Original Article

The Impact of the COVID-19 Pandemic on Patients with Breast Cancer, Diagnostic Delays and Disease Progression: A Retrospective Study

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Received: 25 January 2025
Revised: 03 July 2025
Accepted: 11 July 2025

What's Known

- The COVID-19 pandemic led to delays in breast cancer diagnosis and treatment, resulting in patients presenting with larger tumors, increased axillary involvement, and more advanced disease stages.
- Previous studies reported decreased cancer screenings and delayed diagnoses caused by COVID-19 restrictions, leading to more advanced disease at presentation.

What's New

- This study provided unique regional data from Shiraz, Iran, quantifying the rise in tumor size, axillary lymph node involvement, and advanced staging among breast cancer patients during the pandemic.
- The findings highlighted a significant post-pandemic decline in the utilization of adjuvant chemotherapy and intraoperative radiotherapy, underscoring critical gaps in subsequent patient management.

Abstract

Background: Breast cancer is the most frequent malignancy among women. The COVID-19 pandemic significantly impacted healthcare systems, potentially affecting the management of this disease. Due to the critical importance of early diagnosis and treatment, and the limited data on the pandemic's specific effects, this study aimed to determine the correlation between the COVID-19 pandemic and various breast cancer parameters.

Methods: This retrospective study included patients with breast cancer in Shiraz, Iran. Patients were divided into two groups, including those diagnosed before and after the start of the COVID-19 pandemic (from September 2018 to March 2021). Variables included demographic, clinical, and management features. Continuous variables were reported as mean±SD, and the categorical data were reported as frequency and percentage. The significance level was set as $P<0.05$.

Results: The study documented 1,435 patients: 811 patients were diagnosed before the pandemic, and 624 patients were diagnosed after. The mean initial tumor size at the time of diagnosis was significantly larger in the post-pandemic group than the pre-pandemic group (2.29±1.44 vs. 2.11±1.39 cm, respectively; P=0.001). The distribution of cancer stages also differed significantly (P=0.001). While the prevalence of stage 1 disease was similar between groups (30.1% vs. 28.9%), the prevalence of stage 2 (14.8% vs. 8.5%) and stage 3 (10.1% vs. 7.0%) was significantly higher in the post-pandemic group (Stage 1: 30.1 vs. 28.9%, Stage 2: 8.5 vs. 14.8%, Stage 3: 7 vs. 10.1%; P=0.001).

Conclusion: Following the COVID-19 pandemic, patients presented with significantly larger breast tumors, increased axillary involvement, and more advanced stages after the COVID-19 pandemic.

Please cite this article as: Rezvani AR, Heydarzadeh R, Golchin Vafa R, Sohrabizadeh S, Rahmani MH, Zangouri V, Molavi Vardanjani H, Zarifkar H, Zarifkar H, Zarifkar H, Shahriarirad R. The Impact of the COVID-19 Pandemic on Patients with Breast Cancer, Diagnostic Delays and Disease Progression: A Retrospective Study. Iran J Med Sci. doi: 10.30476/ijms.2025.105608.3951.

Keywords ● Breast neoplasm ● COVID-19 ● Delayed diagnosis ● Pandemics

Introduction

Early diagnosis is the most critical factor in improving survival and longer-term quality of life for cancer patients.[1] Unfortunately, standard protocols for the early detection of cancer were disrupted by the coronavirus disease 2019 (COVID-19) pandemic, a global health concern that emerged in December 2019.[2]

The management of various cancers, including breast cancer, was significantly affected, creating critical challenges for patients.[3]

Furthermore, cancer has been established as a significant risk factor and comorbidity for COVID-19, with infection potentially leading to more severe and even fatal events in these patients.[4-6] Regarding the enormity of this pandemic, numerous complications emerged. The outbreak impacted not only the diagnosis and treatment of several severe diseases but also their follow-up protocols. Recent studies have demonstrated a clear correlation between the COVID-19 pandemic and the efficiency of healthcare systems.[7-10] In Iran, this disruption was associated with a decrease in life expectancy of one year.[11]

Breast cancer is the most common malignancy among women and, after lung cancer, the most life-threatening. It affected 7.8 million people by the end of 2020.[12] Research by Minami and colleagues indicated that the treatment delay was an important factor in disease progression among patients with breast cancer.[13] Results from a meta-analytic study by Marty and colleagues demonstrated a higher rate of metastatic tumors, particularly breast cancer, following the COVID-19 pandemic.[14] The pandemic has significantly influenced breast cancer management, leading to alterations in various factors, such as tumor size, grade, stage, lymph node involvement, and care delays.[15]

Given the importance of timely diagnosis and treatment, a survey in Guangzhou, China, demonstrated that poor follow-up resulted in more advanced clinical stages and a poorer prognosis of breast cancer.[16] Moreover, Alaidy and colleagues showed that postponed diagnosis could lead to increased tumor size.[17] However, some researchers argued that the local recurrence of some types of breast cancers was more closely associated with the tumor size than with delays in late radiotherapy.[18] The COVID-19 pandemic is a likely contributor to these outcomes. As a notable example, a study noted that unprecedented pressures on the health system led to a decline in patient referrals to oncologists, depriving many of effective anticancer treatments and resulting in increased morbidity and mortality during the pandemic.[19]

Due to the critical importance of early diagnosis and treatment in breast cancer, and given the limited investigation into the specific effects of the COVID-19 pandemic on these processes, this study was conducted to determine the correlation between the pandemic and key breast cancer parameters. These parameters, assessed at diagnosis and after primary treatment, included tumor size, stage, and referral for adjuvant therapy. Elucidating this relationship would further help us to make better decisions about cancer patients, particularly those with breast cancer, during future pandemics or other major global health crises.

Patients and Methods

Study Design and Variables

This retrospective study utilized data from patients with breast cancer, including 811 patients diagnosed in the year before the COVID-19 pandemic (from September 2018 to September 2019) and 624 patients diagnosed in the year after its onset (from March 2020 to March 2021). Patient information was obtained from Shiraz Breast Cancer Registry (SBCR) and cancer centers affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). The registry included data on baseline characteristics, clinical history, physical examination, imaging, disease course, prognosis, and surgical and pathological parameters.[20]

Patients were divided into two groups based on whether they were diagnosed before or after the start of the pandemic. The compared variables included age, tumor size, stage, subtype (luminal A, luminal B, triple-negative, and HER2-enriched), multifocality, *in situ* component, tumor necrosis, type of involvement (perineural, vascular, or both), receptor status, type of surgery (breast-conserving surgery [BCS] or mastectomy), type of axillary management (axillary lymph node dissection [ALND], sentinel lymph node biopsy [SLNB], or both), and the use of adjuvant chemotherapy, radiotherapy, intra-operative radiotherapy (IORT), and hormonal therapy. Due to the well-established importance of neoadjuvant chemotherapy in selected cases, a subgroup analysis comparing these variables was also performed for patients who received neoadjuvant chemotherapy and for those who did not.

Inclusion and Exclusion Criteria

The inclusion criteria were female sex of any age, a diagnosis of breast cancer within one year before or after the start of the COVID-19 pandemic (December 2019), and having relatively complete medical records regarding tumor size, stage, subtype, type of surgery, axillary management, lymph node involvement, and chemotherapy. Patients with metastatic disease at diagnosis were excluded.

Ethical Considerations

This study protocol was approved by the Ethics Committee of Shiraz University of

Medical Sciences (approval ID: IR.SUMS.MED.REC.1399.628). All patients were informed about the use of their data for research. Due to the retrospective nature of the study, the requirement for written informed consent was waived by the Ethics Committee. Patient information was obtained from hospital records, de-identified before analysis, and confidentiality was guaranteed and protected. Permission to conduct the study and access records was granted by the university administrators. Additionally, the study was conducted in accordance with the relevant guidelines and regulations and the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software (version 26, IBM, Chicago, USA). Continuous variables were described as mean±SD, and categorical variables were presented as frequency and percentage. Independent sample *t* tests were used to compare normally distributed continuous variables (e.g., tumor size) between the pre- and post-pandemic groups. Paired sample *t* tests were applied where necessary to compare pre- and post-pandemic values within the same patient group. The Wilcoxon signed-rank test was used for non-normally distributed repeated measures. For categorical data comparisons (e.g., stage, receptor status), Pearson's Chi square test was applied, and the Kruskal-Wallis test was used for non-normally distributed categorical data. Effect sizes were recalculated as Cohen's d for continuous variables and Cramér's V or the Phi coefficient for categorical variables. Statistical significance was defined as $P<0.05$.

Results

Demographic

The study included 1,435 patients; 811 patients were diagnosed with breast cancer before the pandemic, and 624 patients were diagnosed after. The mean age of the participants was 49.1±11.4 in the pre-pandemic group and

Table 1: Breast tumor size, stage, and subtypes before and after the COVID-19 pandemic

Variable		Subgroup	Year Group		P value
			Pre-pandemic (2018-2019)	Post-Pandemic (2020-2021)	
Tumor size (cm, mean±SD)		Neoadjuvant CT	1.58±0.47	1.57±0.68	0.428
		No neoadjuvant CT	2.28±1.3	2.55±1.3	0.002
		Total	2.11±1.39	2.29±1.44	0.001
Stage (n, %)	Neoadjuvant CT	III	19 (8.6)	17 (10.8)	0.042
		II	30 (13.6)	33 (20.9)	
		I	71 (32.1)	47 (29.7)	
		Not defined	101 (45.7)	61 (38.6)	
	Non-neoadjuvant CT	III	38 (6.7)	46 (10.2)	0.001
		II	39 (6.8)	59 (13.1)	
		I	173 (30.3)	133 (29.4)	
		Not defined	321 (56.2)	214(47.3)	
	Total	III	57 (7)	63 (10.1)	0.001
		II	69 (8.5)	92 (14.8)	
		I	244 (30.1)	180 (28.9)	
		Not defined	441 (54.4)	289 (46.2)	
Subtype	Neoadjuvant CT	Enriched-HER2	26 (11.6)	17 (10.2)	0.211
		Triple-negative	36 (16.1)	19 (11.3)	
		Luminal B	44 (19.6)	29 (17.2)	
		Luminal A	86 (38.4)	65 (38.7)	
		Not defined	32 (14.3)	38(22.6)	
	Non-neoadjuvant CT	Enriched-HER2	62 (10.6)	54 (11.8)	0.417
		Triple-negative	47 (8.0)	21 (4.6)	
		Luminal B	91 (15.5)	67 (14.7)	
		Luminal A	286 (48.7)	217 (47.6)	
		Not defined	101 (17.2)	97 (21.3)	
	Total	Enriched-HER2	88 (10.9)	71 (11.4)	0.02
		Triple-negative	83 (10.2)	40 (6.4)	
		Luminal B	135 (16.6)	96 (15.4)	
		Luminal A	372 (45.9)	282 (45.2)	
		Not defined	133 (16.4)	135 (21.6)	

Chi square test was used; $P<0.05$ was considered statistically significant. COVID: Coronavirus disease; CT: Chemotherapy

49.3±11.7 in the post-pandemic group.

Tumor Size

The mean tumor size was significantly larger in the post-pandemic group (2.29±1.44 cm) than in the pre-pandemic group (2.11±1.39 cm). This difference was statistically significant (P=0.001, Cohen d: -0.127, indicating a small effect size). Among patients who did not receive neoadjuvant chemotherapy, the tumor size was also significantly larger in the post-pandemic group (2.55±1.3 cm vs. 2.28±1.3 cm; P=0.002). In contrast, no significant differences in tumor size were observed before and after the pandemic in the subgroup that received neoadjuvant chemotherapy (P=0.428, table 1).

Stage

More patients presented with stage 3 cancer after the pandemic (63, 10.1%) than the occurrence of stage 3 cancer before this outbreak (57, 7%; P=0.001, Cramer's V=0.085, indicating a small effect size). The prevalence of stage 2 was also higher post-pandemic (92, 14.8%) than pre-pandemic (69, 8.5%). Conversely, the prevalence of stage 1 was lower in the post-pandemic group (180, 28.9%) than the pre-pandemic group (244, 30.1%, table 1).

Subtypes

The distribution of breast cancer subtypes before the COVID-19 pandemic was as follows: 372 (45.9%) luminal A, 135 (16.6%) luminal B,

Table 2: The characteristics of breast tumors before and after the COVID-19 pandemic

Variable		Subgroup	Year Group		P value
			Pre-pandemic (2018-2019) n (%)	Post-Pandemic (2020-2021) n (%)	
In situ component (n, %)		Neoadjuvant CT	91 (20.8)	55 (17.0)	0.528
		Non-neoadjuvant CT	329 (75.2)	254 (78.4)	0.378
		Not defined	17 (4.0)	15 (4.6)	
		Total	437 (53.9)	324 (51.9)	0.461
Tumor necrosis (n, %)		Neoadjuvant CT	76 (22.2)	43 (16.3)	0.363
		Non-neoadjuvant CT	250 (73.1)	210 (79.5)	0.482
		Not defined	16 (4.7)	11 (4.2)	
		Total	342 (42.2)	264 (42.3)	0.501
Involvement (n, %)	Neoadjuvant CT	Perinodal	5 (2.5)	4 (3.4)	0.006
		Vascular	78 (38.6)	31 (26.1)	
		Both of them	23 (11.4)	14 (11.7)	
		None of them	96 (47.5)	70 (58.8)	
	Non-neoadjuvant CT	Perinodal	40 (6.6)	39 (7.7)	0.001
		Vascular	150 (24.3)	102 (20.2)	
		Both of them	69 (11.3)	75 (14.9)	
		None of them	350 (57.8)	289 (57.2)	
	Total	Perinodal	45 (5.6)	43 (6.9)	0.001
		Vascular	228 (28.2)	133 (21.3)	
		Both of them	92 (11.3)	89 (14.3)	
		None of them	446 (54.9)	359 (57.5)	
Multifocal (n, %)		Neoadjuvant CT	20 (22.0)	13 (18.3)	0.492
		Non-neoadjuvant CT	67 (73.6)	52 (73.2)	0.378
		Not defined	4 (4.4)	6 (8.5)	
		Total	91 (11.2)	71 (11.4)	0.427
Positive estrogen receptor (n, %)		Neoadjuvant CT	129 (23.0)	72 (17.3)	0.001
		Non-neoadjuvant CT	408 (72.7)	330 (79.1)	0.002
		Not defined	24 (4.3)	15 (3.6)	
		Total	561 (69.1)	417 (66.8)	0.001
Positive progesterone receptor (n, %)		Neoadjuvant CT	108 (21.6)	61 (16.1)	0.001
		Non-neoadjuvant CT	369 (73.9)	304 (80.2)	0.001
		Not defined	22 (4.5)	14 (3.7)	
		Total	499 (61.5)	379 (60.7)	0.001
Positive HER2 receptor (n, %)		Neoadjuvant CT	74 (33.3)	33 (23.9)	0.029
		Non-neoadjuvant CT	137 (61.7)	100 (72.5)	0.178
		Not defined	11 (2.0)	5 (3.6)	
		Total	222 (27.4)	138 (22.1)	0.008

Chi square test was used. P<0.05 was considered statistically significant. COVID: Coronavirus disease; CT: Chemotherapy

83 (10.2%) triple negative, 88 (10.9%) enriched-HER2, and 133 (16.4%) undefined. After the pandemic, the distribution was: 282 (45.2%) luminal A, 96 (15.4%) luminal B, 40 (6.4%) triple negative, 71 (11.4%) enriched-HER2, and 135 (21.6%) undefined. A significant difference was found specifically for the triple-negative subtype (P=0.02). No other significant differences in subtype distribution were observed between the pre- and post-pandemic periods, either in the overall cohort or when stratified by neoadjuvant chemotherapy status (table 1).

Perinodal and Vascular Involvement

Before the pandemic, the prevalence of perinodal, vascular, and concomitant perinodal and vascular involvement was 45 (5.6%), 228 (28.2%), and 92 (11.3), respectively. After the pandemic, the prevalence was 43 (6.9%) for perinodal, 133 (21.3%) for vascular, and 89 (14.3%) for concomitant involvement. This overall difference in the pattern of involvement was statistically significant (P=0.001, effect size=54.59).

Receptors, Multifocality, Tumor Necrosis, and In Situ Component

The prevalence of progesterone receptors (PR) positivity was significantly lower in the post-pandemic group (379, 60.7%) than the pre-pandemic group (499, 61.5%; P=0.001, Cramer's V=0.11). This decrease was observed in both the neoadjuvant and non-neoadjuvant subgroups. Similarly, the prevalence of HER2 receptor positivity was lower after the pandemic than before (138, 22.1% vs. 222, 27.4%; P=0.008, Cramer's V=0.10). The reduction in HER2 positivity was observed in both subgroups, though it was not statistically significant in the non-neoadjuvant group. Moreover, the frequency of estrogen receptor (ER) was significantly lower after the pandemic in total and in each subgroup analysis. No significant differences

Table 3: The management of breast tumors before and after the COVID-19 pandemic

Variable		Subgroup	Year group		P value
			Pre-pandemic (2018-2019)	Post-pandemic (2020-2021)	
Type of surgery (n, %)	Neoadjuvant CT	BCS	115 (49.8)	64 (44.7)	0.776
		Mastectomy	111 (48.0)	74 (51.7)	
		Mastectomy and BCS	5 (2.2)	5 (3.6)	
	Non-neoadjuvant CT	BCS	420 (74.6)	351 (73.1)	0.240
		Mastectomy	126 (22.4)	103 (21.2)	
		Mastectomy and BCS	17 (3.0)	26 (5.4)	
	Total	BCS	535 (66.0)	415 (66.5)	0.153
		Mastectomy	237 (29.2)	177 (28.3)	
		Mastectomy and BCS	22 (2.7)	31 (5.0)	
		Not defined	17 (2.1)	1 (0.2)	
Axillary management (n, %)	Neoadjuvant CT	ALND	103 (46.6)	54 (43.9)	0.006
		SLNB	97 (43.9)	50 (40.6)	
		SLNB and ALND	21 (9.5)	19 (15.5)	
	Non-neoadjuvant CT	ALND	80 (14.2)	67 (14.1)	0.786
		SLNB	399 (70.6)	327 (68.7)	
		SLNB and ALND	86 (15.2)	82 (17.2)	
	Total	ALND	183 (22.6)	121 (19.4)	0.191
		SLNB	496 (61.2)	377 (60.4)	
		SLNB and ALND	107 (13.2)	101 (16.2)	
		Not defined	25 (3.0)	25 (4.0)	
Adjuvant therapy (n, %)		Neoadjuvant CT	74 (36.2)	26 (21)	0.004
		Non-neoadjuvant CT	480 (83.9)	381 (80)	0.018
		Total	556 (68.5)	407 (65.2)	0.203
Radiotherapy (n, %)		Neoadjuvant CT	183 (89.7)	110 (88.8)	0.143
		Non-neoadjuvant CT	390 (68.4)	368 (77.3)	0.001
		Total	574 (70.8)	478 (76.6)	<0.001
IORT (n, %)		Neoadjuvant CT	3 (1.5)	0 (0)	0.239
		Non-neoadjuvant CT	59 (5.1)	13 (2.7)	0.001
		Total	64 (7.9)	13 (2.1)	<0.001
Hormonal therapy (n, %)		Neoadjuvant CT	133 (65.2)	83 (67)	0.165
		Non-neoadjuvant CT	406 (71.7)	347 (72.9)	0.013
		Total	539 (66.5)	430 (68.5)	0.01

Chi square test was used. P<0.05 was considered statistically significant. ALND: Axillary lymph node dissection; BCS: Breast-conserving surgery; COVID: Coronavirus disease; CT: Chemotherapy; SLND: Sentinel lymph node dissection

were observed in multifocality, tumor necrosis, or the presence of an *in situ* component before and after the pandemic (table 2).

Type of Surgery

Before the pandemic, the number of patients who underwent BCS, mastectomy, or both was 535 (66%), 237 (29.2%), and 22 (2.7%), respectively. After the pandemic, the corresponding figures were 415 (66.5%) for BCS, 177 (28.3%) for mastectomy, and 31 (5.0%) for both procedures (P=0.153). Additionally, the frequency of ALND was 182 (22.6%) before and 121 (19.4%) after the pandemic. The SLNB was performed on 496 patients (61.2%) before and 377 (60.4%) patients after the pandemic. The prevalence of concomitant ALND and SLNB increased from 13.2% to 16.2% after the COVID-19 pandemic (P=0.191, table 3).

Adjunctive Therapies

The prevalence of radiotherapy increased significantly from 70.8% to 76.6% (P<0.001, Cramer's V=0.23). This increase was more pronounced in the non-neoadjuvant chemotherapy group, with no significant difference observed in the neoadjuvant chemotherapy group. On the other hand, the frequency of IORT decreased significantly from 64 (7.9%) to 13 (2.1%) after the pandemic (P<0.001, Cramer's V=0.23). The prevalence of hormonal therapy was 539 (66.5%) before and 430 (68.5%) after the pandemic (P=0.01). In the neoadjuvant chemotherapy group, there were no significant differences in the use of IORT or hormonal therapy before and after the COVID-19 pandemic (table 3).

Discussion

This study provided a unique quantification of the COVID-19 pandemic's impact on breast cancer presentation and management in Shiraz, Iran, revealing increases in tumor size, axillary involvement, and advanced stages at diagnosis. The findings of the present study highlighted significant post-pandemic declines in the use of adjuvant chemotherapy and intraoperative radiotherapy, underscoring critical gaps in patient management. Breast cancer is a serious public health problem, accounting for 24% of all cancers and 15% of cancer-related deaths.[21] Early diagnosis and regular follow-ups are the most significant factors for improving treatment success and decreasing mortality.[22] In recent years, the COVID-19 pandemic emerged as one of the most significant global public health challenges of the century,[23-25] disrupting these very principles of cancer care.

This study demonstrated that the pandemic had a measurable impact, leading to statistically significant changes in tumor size, cancer stage, and treatment modalities. However, the small effect sizes for tumor size (Cohen's d=-0.127) and cancer stage (Cramér's V=0.085) suggested that while these changes were statistically significant, their clinical significance might be limited. This finding was in agreement with previous studies that reported delays in cancer diagnosis and treatment during the pandemic, resulting in more advanced disease at presentation.[26, 27]

A systematic review by Li and colleagues on the short-term impact of the COVID-19 pandemic found a substantial decrease in breast cancer screening volumes and diagnosis rates, coupled with an increase in the proportion of advanced-stage cancers at diagnosis.[26] Similarly, research conducted in France indicated a 20% decrease in diagnosed breast cancers during the pandemic, followed by a 48% increase after lockdown.[27] Koca and colleagues also revealed that during the pandemic, a significant reduction of 79.8% was observed in the rate of screening mammography, leading to a 47.7% decrease in the number of patients diagnosed and surgically managed during this period.[22] These disruptions resulted in fewer crucial and elective surgical procedures and reduced hospital admissions for breast cancer patients than the pre-pandemic era.[28, 29] Consistent with this global trend, the present study confirmed that the COVID-19 pandemic had a measurable impact on breast cancer diagnosis and management. A significant increase in tumor size and a more advanced disease stage at presentation was observed after the pandemic. However, the small effect sizes for these parameters suggested that while the changes were statistically significant, their clinical magnitude might be limited.

The observed increase in tumor size and more advanced staging in our post-pandemic cohort might be attributed to reduced access to screening and diagnostic services during lockdowns and healthcare resource reallocation. However, the small effect sizes suggested that while these changes were statistically significant, their long-term clinical impact on patient outcomes might be limited. This finding underscored the clinical importance of maintaining cancer screening and diagnostic services during public health crises to prevent treatment delays.

Our findings were consistent with several international studies. Research conducted in Turkey showed that the pandemic led to patients presenting with larger breast tumors and an

increased axillary involvement, and neoadjuvant chemotherapy.[22] Furthermore, Linck and colleagues estimated that delayed diagnosis would result in breast cancers, detected after COVID-19, having larger tumor sizes and higher rates of lymph node invasion.[27] These changes could be attributed to the reduction in cancer screening rates during the pandemic era.[23] Conversely, other studies reported similar trends that did not reach statistical significance. A previous study after the COVID-19 duration found a non-significant 38% decrease in small tumors, an 80% increase in locally advanced cancers, and a 64% increase in lymph node invasion rates.[27] Similarly, another study reported larger tumor sizes and more lymph node involvement after the pandemic. However, these differences were not statistically significant.[30] In contrast to our significant findings, another study demonstrated that larger tumor sizes and more metastatic lymph nodes post-pandemic did not reach statistical significance.[28]

This study found a significant increase in the number of patients diagnosed with Stage 2 and Stage 3 breast cancer after the pandemic, but not with Stage 1. A study from France indicated that delayed diagnosis was a key factor in later-stage progression for breast cancer patients, with more aggressive cancers being detected at advanced stages in the post-pandemic period.[27] Similar to our findings, Li and colleagues showed a shift in the stage distribution at diagnosis during the pandemic, with lower proportions of early-stage cases and higher proportions of advanced cases than in the pre-pandemic period.[26] However, some researchers reported no notable pandemic-induced variations in tumor grade or hormone receptor status.[30]

Our analysis indicated an increase in perineural involvement, both alone and along with vascular invasion, post-pandemic, while isolated vascular involvement decreased. The significant difference in the overall pattern of invasion (P=0.001) aligned with prior studies, suggesting that diagnostic delays could lead to more locally advanced disease. However, since the effect sizes for tumor size and stage shifts were relatively small, the clinical implications of these changes should be interpreted with caution.

The decrease in PR and HER2 positivity after the pandemic, while statistically significant, was associated with small effect sizes (Cramér's V=0.11 and 0.10, respectively). This suggested that these changes might reflect natural fluctuations in tumor biology rather than a definitive pandemic-induced shift in breast cancer subtypes. Further research is required to explore the potential biological and environmental factors contributing to these changes in receptor status. The increase in radiotherapy utilization and the decrease in IORT after the pandemic highlighted changes in treatment patterns, likely due to resource constraints and evolving clinical guidelines during the pandemic. The moderate effect sizes for these treatment changes (Cramér's V=0.23) suggested a more pronounced potential impact on patient care and outcomes compared to the changes in tumor size and stage. Regarding tumor biology, the prevalence of PR positivity declined in both neoadjuvant and non-neoadjuvant groups after the pandemic. Furthermore, a significant decrease was also observed in ER frequency, both overall and within each subgroup. Similarly, HER2 positivity diminished, although this change was not statistically significant in the non-neoadjuvant group. Notably, previous research emphasized the positive impact of neoadjuvant systemic treatment on disease-free survival in real-world cohorts of HER2-positive breast cancer.[31] Conversely, no significant disparities were found for multifocality, tumor necrosis, or the presence of an *in situ* component when comparing the post-pandemic and pre-pandemic periods.

The findings of the present study revealed substantial shifts in adjuvant treatment patterns following the pandemic. Despite the observed increase in more advanced cancer stages, the rate of adjuvant chemotherapy decreased, particularly within the neoadjuvant group. This suggested a concerning gap in the standard management of breast cancer patients during this period. Furthermore, while the utilization of radiotherapy saw a substantial uptick—primarily in the non-neoadjuvant group—the use of IORT experienced a marked decline. Furthermore, the prevalence of hormonal therapy escalated after the pandemic. However, no significant changes in IORT or hormonal therapy were observed within the neoadjuvant subgroup.

Despite an observed increase in the stage of patients with breast cancer at diagnosis, the rate of adjuvant chemotherapy declined after the COVID-19 pandemic. This decline was noted across specific patient groups, particularly those who had received neoadjuvant therapy, suggesting a systemic neglect in proper patient management. This is concerning, as a systematic review revealed that postponing adjuvant radiotherapy by more than 8 weeks following surgery doubled the risk of local recurrence in patients diagnosed with breast cancer.[32] Thus, the decline in the rates of adjuvant chemotherapy, as a crucial step in the management of select patients, exemplified

how the COVID-19 pandemic led to insufficient application of treatment modalities, as well as the diagnostic problems previously discussed.

This study had several limitations. Its retrospective, single-center design relied on hospital records that contained missing information. Furthermore, the lack of long-term follow-up and cost-effective analysis of screening methods might be considered another limitation of our study, which warrants further investigations. Other limitations included the single-center design and the small effect sizes for key variables such as tumor size and cancer stage, which suggested that the clinical significance of these findings should be interpreted with caution. These findings reinforced the need to ensure the continuity of cancer screening programs, particularly during public health crises, to prevent delays in early diagnosis. Future prospective, multi-center studies with larger, more diverse samples and longer follow-up periods are warranted to validate these trends and fully understand the pandemic's long-term impact on breast cancer outcomes.

Conclusion

The COVID-19 pandemic led to notable shifts in breast cancer diagnosis and treatment. This study documented a trend toward larger tumor sizes, greater axillary involvement, and more advanced stages at diagnosis following the pandemic, likely due to delayed diagnoses influenced by misinterpretation of social distancing guidelines. Treatment trends also shifted, with increased use of radiotherapy and decreased use of adjuvant chemotherapy and IORT. Although many of these changes were associated with small effect sizes, the findings underscored the critical need to maintain access to screening and care during public health crises.

Future research should explore the long-term survival impact of these care disruptions, assess the resilience of national screening programs, develop rapid diagnostic platforms, and incorporate data from low- and middle-income countries to better understand global responses and outcomes.

Acknowledgment

We would like to express our sincere gratitude to Shiraz Breast Cancer Research Center for providing the majority of the patients' data for this study. This project was part of the MPH dissertation of Dr. Alireza Rezvani (grant number: 22259).

Authors' Contribution

A.R: Study concept, data analysis, and drafting; R.H: Data collection, literature review, and drafting; S.S: Data collection, literature review, and drafting; Mh.R: Data collection, literature review, and drafting; R.GhV: Data collection, literature review, and drafting; V.Z: Study concept and design, and critically reviewing the manuscript; H.MV: Study concept and design, and critically reviewing the manuscript; H.H: Data interpretation, data gathering and reviewing the manuscript; H.Z: Data interpretation, data gathering and reviewing the manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of AI

The authors declare that no AI tools were used in the preparation of this manuscript.

Conflict of Interest: None declared.

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