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Full length Research Article

Impact of the COVID-19 Pandemic on Histopathological Diagnosis of Breast Tumours in Calabar, Nigeria

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Summary: The Coronavirus-19 transmitted through physical contact, droplets, and fomites caused severe respiratory disease resulting in high mortality worldwide. The COVID-19 pandemic caused innumerable hardships, panic, and restrictions of movement which negatively affected the assessment of healthcare services like breast cancer diagnosis in many countries. The results from the histopathological diagnosis of breast tumours have been routinely employed for the treatment and management of these diseases. This study investigated the impact of the COVID-19 pandemic on the histopathological diagnosis of breast tumours in Calabar. A retrospective study of the newly diagnosed breast tumours recorded in the Histopathology Laboratory register during the COVID-19 and the post-COVID-19 recovery from January 2020-February 2021 was compared with cases diagnosed before the pandemic from January 2018 to February 2019. Descriptive and inferential statistics and the Artificial Neural Network (ANN) of Statistical Package for Social Sciences (SPSS) were used for data analysis. New breast tumours diagnosed based on month showed low rates of 2.4% and 1.2% during the first and second waves of the pandemic respectively. The diagnosed cases increased to 11.8% and 8.2% after the first and second waves of the virus respectively. There was a significantly strong negative correlation between the COVID-19 pandemic and lockdown measures with breast tumour diagnosis (r=-0.919, p=0.001). More benign tumours of 56(58.3%) cases with a mean age of 25.3±11.1 years were recorded before the pandemic and were statistically significant (F=64.260, p=0.004). More malignant cases of 48(57.1%) with a mean age of 47.5±11.7 years were recorded during the pandemic. The diagnosis of malignant tumours was statistically significant between both periods (F=183.550, p=0.001). The ANN model predicted a 25% reduction in breast tumour diagnosis during the pandemic. There was a 100% impact of the pandemic on tumour type, the nature of specimen, and mean age of subjects. The COVID-19 pandemic disrupted the assessment of healthcare services as a smaller number of women were diagnosed with breast tumours during the period. This may have caused delays and late presentation leading to the diagnosis of more malignant tumours. There is a need to put adequate measures to encourage the assessment of diagnostic services during pandemics as delays may lead to an increase in morbidity and mortality.

Keywords*: COVID-19 pandemic; breast tumours; malignant; benign; diagnosis; artificial neural networks*

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INTRODUCTION

Early detection and treatment of breast cancer are vital for better management and survival (BSWG *et al*., 2021). Research has shown that the COVID-19 pandemic affected and caused disruptions in the assessment of breast cancer diagnosis, screening, and other healthcare services in most countries (BSWG *et al*., 2021; Vrdoljak *et al*., 2021). The COVID-19 virus was first reported in December 2019 in Wuhan, China (WHO, 2020a). The COVID-19 virus is a coronavirus that causes severe respiratory disease and is transmitted by physical contact, droplets, and fomites with a high rate of mortality (WHO, 2020b).

1n 2020, COVID-19 spread worldwide and the index case in Nigeria was reported on 27th February 2020 while another confirmed case was reported on 9th March 2020 (NCDC, 2020a). The outbreak of COVID-19 in Nigeria led to lockdown measures by the government by the end of March 2020 restricting movement and causing a scare in physical contact with persons. Healthcare services were still rendered but witnessed a poor turnout of patients. In Calabar, Cross River State, although, there was no report of confirmed COVID-19 cases until November 2020, when 87 new Covid-19 cases were reported in Cross River State (NCDC, 2020b), there was a poor turnout of patients for histopathological diagnosis.

The prevalence of breast cancer in Calabar is increasing and worrisome as most occur among women below 50 years of age (Ebughe *et al*., 2016; Udonkang *et al*., 2021a). Also of concern is the fact that most women present late for histopathological diagnosis. This has led to an increase in morbidity and mortality from the disease in the study area

(Ebughe *et al*., 2016). It is therefore pertinent to state that any negative condition such as the COVID-19 pandemic that puts a challenge in the assessment of diagnostic services further delays disease diagnosis for the affected persons.
As such, adequate healthcare measures to encourage the assessment of diagnostic services are paramount even during pandemics to avoid delay and reduce the associated morbidity and mortality. To date, there is a paucity of data about the effect of the pandemic on breast cancer diagnosis in Calabar. This study assessed the effect of the COVID-19 pandemic and lockdown measures on the histopathological diagnosis of breast tumours in Calabar.

MATERIALS AND METHODS

Study design/subjects/data collection: This was a retrospective study in a tertiary hospital-based cancer diagnostic center. Data from the pre-COVID-19 period of January 2018 to February 2019 and the COVID-19 period from January 2020 to February 2021 were used. All clinical data and histopathological reports from 180 female subjects aged 13-84 years were retrieved from the register of the Histopathology Laboratory, University of Calabar Teaching Hospital, Calabar. Data included the age of the subject, the nature of the tissue, laterality, and histopathological diagnosis. Histopathological diagnosis of breast tumours was based on the Scarff-Bloom-Richardson tumour grading system with Haematoxylin and eosin-stained sections.

Ethical approval and study population: Ethical approval was obtained from the University of Calabar Teaching Hospital Research and Ethics Committee with approval numbers UCTH/HREC/33/694 and UCTH/HREC/33/527.

The sample size calculation of the study was based on the sample size formula of difference in two proportions (Goyal, 2013) given as Z2P1(1-P1) + P2(1-P2) /d2 where Proportions, P1=80%, P2=90%, Z is confidence interval at 95% =1.96, and d is relative precision =10%. This gave the sample size of 96 per period resulting in 192 subjects but data from 180 eligible subjects within the study period was used after appropriate sampling was done. Inclusion criteria involved adding all women who had complete clinical data and were diagnosed with breast tumour within the study period. Women with incomplete data and men were excluded.

Statistical analysis: Statistical Package for Social Sciences (SPSS) version 20 (Armonk, New York: IBM Corporation) was used to analyze the data. Descriptive statistic was used to analyze the demographic characteristics and histopathological diagnosis of the breast tumours. Pearson correlation was used to establish the association between the COVID-19 outbreak during the pandemic months and newly diagnosed breast tumours. Chi-square was used to analyze the associations among the clinical characteristics of the breast tissues of subjects. Analysis of Variance showed the association between the mean ages of the subjects and types of benign and malignant tumours between the pre-COVID-19 and the COVID-19 periods. All results were statistically significant at a probability level less than or equal to 0.05. The Multilayer Perceptron (MLP) model of artificial neural network (ANN) of SPSS version 20 was used to test the accuracy of the impact of the pandemic on breast tumour diagnosis.

Artificial neural network design: In the MLP model used to build the neural network, period (pre-COVID-19 and COVID-19) was the dependent variable. The factors (tumour type, nature of specimen, mean age) and sub-factors (benign, malignant, unclassified type, lump, biopsy, mastectomy, unclassified nature of tissue, mean age) were the independent variables. The datasets were assigned randomly to moderate training conditions into training (60%), testing (20%), and holdout (20%) layers. The training data was used for weight determination and model building. The testing data was used to find errors, and the holdout data was used for model validation. The activation function was hyperbolic tangent (tanh) for the hidden layer. The output layer used the softmax function as the activation function. The batch training option was used for training. Initial lambda was set at 0.0000005, initial sigma was at 0.0005, interval center was 0, and interval offset was ±0.5. Cross entropy served as the error function because of the softmax function.

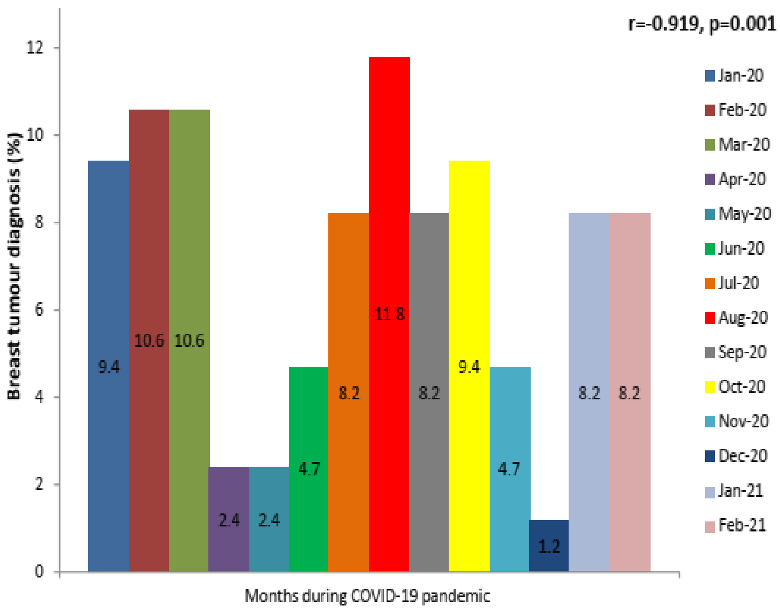

Figure 1:
The association between the Covid-19 pandemic months and newly diagnosed breast tumour

RESULTS

Fig. I is the association between the COVID-19 pandemic months and newly diagnosed breast tumours. During the pandemic, 10.6% of breast tumours were diagnosed in February and March 2020 before the lockdown. During the first wave of the pandemic and the lockdown of April and May 2020, 2.4% of cases were reported respectively. When the lockdown was lifted in June 2020, the cases increased gradually to a peak of 11.8% in August 2020. There was another decrease from 4.7% in November 2020 to 1.2% of cases in December 2020 during the second wave of the virus. However, post-COVID-19 increases in diagnosed cases were observed in January and February 2021 with 8.2% of cases respectively. There was a significantly strong negative correlation between the COVID-19 pandemic and new breast tumour diagnosis (r=-0.919, p=0.001).

In Table 1, the clinical characteristics of the breast tissues of the subjects are shown. The characteristics of subjects who were diagnosed with breast tumours during the pre-COVID-19 period showed more benign cases 56(58.3%) while more malignant cases were recorded during the COVID-19 pandemic 48(57.1%) and were statistically significant ($\chi2$=9.391, p=0.009). Unilateral breast lesions of either part were the most recorded during both periods. Breast laterality was not statistically significant ($\chi2$=5.065, p=0.167). More lumps 55(57.9%) during the pre-COVID-19 and more biopsies 45 (52.9%) during the pandemic were used for diagnosis. The nature of the specimen was statistically significant ($\chi2$=29.926, p=0.001). The age range of subjects was between 13-84 years. The mean ages of the subjects were 35.2±15.4 and 39.2±14.6 during the pre-COVID-19 and in the COVID-19 periods respectively but were not statistically significant ($\chi2$=0.216, p=0.642).

Table 1:
The clinical characteristics of the breast tissues of the subjects

Parameter	Pre-COVID-19 period n (%)	COVID-19 period n (%)	Statistics
Type of tumour			
Benign	56 (58.3)	37 (17.1)	
Malignant	35 (36.5)	48 (57.1)	
Suspicious	4 (4.2)	0 (0)	**χ^2=9.391, p=0.009**
Total	95 (100.0)	85 (100.0)	
Breast laterality			
Right	37(38.9)	35(38.5)	
Both	7(7.4)	1 (7.3)	**χ^2 =5.065, p=0.167**
Left	35(36.8)	38 (37.5)	
Unclassified	16(16.8)	11 (16.7)	
Total	95 (100.0)	85(100.0)	
Nature of tissue			
Lump	55 (57.9)	28 (32.9)	**χ^2=29.926, p=0.001**
Biopsy	22 (23.1)	45 (52.9)	
Mastectomy	15(15.8)	2 (2.3)	
Unclassified	3(3.2)	10 (11.8)	
Total	95 (100.0)	85 (100.0)	
Mean age (years)	35.2±15.4	39.2±14.6	**χ^2=0.216, p=0.642**

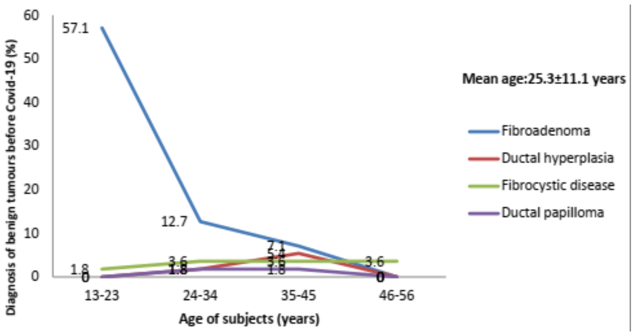

Figure 2:
The association between age and types of benign tumours during the pre-COVID-19 period.

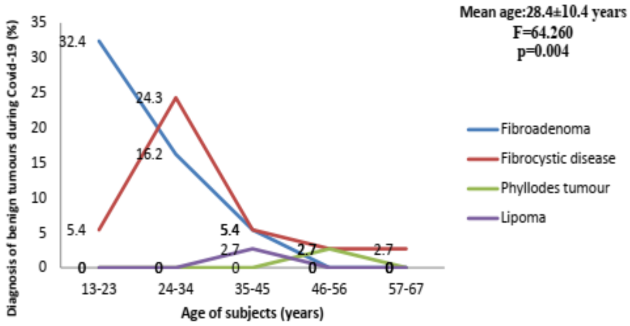

Figure 3:
The association between age and types of benign tumours during the COVID-19 pandemic.

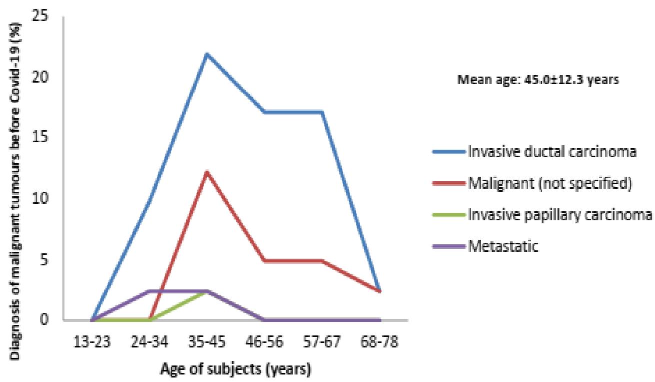

Figure 4:
The Association between age and types of malignant tumours during the pre-COVID-19 period.

The association between age and types of benign tumours during the pre-COVID-19 period is shown in Fig. 2. Among the benign tumours, fibroadenoma was the most diagnosed 43(76.8%) with a mean age of 25.3±11.1 and the majority 32(57.1%) recorded in 13-23 years during the pre-Covid period. The association between age and types of benign tumours in the COVID-19 period is shown in Fig. 3. Less fibroadenoma 20(54.1%) were diagnosed with a mean age of 28.4±10.4 years and the majority in the age range 13-23 years. There was a statistical difference in the diagnosis of benign tumours between the pre-COVID-19 and the COVID-19 periods (F=64.260, p=0.004).

Fig.4 is the association between age and types of malignant tumours during the pre-COVID-19 period. Among the malignant tumours, more invasive ductal carcinomas (IDC) 28(68.3%) with a mean age of 45.0±12.3 and peak occurrence of 9(21.9%) at 35-45 years were diagnosed. Fig.5 is the association between age and types of malignant tumours during the COVID-19 period. During the pandemic, 31(64.6%) cases with a mean age of 47.5±11.7 years and peak occurrence of 15(31.3) in 35-45 years were diagnosed. The diagnosis of malignant tumours was statistically significant between both periods (F=183.550, p=0.001).

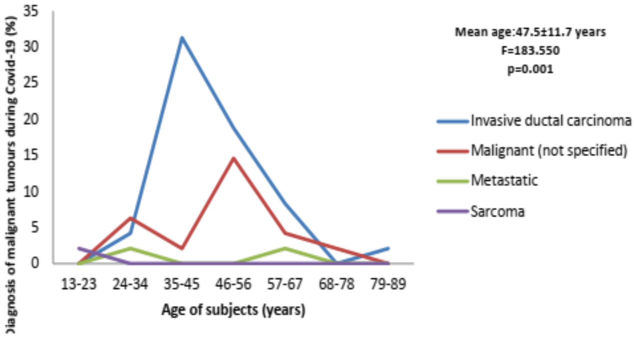

Figure 5:
The association between age and types of malignant tumours during the COVID-19 pandemic

Table 2:
Summary of MLP results for breast tumours diagnoses during both periods.

MLP RESULTS				
Parameter		N (%)	Cross entropy error	
Sample	Training	9 (64.3)	4.735	
	Testing	1 (7.1)	0.286	
	Holdout	4 (28.6)		
	Total	14 (100)		
Training time	0:00:00.02			
Classification		Pre-COVID-19	COVID -19	% Correct Prediction
Training	Overall %	56.6	44.4	66.7
Testing	Overall %	0	100	100
Holdout	Overall %	75	25	25
ROC Area	Pre-COVID-19	0.813		
	COVID-19	0.813		
Independent variable importance	Relative importance	Normalized importance (%)		
Sub-factors	0.409	69.3		
Factors	0.591	100		

Multilayer Perceptron results: The Summary of MLP results for breast cancer diagnosis during both periods is shown in Table 2. The automatic random selection assigned 9 nodes to the training layer. The testing layer had 1 node and the holdout layer had 4 nodes. The cross-entropy error for the training layer was 4.735 but reduced to 0.289 in the testing layer. This shows the error function that the network minimizes during the training phase. The small value of this error indicates the power of the model to predict the outcome. The classification results showed that the overall percent prediction for training was 66.7% (pre-COVID-19=56.6%, COVID-19=44.4%), testing was 100% (pre-COVID-19=0%, COVID-19=100%), and the hidden layer was 25% (pre-COVID-19=75%, COVID-19 =25%). The overall percent prediction for cases during the pre-COVID-19 period was 75% and reduced to 25% during the COVID-19 period. The accuracy of prediction was 25% during the COVID-19 outbreak. The areas under the Receiver Operating Characteristic (ROC) curve for the pre-COVID-19 and COVID-19 periods were 0.813 respectively. This indicates a good classification of the cases diagnosed during both periods.

The impact of the periods on the factors and sub-factors was indicated by the normalized importance. The pandemic had a 100% impact on the factors and a 69.9% impact on the sub-factors respectively. Fig. 6 is the MLP neural network of factors and sub-factors of breast tumour during both periods. The neural network shows the summary of these interactions.

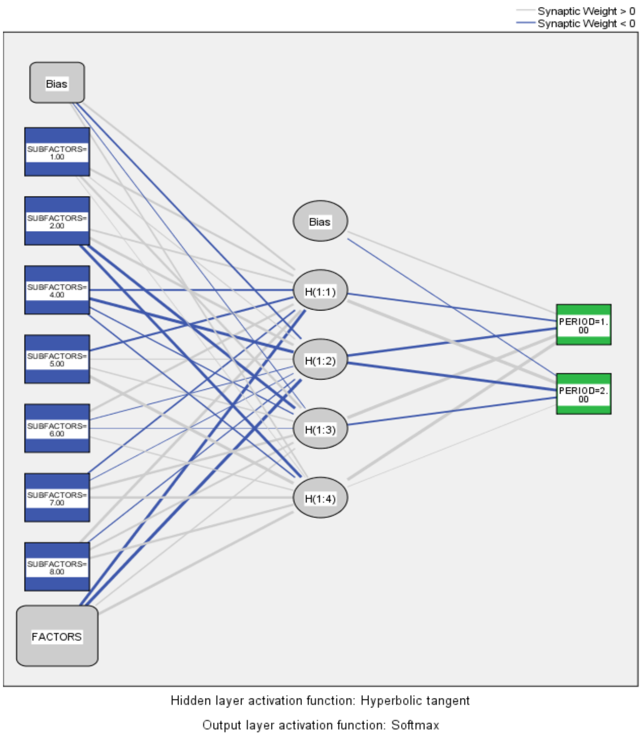

Figure 6:
The MLP neural network of factors and sub-factors of breast tumours during both periods
Keys: PERIOD(1)=pre-COVID-19, PERIOD(2)=COVID-19, FACTORS (tumour type, nature of specimen, mean age) and SUB-FACTORS (1=benign, 2=malignant, 3=unclassified-type, 4=lump, 5=biopsy, 6=mastectomy, 7=unclassified-nature of tissue, 8=mean age)

DISCUSSION

The COVID-19 pandemic and lockdown measures caused disruptions and inaccessibility to most medical services (Bosch *et al*., 2022). This research evaluated the outcome of this pandemic on the histopathological diagnosis of breast tumours. In this study, there was a reduction in the number of newly diagnosed cases of breast tumours. This may be attributed to the panic and COVID-19 lockdown measures imposed by the government during the period. Although diagnostic services were not halted there was a low turn up for assessment of these services by the public. This is similar to the report of decreased breast cancer diagnoses by 7% in 2020 (Yong *et al*., 2021).

This study reported the occurrence of breast cancers particularly invasive ductal carcinomas using mostly breast biopsies and fewer mastectomies for diagnosis during the pandemic. Invasive ductal carcinoma has been the commonest breast cancer affecting women in Calabar. This is similar to previous reports (Ebughe *et al*., 2016; Udonkang *et al*., 2021). The increase in biopsies confirms the increase in advanced disease from benign tumours that use mostly lumps for diagnosis. The fewer mastectomies indicate a few late stages of disease at diagnosis. Overall, this showed that there might have been a delay in seeking early diagnosis during the pandemic resulting in an increased risk of developing advanced disease. Delays in seeking early diagnosis have been previously reported in Calabar (Ebughe *et al*., 2019). A similar delay in diagnosis during the COVID-19 pandemic was reported in Croatia (Vrdoljak *et al*., 2021).

Another finding shows that the benign tumours affected younger women of 13-23 years in confirmation of the benign changes associated with lumps among women of this age. The invasive ductal carcinomas affected mostly women of 35-45 years in the study. This confirms that the new cases were mostly among premenopausal women below 50 years of age. New cases of breast cancer have continued to affect younger women of reproductive age as reported in previous work (Udonkang *et al*., 2021a). The effect of age has been linked to the persistent influence of reproductive hormones on breast physiology during reproductive life (Lee and Sultanian, 2015). The numerous cellular and extracellular matrix changes especially involving collagen fibres may also be aetiological to the development of cancers following the early onset of benign diseases as supported by previous work on collagen changes in breast tumours (Udonkang *et al*., 2021a; Udonkang *et al*., 2021b).

The MLP neural network gave a good prediction of the effect of the COVID-19 pandemic on the diagnosis of breast tumours. Also, the MLP model gave a good performance classification of the cases diagnosed during both periods as seen with the result of the area under the ROC curve. The model gave an accuracy of reduction in breast tumour diagnosis during the pandemic. The MLP model has been proven to give a correct classification of performance when applied (Zacharis, 2016). This is similar to the ability of MLP to predict risk factors and biomarkers in leiomyoma (Udonkang *et al*., 2022). Tumour type, the nature of specimen, and mean age were factors that were greatly impacted during the pandemic. This confirms earlier results of diagnosis of more invasive ductal carcinomas, more biopsies, and the occurrence of most diseases in younger women below 50 years (Udonkang *et al*., 2021a) in the study area.

In summary, the COVID-19 pandemic caused a decrease in the newly diagnosed cases of breast tumours in Calabar. One reason may have been the lockdown measures which negatively affected the movement of people. Most persons were as well overwhelmed by the fear of contracting the virus during visits to the hospital. Also, a change in the attitude of healthcare providers in attending to patients by adopting a case-by-case prioritization approach may have been an additional contributory factor. These factors have been stated in similar studies of the effect of COVID-19 on other healthcare services in Nigeria (Olabumuyi *et al*., 2020; Ekpenyong *et al*., 2020).

The strength of this study is based on its novelty and availability of data from the Register of the Histopathology laboratory of the women diagnosed with breast tumours and the application of neural networks in data analysis. The limitation of this study was on incomplete classification of data of some subjects from the records which lead to some exclusion.

In conclusion, the COVID-19 lockdown measures caused a reduction in the number of newly diagnosed breast tumours during the pandemic months when compared to the pre-COVID-19 and post-COVID-19 months. More benign tumours were diagnosed among younger women in their twenties while women below 50 years were mostly diagnosed with cancers. There is a need to put adequate measures to ensure unrestricted access to diagnostic services even during pandemics to reduce the morbidity and mortality associated with delay in early breast cancer diagnosis.

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