to assess the patients' demographics and clinical characteristics. Continuous variables were described using the mean (+/-SD) or median (range) and compared using Student's t-test or Mann-Whitney U-test depending on the parameter distribution. Categorical variables were described using numbers and percentages and compared using Chi square test. SPSS (version 20.0) was used for all analyses; results were considered statistically significant at a two-sided p-value of less than 0.05.

Results:

Patients' characteristics

A total of 517 consecutive breast cancer patients were identified, among which 515 had complete staging data. All were females except 7 male patients (1.4%). Median age was 50 years (Q1-Q3, 42-60), and 342 (66.1%) were premenopausal. Regarding the stage at presentation, only 4 presented with stage 0 (in situ), 29 (5.6%) presented with stage I, 209 patients (40.6%) with stage II, 206 (40.0%) with stage III, and 67 (13.0%) with stage IV. Among the 438 patients with available surgery data, 153 patients (34.9%) underwent breast-conserving surgery (BCS) while 65.1% had mastectomy. 356 patients had an estrogen receptor (ER) positive disease (68.9%), while HER2 was over-expressed in 113 patients (21.9%). Table 1 summarizes the patient characteristics.

Impact of COVID-19 on the disease presentation and management

A total of 171 patients were diagnosed in pre-COVID-19 group, 145 in COVID-19 group and 201 in post-COVID-19 group. Stage 4 was diagnosed more frequently during COVID-19 pandemic – 20.0% versus 10.5% in pre-COVID-19 and 10.1% in post-COVID-19 (p=0.003). Early-stage breast cancer (stage 0-2) proportion was significantly higher in pre-COVID-19 (55.0%) and post-COVID-19 (50.3%) compared with the COVID-19 group (33.1%) (P<0.001). Figure 1 compares the stages at presentation across the 3 groups. Visceral metastases were present at diagnosis in more patients during COVID-19 pandemic (10.3%) compared with the pre-COVID-19 (6.4%) and post-COVID-19 (4.0%) periods (p=0.037). The proportion of males did not differ between the 3 groups (p=0.961), neither did age at presentation (p=0.982).

Regarding the management, a similar proportion of patients had mastectomy during COVID-19 pandemic (72.9%) compared with 63.8% in pre-COVID-19 and 60.8% in post-COVID-19 (p=0.098). Table 2 demonstrates the disease characteristics in the groups.

Table 1: Patient characteristics

	Number (%)
All patients:	517 (100%)
Complete staging data	515 (99.6%)
Missing staging data	2 (0.4%)
Sex:	
Female	510 (98.6%)
Male	7 (1.4%)
Hormonal status:	
ER positive	356 (68.9%)
HER2 positive	113 (21.9%)
Triple negative	48 (9.2%)
Stage:	
CIS	4 (0.8%)
I	29 (5.6%)
II	209 (40.6%)
III	206 (40.0%)
IV	67 (13.0%)
Type of surgery:	438 (100%)
Conservative	153 (34.9%)
Mastectomy	285 (65.1%)
Menopausal status:	
Premenopausal	342 (66.1%)
Postmenopausal	175 (33.9%)
Year:	517
2019 (pre-COVID-19)	171
2020 (during COVID-19)	145
2021 (post-COVID-19)	201

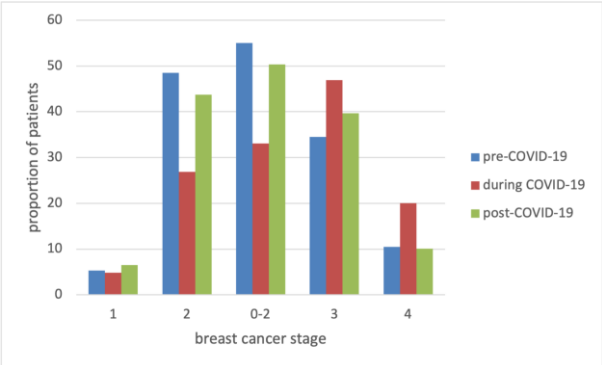

Figure 1: Stage at presentation across the 3 groups (pre-COVID-19 in blue, COVID-19 group in red, and post-COVID-19 in green).

Table 2: Disease characteristics across the 3 groups

		Year			Total	P value
		2019 (pre-COVID-19)	**2020 (during COVID-19)**	**2021 (post-COVID-19)**		
Stage (n=515)		N=171	N=145	N=199		.003
	CIS	2 (1.2%)	2 (1.4%)	0 (0.0%)	4	
	1	9 (5.3%)	7 (4.8%)	13 (6.5%)	29	
	2	83 (48.5%)	39 (26.9%)	87 (43.7%)	209	
	0-2	94 (55.0%)	48 (33.1%)	100 (50.3%)	242	
	3	59 (34.5%)	68 (46.9%)	79 (39.7%)	206	
	4	18 (10.5%)	29 (20.0%)	20 (10.1%)	67	
Type of surgery (n=438)		N=149	N=118	N=171		.098
	Conservative	54 (36.2%)	32 (27.1%)	67 (39.2%)	153	
	Mastectomy	95 (63.8%)	86 (72.9%)	104 (60.8%)	285	
Site of metastasis (n=517)		N=171	N=145	N=201		
	No metastasis	153 (89.5%)	116 (80.0%)	181 (90.0%)	450	.037
	Bone	7 (4.1%)	14 (9.7%)	12 (6.0%)	33	
	Visceral	11 (6.4%)	15 (10.3%)	8 (4.0%)	34	

Discussion:

The COVID-19 pandemic has delayed screening programs in both developed and developing countries, also affecting early detection of breast cancer [23]. In Egypt, the COVID-19 lockdown resulted in breast cancer screening suspension, as many specialists and units have been redirected to treat patients with COVID-19. In this study, we found that breast cancer was diagnosed at a more advanced stage during the COVID-19 pandemic compared with the pre-lockdown and post-lockdown periods, which differs from the Mayo Clinic retrospective results, where no impact of the COVID-19 pandemic on breast cancer staging at presentation was found [22]. The leading international professional societies issued specific guidelines on patient management during the COVID-19 lockdown. According to the European Society of Medical Oncology (ESMO), new diagnosis of non-invasive cancer had a medium priority for in-person care, and most visits should be converted to telemedicine. However, this option is not widely available in developing countries, including Egypt [24].

This is the first study to report initial breast cancer staging statistics during the COVID-19 lockdown in Egypt, but the values obtained for the pre- and post-COVID-19 periods are comparable to those recently published in literature. In our sample, early breast cancer was diagnosed in approximately half of patients outside the lockdown period, while stage IV accounted for 10.3-10.6% of cases. Similar rates were indicated in a paper involving three hospitals in Alexandria, Egypt: in the period from 2007 to 2016, 48% of patients had initially localized disease [5]. In another single-center study, which included 400 patients, 47.5% of women presented with advanced breast cancer (7.5% with stage IV) [25]. Stage 4 proportion obtained in earlier studies was comparable or even higher than that during COVID-19 in our sample, ranging from 16% to 26% of cases, possibly due to growing public awareness in recent times [26,27]. Male breast cancer rate in our sample was also consistent with the previously reported value: 1.4% and 2%, respectively [28]. These similarities suggest that the study results could reflect patterns observed across the country.

We found that the surgical breast conservation rate decreased significantly during the COVID-19 pandemic, which is consistent with the results of the Indian study by Javaykumar et al, but our study also demonstrates that this indicator improved in the post-COVID-19 period [14]. COVID-19 pandemic was associated with a significantly higher rate of visceral metastasis at diagnosis compared with the pre-pandemic value, which also improved in the post-COVID-19 group.

The limitations of this study include a single registry as the data source, which did not allow to assess the total number of screening mammograms obtained in different periods. Analyses conducted in different regions of the USA report inconsistent results on screening rate recovery – in one cohort, pre-pandemic rate was achieved by the end of 2020, while in another the rate was still decreased in 2021 [29,30]. Given the differences in the number of admissions and staging between the COVID-19 and post-COVID-19 groups in our analysis, we assume that the screening resumed in our country by 2021. Our study is also lacking a survival assessment, as the survival data are not yet mature for the analysis. We suppose that the shift in

staging at presentation will lead to negative survival consequences. Maringe C. et al estimated that the number of breast cancer deaths in England will increase by 7.9-9.6% due to the COVID-19 crisis [31].

Mobile mammography services can be helpful when epidemiological situation dictated the need to minimize public transport usage. A positive experience with mobile breast cancer screening under the Women Health Outreach Program in Egypt has been described [32]. Another important steps for maintaining cancer screening during a pandemic are to educate patients about personal protective measures and segregate patient flows, as many people avoid scheduled visits due to fear of COVID-19 exposure [33].

This retrospective study showed that COVID-19 pandemic was associated with a more advanced initial breast cancer stage and a more frequent presence of visceral metastasis at diagnosis. All these indicators improved to the pre-COVID-19 values after the mass vaccination was initiated and the restrictions were lifted, but the consequences for breast cancer mortality remain to be assessed in the upcoming years.

List of abbreviations:
BCS – breast conserving surgery
COVID-19 – coronavirus disease 2019
ER – estrogen receptor
ESMO - European Society of Medical Oncology
EUA – Emergency Use Authorization
FDA – U.S. Food and Drug Administration
HER2 – human epidermal growth factor receptor 2

Declarations:
Ethics approval and consent to participate. The ethical approval was obtained from the Ethical Committee, Faculty of Medicine, Beni-Suef University, Egypt (Approval No. FMBSUREC/ 06112022/Shaaban). The Committee concluded that there was no need for obtaining informed consent, as the data was anonymous.

Consent for publication. Not applicable.

Availability of data and materials. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. MES and SMS – research concept, data analysis, manuscript drafting. SG – literature search, finalizing the manuscript. All authors read and approved the final manuscript.
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