



COVID-19 effects on breast cancer patients: symptom presentation and critical intervals in a Malaysian hospital

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Background: Coronavirus disease 2019 (COVID-19) is distressing especially in countries where resources are thin. In Malaysia, there is concern over its effects on the wellbeing of non-COVID patients. We compare critical intervals between pre-pandemic and pandemic breast cancer patients.

Methods: This cohort study involved 100 patients, 50 diagnosed pre-pandemic and 50 diagnosed during the pandemic. Symptoms were categorized into three (breast lump, non-breast lump and non-breast symptoms). Presentation interval was the time from symptoms to first presentation at a clinic. Diagnosis interval was the time from first presentation to diagnosis, and treatment interval was the time from diagnosis to initial treatment.

Results: Mean times for presentation, diagnosis and treatment intervals in the pre-pandemic group were 14.48 months, 10.94 days, and 21.18 days, respectively. The pandemic group recorded 34.64 months, 17.14 days, and 17.14 days, respectively. Three main presenting symptoms in pre-pandemic and pandemic groups were breast lumps (92% and 98%), followed by non-lump breast symptoms (14% and 30%) and non-breast symptoms (2% and 6%).

Conclusions: The extended presentation and diagnosis intervals may be a result of movement restrictions during the outbreak. Screening should not be neglected. The pandemic should not set us back but aids us in a global reset.

Keywords: Breast cancer; COVID-19 pandemic; presenting symptoms; critical intervals; oncology

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Introduction

The novel coronavirus (2019-nCoV) respiratory disease outbreak was first reported in Wuhan, China, in December 2019 and the World Health Organization (WHO) declared it a pandemic at the end of January 2020. It was subsequently renamed the coronavirus disease 2019 (COVID-19) and up to Oct 10, 2020, the disease had claimed more than one million lives and infected more

than 37 million people worldwide. COVID-19 is caused by the SARS-Co-V2 virus, which has a mortality rate of 3.4% (estimated by WHO on March 3, 2020). In Malaysia, infection was first reported among Chinese tourists on Jan 25, but local cases began to surface in March, with the first two fatalities reported on the 17th of that month.

As cases began to increase rapidly, a nationwide Movement Control Order (MCO) was imposed by the

government since March 2020 in several stages and lasted beyond a year. The restrictive order had effectively disrupted the country's socio-economic activities while trying to curb the spread of the virus and avoid overloading the healthcare system. Initially, "non-essential" businesses, houses of worship and learning institutions were ordered to close. Mass gatherings and social events were prohibited. Since then, the country had gone through four MCO phases, each with different strategies to contain the outbreak as recommended by WHO. Multiple waves of infection have resulted in dire economic situation for the country. Currently, the government allowed businesses to resume, but social restrictions and safety rules, like the mandatory use of face mask and physical distancing, remained in force. More cases are being detected as testing has been ramped up.

Breast cancer is the most common malignancy among women and the fourth most fatal among all cancers. Hence, control strategies increasingly encompass early diagnosis of symptomatic cancer, alongside primary prevention policies and screening programmes. They are crucial in improving the survival rate of patients (1,2). In Malaysia, according to the Malaysia National Cancer Registry Report (MNCRR) 2012–2016, breast cancer cases have increased in the past 10 years, and it remains the second-highest cause of death (3). It is the most common form of cancer among women in the country (4), and optimum treatment outcome depends on early detection and adherence to treatment.

Therefore, with various hurdles and restrictions in place to curb the pandemic, concern has been raised on how they may affect treatment of non-COVID diseases like breast cancer in hospitals. The long waiting time between diagnosis and initiation of therapy is of prognostic concern because it has been identified as a leading cause of stage progression, disease worsening and higher risk of treatment complications (5). The delay in treatment can be attributed to patient and system factors (6-9). Patient delay is the time lapsed before a person decides to seek help upon discovery of symptoms. System delay is the prolonged time taken to evaluate, diagnose and treat a patient who has sought help (1).

A meta-analysis of 87 studies provided compelling evidence of low survival rates among women who initiated treatment between three and six months after the appearance of breast cancer-related symptoms than women who waited less than three months (1,3,10). Due to COVID-19 restrictions, patient and system delays in middle-income countries like Malaysia will definitely increase as resources and focus are diverted to battling the coronavirus. Although Malaysia has a system to expedite

investigations and diagnosis of symptomatic individuals, prioritization of care for COVID-19 patients may affect this cohort.

The University of Malaya Medical Centre (UMMC), a premier teaching hospital in the capital of Kuala Lumpur, has been upgraded into a hybrid hospital to treat COVID-19 patients. Mobilization of healthcare personnel and restrictions on non-COVID clinical services have been implemented during the MCO. Therefore, we aim to examine how the pandemic has affected breast cancer patients in UMMC in terms of symptom presentation, together with the intervals in presentation, diagnosis and treatment. The early detection, diagnosis and intervention of other morbid diseases must not be neglected and adjustments must be made to accommodate the non-COVID patients. We present the following article in accordance with the STROBE reporting checklist (available at <https://jphe.amegroups.com/article/view/10.21037/jphe-22-21/rc>).

Methods

This cohort study was conducted in UMMC with consent from the hospital's ethics committee. Data of 100 breast cancer patients were collected from the electronic medical records and divided into two groups. There were 50 patients in the pre-pandemic group diagnosed in 2019, while another 50 in the pandemic group were diagnosed between March to June 2020. Convenience sampling method was used for the pandemic group while simple randomised sampling of 50 patients were conducted in the prepandemic group. All patients were seen in breast surgery clinic.

We examined and compared the presenting symptoms of breast cancer among women in the pre-pandemic and pandemic groups. Symptoms were divided into three categories—breast lump, non-breast lump and non-breast symptoms. Presentation interval was defined as time taken from the discovery of symptoms to the first presentation at primary care. Diagnosis interval was defined as time taken from the first presentation to diagnosis disclosure, and treatment interval was defined as time taken from diagnosis disclosure to initial treatment.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 27 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean \pm standard deviation when the

Table 1 Demography of pandemic [2020] and pre-pandemic [2019] breast cancer patients in University of Malaya Medical Centre

Variable	Overall breast cancer patients (n=100)	Pre-pandemic patients (n=50)	Pandemic patients (n=50)	T test/Chi-square	P value
Mean age (years ± SD)	59.27±11.75	60.4±12.13	58.14±11.36	0.962	0.339
Malay	28 (28%)	10 (20%)	18 (36%)	3.277	0.351
Chinese	53 (53%)	30 (60%)	23 (46%)		
Indian	15 (15%)	8 (16%)	7 (14%)		
Other	4 (4%)	2 (4%)	2 (4%)		

data were normally distributed, or in median with the interquartile range when the data were not normally distributed. Comparison of means was performed using the *t*-test or Mann-Whitney test ($P<0.05$). Categorical variables were expressed in percentages and analysed using the Chi-square test or Fisher's exact test ($P<0.05$), where applicable.

Ethical consideration

This study was conducted in accordance with the World Medical Association Declaration of Helsinki (as revised in 2013). Medical ethics approval was granted by University of Malaya Medical Centre (MREC ID No: 202043-8440). Informed consent was not applicable due to the retrospective nature of this study.

Results

Table 1 depicts the baseline demography of breast cancer patients in UMMC. The pre-pandemic group's mean age was 60.4, whereas the pandemic group was slightly younger at 58.14. Overall, the majority of patients were Chinese (53%), followed by Malay (28%), Indian (15%) and other races (4%). These distributions were similar in both groups and the figures were reflective of the hospital's local demography.

Table 2 shows the mean timelines for presentation (14.48 months), diagnosis (10.94 days) and treatment (21.18 days) in the pre-pandemic group, while mean timelines in the pandemic group were 34.64 months, 17.14 days, and 17.14 days respectively. However, one patient from the pandemic group has unknown presentation interval. The diagnosis interval was statistically significant between breast cancer patients before and during the pandemic ($P<0.01$), whereby the average days to reach a diagnosis at UMMC had nearly doubled. These were due to longer time taken for pathology and radiology examination resulted from

restrictions due to sanitation and maximum capacity enforced. Meanwhile, the presentation and treatment intervals were not significantly different between the two groups. These intervals were slightly longer than those observed (1), even though the authors presented their results in median intervals.

The patients presented their symptoms with three main complaints, namely breast lump, non-breast lump symptoms (cutaneous or nipple symptoms) and metastatic symptoms. Breast lump was still common among women with breast cancer and had relatively high predictive value for malignancy. Most patients (52%) in the pre-pandemic group were discovered with breast lumps that were 2–5 cm in size, followed by 22% who presented with small lumps less than or equal to 2 cm. A total of 18% of patients had huge lumps of more than 5 cm. Only 8% came with non-palpable breast lumps (*Table 3*). In comparison, 72% of patients in the pandemic group presented with breast lumps of between 2–5 cm, followed by large lumps of more than 5 cm (14%) and small ones of less than or equal to 2 cm (12%). The figure for those with non-palpable lumps had reduced to 2%. The mean lump size in the pandemic group was larger at 3.50 cm compared to the pre-pandemic group, which was 3.18 cm. However, these values were not statistically significant.

Referring to *Table 3*, patients with non-breast lump symptoms in the pre-pandemic group (14%) had more than doubled in the pandemic group (30%). Most of these were due to breast skin changes, such as puckering or redness. Only a small number presented with nipple discharge. Three patients (6%) in the pandemic group presented with metastatic *de novo* disease, such as dyspnea, bone pain, jaundice or neurological symptoms. In contrast, only one patient (2%) in the pre-pandemic group presented with that condition. It was important to note that even though patients did not experience metastatic symptoms, staging scans showed almost equal numbers of patients having metastatic disease, which was 14% in the pre-pandemic group and 12% in the pandemic group.

Table 2 Breast cancer presentation, diagnostic and treatment intervals at University of Malaya Medical Centre before and during the COVID-19 pandemic

Variable	Overall breast cancer patients (n=100)	Pre-pandemic patients (n=50)	Pandemic patients (n=50)	T test/Chi-square	P value
Presentation interval (months), mean ± SD	24.56±101.78	14.48±32.45	34.64±140.25	-0.990	0.324
≤1 month	49 (49%)	30 (60%)	19 (38%)	4.460	0.035
>1 month	50 (50%)	20 (40%)	30 (60%)		
Diagnosis interval (days), mean ± SD	14.04±9.05	10.94±7.88	17.14±9.16	-3.628	<0.01
≤7 days	27 (27%)	21 (42%)	6 (12%)	13.566	0.001
8–14 days	30 (30%)	15 (30%)	15 (30%)		
>14 days	43 (43%)	14 (28%)	29 (58%)		
Stage of diagnosis				2.681	0.613
0	5 (5%)	1 (2%)	4 (8%)		
1	31 (31%)	17 (34%)	14 (28%)		
2	26 (26%)	14 (28%)	12 (24%)		
3	25 (25%)	11 (22%)	14 (28%)		
4	13 (13%)	7 (14%)	6 (12%)		
Treatment interval (days), mean ± SD	23.43±16.9	21.18±15.15	17.14±9.16	-1.337	0.184
≤60 days	97 (97%)	50 (100%)	47 (94%)		0.242
60–120 days	2 (2%)	0 (%)	2 (4%)		
>120 days	0 (0%)	0 (%)	0 (%)		

In *Table 4*, the majority of patients in the pre-pandemic group were presented as stage 1 (34%), followed by stage 2 (28%), stage 3 (22%), stage 4 (14%) and in-situ carcinoma stage 0 (2%). However, the pandemic group has a slight difference in presentation, with majority at stage 1 and 3 (28% each), followed by stage 2 (24%) and stage 4 (12%). It was surprising to note that more patients presenting with stage 0 (8%) were detected despite screening programmes being halted altogether in public hospitals nationwide. Nonetheless, the difference between these two cohorts was not statistically significant. They may present with more advance disease later if they have not gone for screening in the private sector.

Table 5 shows that neoadjuvant therapy was also offered during the pandemic. But the number had decreased to around 22% compared to 32% in the pre-pandemic group, even though the number of patients with locally advanced disease was almost equal. Despite not being statistically significant, these figures might reflect the severity of logistical issues faced by the hospital during the pandemic.

Discussion

Breast cancer is most common cancer among women in Malaysia (2) and its control strategies increasingly encompass early diagnosis alongside primary prevention policies and screening programmes (10,11). As more healthcare personnel and resources were deployed to battle COVID-19, concern had risen over the implementation of those control strategies. Treatment had also become complicated with movement restrictions like the various MCO phases in Malaysia. Screening programmes for breast cancer has been a focus of public health awareness campaigns in the country. In spite of all these efforts being actively pursued, many patients still continued to present at long intervals. This study found that the mean timelines for presentation, diagnosis, and treatment interval during the COVID-19 pandemic group were all longer than the pre-pandemic group. This was an alarming development as longer intervals to diagnosis had been shown to be associated with lower five-year survival of breast cancer patients, and additionally, a prolonged diagnostic experience

Table 3 Presentation symptoms of patients before and during the COVID-19 pandemic

Variable	Overall breast cancer patients (n=100)	Pre-pandemic patients (n=50)	Pandemic patients (n=50)	T test/Chi-square	P value
Breast lump size on presentation (cm), mean \pm SD	3.34 \pm 2.66	3.18 \pm 2.81	3.50 \pm 2.52	-0.603	0.548
\leq 2 cm	17 (17%)	11 (22%)	6 (12%)	5.133	0.162
2–5 cm	62 (62%)	26 (52%)	36 (72%)		
>5 cm	16 (16%)	9 (18%)	7 (14%)		
Not palpable	5 (5%)	4 (8%)	1 (2%)		
Non breast lump indicate symptoms					
Yes	22 (22%)	7 (14%)	15 (30%)	3.730	0.053
No	78 (78%)	43 (86%)	35 (70%)		
Skin redness	8 (8%)	6 (12%)	2 (4%)		
Ulcer	1 (1%)	1 (2%)	–		
Skin ulceration	1 (1%)	–	1 (2%)		
Nipple retracted	4 (4%)	–	4 (8%)		
Skin puckering	5 (5%)	–	5 (10%)		
Nipple discharge	1 (1%)	–	1 (2%)		
Nipple discharge and inverted	1 (1%)	–	1 (2%)		
Skin redness and nipple retracted	1 (1%)	–	1 (2%)		
No symptom	77 (77%)	43 (86%)	34 (68%)		
NA	1 (1%)		1 (2%)		
Breast lump symptoms indicate metastatic					0.617
Yes	4 (4%)	1 (2%)	3 (6%)		
No	96 (96%)	49 (98%)	47 (94%)		

COVID-19, coronavirus disease 2019; NA, not available.

Table 4 Breast cancer stage at diagnosis

Stage of diagnosis	Overall breast cancer patients (n=100)	Pre-pandemic patients (n=50)	Pandemic patients (n=50)	P value
0	5 (5%)	1 (2%)	4 (8%)	0.613
1	31 (31%)	17 (34%)	14 (28%)	
2	26 (26%)	14 (28%)	12 (24%)	
3	25 (25%)	11 (22%)	14 (28%)	
4	13 (13%)	7 (14%)	6 (12%)	

might also result in poorer experience of subsequent cancer care (3,12,13). These results implied that the pandemic had caused delays in various aspects of breast cancer treatment and hospital protocols should be reassessed so as not to compromise treatment and patient wellbeing.

Disease stage at presentation was an important indicator for overall survival of breast cancer patients. During this pandemic, we found more patients presenting with stage 3 disease compared to the year before, and fewer with stage 1, which was an early manifestation of the disease

Table 5 Treatment provided to breast cancer patients before and during the COVID-19 pandemic

Variable	Overall breast cancer patients (n=100)	Pre-pandemic patients (n=50)	Pandemic patients (n=50)	T test/Chi-square	P value
Neoadjuvant therapy (chemo/hormonal)				1.138	0.286
Yes	27 (27%)	16 (32%)	11 (22%)		
No	73 (73%)	34 (68%)	39 (78%)		
Palliative care				0.002	0.967
Yes	14 (14%)	7 (14%)	7 (14%)		
No	86 (86%)	43 (86%)	43 (86%)		

COVID-19, coronavirus disease 2019.

with better chances of survival. These findings revealed that the COVID-19 outbreak could have caused patients to present with more advanced disease, hence, worsening their survival. Nevertheless, this study did not address other confounding factors, such as socio-economic status, educational levels, family history of breast cancer and other risk factors of breast cancer.

There was a three-fold increase in patients presenting with symptoms of metastatic breast cancer during the pandemic compared to the pre-pandemic period, but the number was small. Although patients might not have metastatic symptoms, staging scans showed almost equal numbers with metastatic disease. This indicated that breast cancer patients presenting in UMMC during the pandemic might have severe symptoms, and the cause could not be identified. It was also probable that some patients were hesitant in seeking medical attention for their early metastatic symptoms due to fear of coming out during the Movement Control Order. These groups of patients were subsequently rendered palliative treatment.

There were several limitations in this study. The study setting was within a public funded healthcare facility, which was upgraded to treat COVID-19 patients in Malaysia. During the initial phase of the pandemic, public hospitals nationwide, especially tertiary centres, experienced a standstill in their operations due to lack of ventilators and personal protective equipment. Patients who were not diagnosed or suspected of having COVID-19 were deferred and decanted to smaller hospitals, which also might not have adequate expertise or facilities to handle the pandemic. This method of handling COVID-19 patients and the fear of being infected by the new and unknown SARS-Co-V2 coronavirus had led patients with breast cancer and other diseases to delay seeking medical help. On the other hand, highly anxious

patients who sought treatment were told to wait or directed to other hospitals as the system could not cope.

The accuracy and completeness of symptom information relied on patients accurately recalling and describing their condition, besides the ability of the attending clinician to document them correctly and meticulously. In addition, the patients' records were retrospectively reviewed, and the under-reporting of certain aspects might have occurred, especially non-breast lump symptoms. Although we were able to describe overall presentation symptoms and timelines, the sample size was also small due to time limitation. A follow-up study with a larger cohort would be useful in getting the overall picture on a regional or national level, instead of just one hospital. It is also proposed to conduct a post-pandemic study to determine how treatment and healthcare services might recover with the right MCO exit strategy.

To our knowledge, this is one of the few studies from a developing middle-income country with a focus on the impact of COVID-19 outbreak on breast cancer. This analysis substantially amplifies and provides evidence on the effect of this pandemic causing delay in most aspects, from presentation to treatment and also differences in their presenting stage of disease which may severely influence the overall survival. This study concurred with a study done in Pakistan (13) which demonstrated an increment of stage 3 breast cancers in the pandemic period. We have been able to describe a wide range of presenting symptoms, such as those described in other studies (2,14).

Conclusions

This study had described the effects of COVID-19 outbreak on symptom presentation, presenting interval, diagnostic

interval and treatment interval of breast cancer in a tertiary centre in Malaysia. Although the delay in diagnostic interval only was observed to be statistically significant, further assessment would be needed to identify the actual impact. Screening programmes should be reinstated as soon as possible because the optimum outcome in breast cancer treatment is dependent on early detection and adherence to treatment. Our findings highlighted the need to support the diagnostic process in women presenting with the disease during the pandemic, and the enhancement of virtual public health campaigns.

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granted by University of Malaya Medical Centre (MREC ID No: 202043-8440). Informed consent was not applicable due to the retrospective nature of this study.

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