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Research Paper

COVID 19 pandemic: Effect on management of patients with breast cancer; single center retrospective cohort study

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ABSTRACT

Background: (SARS-COV-2) infection, led to a pandemic affecting many countries, resulting in hospitals diverting most of their resources to fight the pandemic. Breast cancer, already a healthcare dilemma, is also affected in this scenario. Our aim was to find out the impact of COVID-19 on presentation of breast cancer stage and its effects on overall onco-surgical management.
Methods: This cohort single-centered retrospective review was carried out at our hospital, over a period of 18 months. Females with known breast cancer were included in the study. Data was collected on performas by a single researcher. Effect of COVID pandemic on presentation stage and its impact on overall management was studied. SPSS 23.0 used for data analysis. A 95% CI was used. Descriptive statistics were presented as range/means. Categorical data was analyzed by Fisher exact test, *t*-test was applied to numerical data, p value $\leq$ 0.05 was considered significant.
Results: Out of 87 patients presenting with suspicious lump, 69 who had malignancy on histo-pathology were included in study. Twelve out of 69 were COVID positive. Sixty patients presented with advanced stage ($\geq$ stage 2b) out of which 21 underwent upstaging of disease due to delay in presentation/management. We found that 9 out of 12 (majority) Covid positive patients had disease upstaging. Overall main reason for delay in presentation was found to be unawareness of disease.
Conclusion: We concluded that COVID-19 pandemic had no impact on presentation delay, breast cancer management/treatment and disease upstaging as compared to figures available for our population before the pandemic. However, our study showed significant correlation between disease upstaging and COVID status. This led us to reconsider our preformed protocols for COVID positive breast cancer patients. Our results can be used by future researchers to investigate if COVID itself can contributes in pathophysiology of upstaging in breast cancer or not.

1. Introduction

In December 2019, novel corona virus (SARS-COV-2) originated from Wuhan, Hubei province of China [1]. Since COVID 19 was declared as a pandemic by WHO on March 11, 2020; hospitals have opted to dispense maximum resources to critical COVID 19 effected patients; this strategy has affected both elective and semi elective procedures [2].It has been observed that patients with chronic illnesses, especially cancer, are at greater risk to develop severe disease course among COVID-19 patients [3].

Breast cancer is the most prevalent cancer among female population and causes 15% of total cancer deaths in developed countries, making it the leading cause of mortality [4]. Pakistan has a (>5.2 times) higher incidence and (>2.8 times higher) mortality rate of breast cancer than the rest of Asia [5]. The late diagnosis of breast cancer is the main reason for a higher mortality rate in Pakistan. This roots from many different factors like lack of awareness about the disease, non-availability of adequate

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screening and diagnostic facilities and social taboos associated with breast related conditions [6]. The recent COVID 19 pandemic and the lockdown which immediately followed it in Pakistan, has added more burden to the above-mentioned challenges faced in cancer care. Furthermore, healthcare workforce is correspondingly insufficient in Pakistan (being a low-income region) to deal with the burden of cancer [6]. Keeping in view this scenario many hospitals in our region have started to triage the cases presenting to hospitals so that unwanted utilization of sources can be minimized, but this strategy and overall lockdown has led to delayed presentation of cancer cases to hospitals notably breast cancer cases.

The primary aim of this study was to determine how the COVID-19 pandemic has affected the presenting stage of breast cancer in our region and its effects on overall onco-surgical management of patients. We also hypothesized that COVID status can have significant impact on presentation, treatment initiation and definitive surgery. Our secondary aim was to correlate COVID status with delay time and its notable impact on overall upstaging of the breast cancer.

2. Methods

This single-centered retrospective cohort study was conducted at department of surgery of a public/private hospital in Karachi, Pakistan after obtaining permission from ethical review committee of hospital. The research registry number is NCT04929964. Patient's data of all operated cases for suspicious lump breast (abnormal findings on ultrasound and mammogram, BIRAD III or above and abnormal FNAC results; C3 or above) from January 1st, 2020 to 30th june 2021, who presented to our hospital was retrieved on standard pre-designed questionnaire forms using old documents and phone calls by a single researcher to exclude observer bias. Informed consent was taken from participants before inclusion in the study. Patients were informed in brief about the reasons for conducting the study and its implications on future management of the disease. Out of these only following patients were included; females with diagnosed breast cancer on histo-pathological examination, age ≥20yrs, all stages of breast cancer, ASA I/II/III patients. Exclusion criteria was; patients who already had their surgery pre covid (December 2019), males, ASA IV/V patients.

Patient presentation time was calculated as the time interval between the appearance of the first symptoms of breast cancer (day 0) and the date of initial presentation to hospital by patient and consultation for breast symptoms. Time taken for start of treatment was calculated by counting number of days from the first presentation day to hospital until the date when definitive treatment for Carcinoma Breast was initiated (chemo/radio/surgery). Time duration for definitive surgery was counted from the day of first presentation to the hospital till the date surgery was conducted (modified radical mastectomy (MRM)/breast conserving surgery (BCS)/toilet mastectomy).

Presentation 'Delay' was defined as a patient reporting to the hospital for medical advice 30 after noticing the first possible symptoms of breast cancer while [7]. Time taken for start of treatment was calculated form time of first presentation to hospital (day 0) till the first day of start of definitive first treatment for breast cancer. We labelled delay in treatment if it was initiated later than 62 days (from day 0) [8].

The questionnaire inquired about the symptoms, date of presentation of the first symptoms, date of first reporting to hospital, reasons for the delayed presentation.

It was a non probability consecutive sampling technique. All patients who were admitted underwent pre anesthesia assessment, pre surgical optimization and COVID testing according to the

hospital protocol. If the patient turned out COVID positive, their symptoms were noted and the COVID team (infectious disease department) was notified. The quarantine protocol at our hospital was complete isolation for 14 days with one PCR-negative report after completing quarantine, with no residual respiratory symptoms of cough, fever, and shortness of breath. This protocol was followed for all elective breast surgery patients admitted in the hospital. All COVID-positive patients underwent the same treatment protocol as non-COVID patients with regards to management of breast cancer. Patients with early breast cancer (up to stage 2A) underwent modified radical mastectomy/breast conservative surgery (therapeutic) first, followed by chemotherapy/radiotherapy, locally advanced cases (stage 2B and above) had neo-adjuvant treatment first followed by surgery (therapeutic), and advanced cases (stage 4/metastatic) underwent palliative treatment. All surgeries were carried out by a single team of general/plastic surgeons of our hospital. Post operative patients were taken care of in general wards/ICU/HDU according to the level of post operative care needed. Follow up of the patients was carried out by the same operating team to provide quality care ensurance.

All the data obtained was analyzed using IBM SPSS version 23.0. Descriptive statistics like age were presented as range and means. Categorical data were analyzed using fisher exact test and t-test was applied to numerical data. In all cases, a 95% confidence interval was used and p value ≤ 0.05 was considered significant. The work has been reported in the line with the STROCSS criteria [9].

3. Results

Eighty seven patients presented with a suspicious lump breast from January 2020 till june 2021. All patients were female, ranging from 25 to 71 years of age (mean 53 ± 5.45). On histo-pathological examination 18 (20.6%) patients had benign lesions, while 69 (79.3%) were diagnosed with breast cancer. Those who presented with a benign lump were excluded from the study. No participant withdrew from the study at any time after giving consent. Sixty (86.9%) out of 69 presented with advanced stage (stage 2b and above) of breast cancer. The overall time duration of presentation, treatment and surgery is shown in Table 1. Fourty five patients had delayed presentation. Overall delay during pandemic with reasons and impact on disease stage is shown in Table 2. Twelve (17.3%) patients turned out to be COVID-positive on PCR testing. All COVID-positive patients were asymptomatic. Among COVID-negative patients, age ranged from 25 to 70 years (mean 51.57 ± 5.99) while in COVID positive cases age range was 45−71 years (mean 59.75 ± 10.89). The time duration of presentation, initiation of treatment and definitive surgical management according to COVID status is shown in Table 3. Results indicated that COVID status did not have a significant effect on presentation delay (fisher's exact test was insignificant) and treatment delay (independent t-test was insignificant). Among 57 COVID negative patients; only 15 (26.31%) were delayed due to COVID lockdown. Overall disease upstaging was identified in 21 (30.4%) of 69 patients. Of the 57 covid negative patients 12 had upstaging of their disease, and the operative management changed from (MRM) to toilet mastectomy in 3 out of the 12 patients (palliative management), while in 9 patients no change in operative plan was required. Half of the COVID-positive patients (6 out of 12) presented late due to COVID lockdown. Majority (9 out of 12 patients) in the COVID positive group had disease upstaging due to delay of definitive treatment and surgery due to their COVID positive status. Among them the patients whose stage remained the same, they underwent MRM(therapeutic intend) followed by adjuvant treatment. Out of the 9 patients who had their disease upstaged due to delay in treatment, 3 patients had their disease upstaged to 2B from 2A.They underwent MRM followed by

Table 1
Overall time duration of presentation, treatment, and surgery.

	Time duration taken to present to hospital (from noticing first symptom)	Time duration for start of definitive treatment (from presentation to hospital)	Time duration from hospital presentation to surgery
Number of patients	69	69	69
Mean in days (SD)	118.48 (±133.60)	95.08 (±123.44)	308.48 (±246.97)
Minimum	0	13	20
Maximum	390	480	1020

Table 2
Overall delay with reasons and impact on stage of disease (n = 23).

		Number of patients	Percentage
Delay In Presentation	No	24	34.8
	Yes	45	65.2
Reason of Delay	COVID lockdown	15	21.7
	no delay seen	24	34.8
	follow up loss and unawareness	9	13
	unawareness	21	30.4
Treatment Delay	No	42	60.8
	Yes	27	39.1
Upstaging	No	48	69.6
	Yes	21	30.4

Table 3
Time duration of presentation, initiation of treatment and definitive surgical management according to COVID status.

Group Statistics							
	COVID status	Number of patients	Mean	Std. Deviation	p-value	95% Confidence Interval of the Difference	
Duration of days for presentation to hospital	Neg	57	119.74	145.15	0.92	Lower	Upper
	Positive	12	112.5	66.52		−149.17	163.64
Duration for definitive treatment in days	Neg	57	101.26	133.82	0.61		
	Positive	12	65.75	53.96		−108.13	179.16
Duration of days from hospital presentation to surgery	Neg	57	340.95	255.67	0.18		
	Positive	12	154.25	129.17		−89.8	463.19
Upstaging	Neg	57	2.16	0.5	0.04		
	Positive	12	2.75	0.5		−1.17	−0.02

adjuvant treatment. The other 3 patients had stage 2 A/B which was upstaged to 3 A/B after delay. They had neo-adjuvant followed by MRM(therapeutic). The course of treatment changed from MRM to toilet mastectomy (palliative) in three patients after upstaging of the disease from stage 3—4. However, a significant correlation was found between COVID positive status and disease upstaging, which is shown in Table 3.

4. Discussion

The Covid-19 pandemic which started in December 2019, is not over yet and at present it cannot be predicted when this is going to end as it depends on multiple factors like infectivity of a person, the isolation measures and lockdown status of affected countries, and emerging immunity [10]. The vaccination campaign is having an impact, albeit slowly, as with current vaccination pace in Pakistan it will take ages for the country to achieve herd immunity.

With the reallocation of the maximum resources by the hospital to the COVID-19 patient care in critical units, resource demanding diseases like breast cancer services have faced serious setbacks. We have tried to quantify what setbacks breast cancer care has taken in our hospital due to this pandemic. We have seen in our study that these patients present extremely late to the hospital due to a myriad of known and unknown reason.

On top of that sometimes they are just lost to follow up for indefinite periods even after the treatment has started. Although we tried to continue with the same treatment protocol for COVID negative and positive patients the patients with positive PCR had to be quarantined as per hospital policy in vogue, which may have contributed to upstaging of disease in a some of these patients.

We determined in our study that most of the patients 60 (87%) presented with advanced (stage 2b and above) of breast cancer. This is comparable to another research in Pakistan where 69.9% females reported in stage III and IV of Breast Cancer [11]. This presentation in advanced stage can be due to longer patient delays from noticing of first symptom to presenting to a health care facility as explained in a meta-analysis by Richard et al. in which a positive relation was seen between patient delay and advanced stage of breast cancer at presentation [11,12]. In our study 45 (65.2%) patients reported late with majority (75%) of them presenting with a delay of 6 months or more, after noticing the initial symptoms. This is in congruence with another study conducted in northern Pakistan where 39%patients reported with a delay of 6 months [12]. Unlike what we expected due to the current situation engendered by COVID -19 pandemic, unawareness (30.4%) still outnumbered COVID lockdown (21.7%) as the main factor causing the delay, while 13% reported both

reasons as the cause of delay. A few cases were lost to follow up due to not understanding the gravity of their disease and did not reported back on time for treatment continuation. Lack of awareness, peculiarly in developing countries, is highlighted as the key factor contributing to delayed presentation and mortality in many studies [13,14]. This plays a significant role in delayed presentation as it roots from illiteracy and inaccessibility of the proper education to understand symptoms of any disease [15−21].Recently, Government of Pakistan has started awareness campaigns regarding Breast Cancer which we believe will have positive impact in near future.

Though our study does not focus on determining the incidence of COVID-19 among Breast Cancer patients, only a small number of breast cancer patients (17.4%) tested positive which indicates that the suggestion, that breast cancer patients are not at higher risk of COVID-19 than the general population by Vuagnat et al., may have notable footing [22]. Moreover, we found out that the COVID status itself doesn't have the significant impact on delay in presentation, definitive treatment or surgery. Though, for those testing positive, we followed the quarantine protocol of 14 days isolation with one PCR negative report after completing quarantine but still it did not cause a noteworthy delay in time from presentation to treatment as we tried to avoid unnecessary treatment and surgical delay [23]. Interestingly, our study highlighted that COVID status does have significant impact on the upstaging of the breast cancer as our data emphasized that a notable number of COVID positive patient underwent upstaging. Plausible explanation may be factors like advanced tumor stage on presentation and high histo-pathological grade of tumor at presentation, combined with treatment delay (chemo/surgery) due to COVID quarantine [24,25]. Future research is needed to investigate that if corona virus itself can contribute in patho-physiology of upstaging.

The limitations of this work include a small number of patients from a single center. So, our results may not be generalizable. For this a multi-centric study with a large sample size needs to study the overall outcome of COVID-19 on breast cancer patients and disease progression among them. We also did not include histo-pathological correlation and response of different types of breast cancer to chemotherapy with disease upstaging and covid status. More research work is needed to find relation of disease upstaging with COVID status.

5. Conclusion

We found that covid-19 pandemic had no significant impact on delay in presentation, breast cancer management/treatment and disease upstaging as compared to figures available for our population before the pandemic. However, our study showed significant correlation between disease upstaging and COVID positive status of patients. These findings made us think to reconsider our protocols of breast cancer care management among Covid positive patients in this pandemic. Our results might help researchers in formulating new breast cancer management guidelines for patients in current or any anticipated future pandemic.

Ethical approval

Ethical review was given by ethical review committee of hospital (PNS Shifa Hospital Karachi), which has board of members and one person as Head. The number allotted to our research was ERC:43.

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Author contribution

Dr Mehwish Mooghal: study design, main concept, data collections, data analysis, writing, reviewing.
Dr Rana Hassan Javaid: study design, concept, data analysis, writing, reviewing.
Wajiha Khan: design, concept, data analysis, writing, reviewing.
Muhammad Muneeb: design, concept, data analysis, writing, reviewing.
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Dr Kamran Rahim: design, concept, data analysis, writing, reviewing.
Dr Hina Tahseen: design, concept, data analysis, writing, reviewing.
Dr Amna Gul: design, concept, data analysis, writing, reviewing.

Conflict of interest statement

None to declare.

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Disclaimer

Nil.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijso.2021.100386.

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