Original Article

A Validation Study Involving Development of Model by Application of Artificial Intelligence in Screening and Prognosis of Breast Cancer

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Abstract

Introduction: Breast Cancer (BC) is a worldwide prevalent carcinoma with varying growth rates. It is also a heterogeneous condition with several clinical manifestations. There is a guideline for effective screening of BC, but the mammograms that are obtained for the same often return false negatives or may not effectively diagnose BC, especially at the early stages. The mortality rates due to BC is also significant and efficient screening may reduce more than 30% of mortality. The assessment and accurate determination of tumour growth is difficult due to the substantial failures of screening BC cases.

Aims and Objectives: This current study intends to introduce methods of screening BC using an Artificial Intelligence capable machine learning system, mainly for accurate and efficient detection of BC and assessing its prognostic outcomes.

Materials and Methods: The study comprises a cohort of 120 BC patients aged between 50 and 65 years old. The study involves the development of serial mammograms for detection of in-vivo growth rate and further assessment of immunohistochemical staining. The study also facilitates the development of a machine learning model for detecting BC cases from serial mammograms and several other factors. Statistical analyses have been conducted for effective significance tests between the newly developed and existing methods.

Results: The newly developed method proved to be successful in accurately assessing several aspects of the tumour, including size, stage, grade, mitotic score, type of histology, Nottinham Prognostic Index (NPI) and many more. The newly developed method is more significant than the existing one in assessing clinico-pathological characteristics. The newly developed method has shown significantly better prognostic ability than the existing one ($p = 0.0284$). Kaplan-Meier Survival Curve has been plotted to analyze the growth of the tumour with its prognosis.

Conclusion: The study has effectively presented the development of a prognostic model for Breast Cancer patients with the application of machine learning algorithms, which can be utilized in the screening of breast cancers and proper management of the same to improve its prognosis.

Keywords: breast cancer, tomosynthesis, artificial intelligence, screening.

INTRODUCTION

Breast cancer (BC) costs the lives of almost half a million women every year [1]. BC is a heterogeneous illness, with tumours displaying various shapes, molecular profiles, behaviour, and therapeutic response. A growing body of research suggests that BC has varying growth rates, which have clinical and legal ramifications [2-5]. Furthermore, BC growth rate based on mammography tumour size will be the governing factor for predicting the pharmacological response to chemotherapeutic treatment and may define the timing of the start of the tumour growth under various scenarios. [6-8]. Such mammographic screening successfully lowered breast cancer mortality in randomized controlled studies performed decades ago. This has been established in several nations to minimize breast cancer-related death rates. Screening and treatment advancements showed a nearly 30 % decline in BC mortality, but still, this is the major reason for the deaths of women suffering from cancers. BC screening is now a governmental (regional or national) initiative in several countries, particularly Europe. Women in a certain age range (typically 50–70) are regularly asked to get a mammographic screening exam under these programmes.

When radiologists read mammograms for screening, they look for lesions with various features that can be grouped into soft tissue abnormalities and calcification clusters. The calcifications important for diagnosing BC are microscopic (nearly 0.2 mm)

with higher contrast. Soft tissue lesions include masses, architectural deformities, and asymmetries. Of course, a change (for the most part, growth) in the discovery itself is a critical indicator of the tumour in the breast. As a result, when interpreting screening mammography, comparing it to earlier pictures is critical for improving both sensitivity and specificity [10-13], as well as providing additional information not available from other contemporaneous digital breast tomosynthesis techniques (DBT) [14]. In European countries, most of the time, the screening is carried out by two separate radiologists. This entire scenario is referred to as "double reading." Each radiologist assesses the images and decides the patient's recall in the next visit. When two independent readers disagree, the third radiologist's opinion is considered, which acts as an arbiter depending on the software configuration.

The double reading technique requires greater resources compared to the single one, but it can detect the BC cases and increase the recall ratings in a similar fashion to that of the positive values [15,16]. When a patient is recalled again after the screening procedures, she has to undergo further tests for the diagnosis to validate and confirm the results she got. The radiologist determines whether the biopsy is required or if the results so far obtained are false positive based on the additional imaging. The type and nature of the lesion will decide the pattern or type of the biopsy either by using a very fine needle, core biopsy or vacuum biopsy etc. In these instances, the biopsy samples are examined pathologically and are utilized to determine the final diagnosis, which reveals whether the screening evaluation was true or false positive. If the test results were normal, the findings are classed as true or false negatives based on whether the lady was diagnosed with breast cancer between screening rounds. The assessment and prediction of the growth of cancer is quite a complex process; the molecular interaction between the tumour microenvironment has become quite difficult. Due to this, the imaging of the BC in series and multiple times is considered the ideal model for studying BC behaviour towards the treatment [14-16].

The convergence of novel AI techniques with very advanced computing systems, maximum internal storage and gathering capabilities are spreading the greater attraction in the field of science and healthcare. The applications of AI are widely utilized and evaluated in the healthcare sector for diagnosis and prognosis of cancer, and it is laso used for decision making.

Methods

The study comprises a cohort of 120 BC patients who visited Veronica Gynae Clinic (India), ages between 50 and 65 years old. These patients had soft tissue abnormalities and had BC, as confirmed by three radiologists blinded to each other. Soft tissue abnormalities included distortion or asymmetry of the breast or the presence of mass. These patients previously missed diagnoses due to insufficiency of BC features. The clinico-pathological features of the patients were noted down. The measurements used for assessing the tumour volume are the diameter of the tumour and the height of the tumour. For the evaluation of tumour volume, the fixed dimensions of various shapes are used; for assessment of the rate of tumour growth, the Gompertz model was considered [17,18].

Development and Use of Serial Mammography derived In-vivo Growth Rate.

The authors used various assumptions of tumour shapes to conclude the optimum combination. The growth rates, including the tumour's volume and shapes, were evaluated to determine the prognostic ability. Cox Proportional hazard regression model was used for univariate analysis of growth rates. This model uses 10-year Breast Cancer Specific Survival (BCSS) data and is also based on Akaike Information Criterion [19]. The data associated with the changes in the volume of the tumour lesion and the interval between the time of screening and diagnosis were utilized for the determination of SM-INVIGOR. The tumour volume at the time of screening and the tumour volume at the time of diagnosis were used for determining the prognosis and eventually evaluating the significance of the comparative assessment of the present tumour volume and the tumour volume during the time of screening and diagnosis.

Assessment of Immunohistochemical staining

For immunohistochemical evaluation of markers like Progesterone Receptor (PR), Estrogen Receptor (ER), Human Epidermal Growth Factor Receptor 2 (HER2), proliferation markers like Ki-67, Minichromosome Maintenance-2, basal markers CK5 and CK6, B-cell lymphoma-2 and Epidermal Growth Factor Receptor (EGFR), 4-µm thick formalin dipped paraffin wax embedded block of resected tumour tissue section was obtained. Immunohistochemical evaluation was carried out on the mentioned tissue sections. Antigen epitopes were retrieved in citrate buffer using a microwave, followed by cooling. Then the slides were rinsed thoroughly with Tris-buffered saline (TBS) at pH 7.6. Positive and negative controls were used to evaluate markers, and the invasive tumour cells were scored based on the clinico-pathological data. The assessment was done for all biomarkers' staining percentages and intensity. Then H-scores were determined.

Developing Machine learning-based Model

To develop machine learning algorithms, the biomarkers' existing clinical and molecular variables were evaluated for developing SM-INVIGOR. This will be beneficial in determining the in-vivo growth in case of single mammogram is available. The mean differences for all the variables were evaluated for significance testing, which can identify tumour growth rates. This was assessed by a two-tailed t-test followed by the ranking of the variables. Multiple classification algorithms were tested with optimized hyperparameters. The machine learning algorithm was validated and selected for use. Various hyperparameters were used for developing a machine learning model. Various combinations of these variables were used to determine the growth rate for each BC patient accurately, and lastly, the output of the machine learning model was compared with the regression-based models. The validation of SM-INVIGOR was obtained by testing the prognostic performance of SM-INVIGOR with that of a newly developed model (VAL-INVIGOR), which has tested in a sample of independent and confirmed 955 BC patients by using Kaplan–Meier survival analysis. Multivariate Cox regression was used to control the confounding effects of clinico-pathological variables. SPSS and differences between the groups did the statistical analysis using the $\chi 2$ test. A two-tailed t-test was used for continuous variables. A significant level was considered to be $P<0.05$. The summary of the whole method of this study is depicted in Figure 1.

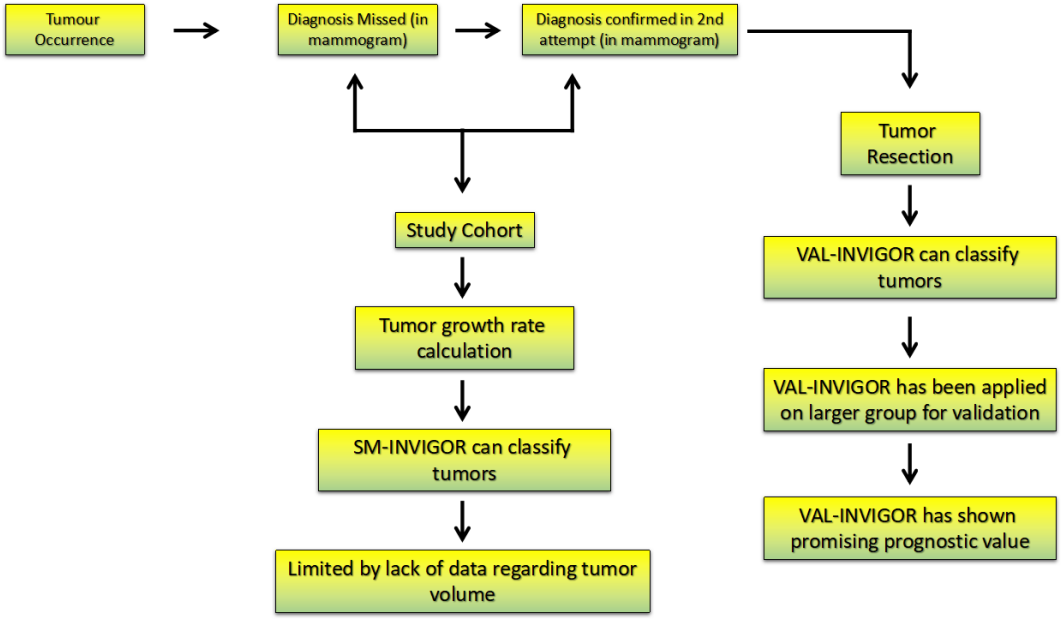

Figure 1: The figure above shows the steps of this current study. This study can be seen in 2 parts. Firstly, the study involves the process of the existing model SM-INVIGOR. Secondly, the study involves the development of a new prognostic model for the assessment of Breast tumour growth, VAL-INVIGOR. Two mammograms are obtained from the patients, one at the screening and finally at the time of final diagnosis. With these results of two mamograms, the study cohort is constituted (n = 120). Then, the growth of the tumour is assessed for each patient in this group, and SM-INVIGOR identifies and evaluates the tumour volume. In Validation Cohort (n = 955), the new model VAL-INVIGOR is followed, which is tested with 955 patients with Breast Cancer for evaluation of tumour growth.

Statistical Analysis

Statistical analysis was conducted by using SPSS 25. Differences in clinico-pathological proportional outcomes were evaluated by the $\chi 2$ test, while a two-tailed t-test analyzed continuous variables. The prognosis (time to event) is analyzed by conducting Kaplan-Meier and Cox Proportional Hazard Regression analysis, considering death as an event. Kaplan-Meier Survival Curve shows the patients in the Study Cohort group predicted by SM-INVIGOR. Kaplan-Meier Survival Curve shows the patients in the Validation Cohort group predicted by VAL-INVIGOR. The level of significance was considered at 5%.

Ethical Approval

The study has obtained required consent from each patient after explaining them the study process in details. The study has been conducted according to the declaration of Helsinki (World Medical Association).

Results

Table 1: The evaluated clinico-pathological characteristics that are found in Study Cohort (SM-INVIGOR) and Validation Cohort (VAL-INVIGOR)

Parameters	Study Cohort (N, %)	Validation Cohort (N, %)
Age		
≦ 60	95, 79.17	866, 90.68
> 60	25, 20.83	89, 9.32
Tumour grade		
Grade I	23,19.17	221,23.14
Grade II	55,45.83	512, 53.61
Grade III	42,35.00	222,23.25
Tumour Size		
≦15	32,26.67	689,72.15
> 15	88,73.33	266,27.85
Lymph Node		
1	63,52.50	612,64.08
2	39,32.50	242,25.34
3	18,15.00	101,10.58
Hormone Receptor Status		
ER-positive	95,79.17	812,85.03
ER-negative	25,20.83	143,14.97
PR positive	62,51.67	496,51.94
PR negative	58,48.33	459,48.06
HER-2 expression		
Positive	28,23.33	101,10.58
Negative	88,73.33	845,88.48
Missing	4,3.33	9,0.94
Intrinsic molecular subtypes		
Luminal A	51,42.50	345,36.13
Luminal B	38,31.67	352,36.86
HER2	6,5.00	82,8.59
BLBC	5,4.17	92,9.63
Triple-negative	16,13.33	55, 5.76
Missing	4,3.33	29,3.04
Ki67		
High	54,45.00	496,51.94
Low	66,55.00	459,48.06
Tumour type		
Invasive only	61,50.83	512,53.61
Invasive lobular	26,21.67	105,10.99
Tubular	18,15.00	246,25.76
Mucinous	9,7.50	9,0.94
Mixed type	6,5.00	83,8.69
Coexisting DCIS		
None	33,27.50	N/A
Low grade	23,19.17	N/A
Intermediate grade	26,21.67	N/A
High grade	38,31.67	N/A
Lymphovascular invasion		
Negative	71,59.17	598,62.62
Definite	34,28.33	215,22.51
Probable	105,87.50	142,14.87
Outcome status		
Alive	94,78.33	643,67.33
Dead	26,21.67	312,32.67

The development of an efficient predictor of BCSS has been discussed in this study. The in-vivo fast-growing lesion or mass

is a conclusion of aggressive form and is expected to lead to poor outcomes. The study featured an evaluation of various growth rate characteristics based on assumptions about the 3D structure of the tumours. The tumour growth rate was classified in SM-INVIGOR into slow and fast-growing subgroups. This resulted in a minimum cross-validation AIC of 151.996. In this study, the tumour volume ranged from 48 mm3 to 52698 mm3 (2956 ± 8991 mm3) during the time of screening, while during the time of diagnosis, the tumour volume ranged between 55 and 56328 mm3 (mean = 6102 ± 8951 mm3). The mean difference between screening and diagnosis was 19 months, ranging from 3 to 36 months. The mean value of the growth rate of the tumour was found to range from 0 to 0.48 mm3/day.

In our study, SM-INVIGOR used a cut-off value of 0.045 mm3/day for classification of tumor into slow (n = 84) and fast growing (n = 36).

The study also highlights that fast-growing tumours are associated with those clinico-pathological characteristics that usually lead to poor prognosis. These poor prognostic outcomes may include high grade tumor (p=0.0185), larger histological tumor (p = 0.0024), increased mitotic activities (p = 0.0133). The study also revealed that Ki67 had significantly predicted slow-growing and fast-growing tumours (p = 0.0002).

Table 2: Univariate association between clinico-pathological characteristics and study cohort (SM-INVIGOR); and between clinico-pathological characteristics and validation cohort (VAL-INVIGOR).

Clinico-pathological characteristics	Study Cohort (SM-INVIGOR)	Validation cohort (VAL-INVIGOR)
Size	Significant	Significant
Stage	Insignificant	Significant
Grade	Significant	Significant
Tubule formation	Insignificant	Significant
Nuclear pleomorphism	Insignificant	Significant
Mitotic score	Significant	Significant
Lymph vascular invasion	Significant	Significant
Type of histology	Insignificant	Significant
Nottinham Prognostic Index	Significant	Significant
Molecular subtypes	Insignificant	Significant

It has also been shown that patients with higher tumour growth showed significantly poor survival with a BCSS of 70.28% compared to tumours with a slower growth rate (BCSS = 90.12%). It is also revealed that SM-INVIGOR has shown significant prognostic ability (p = 0.0284). Multivariate analysis has shown SM-INVIGOR variable is the only significantly associated with BCSS. Table 3 shows the details of the Multivariate analysis.

Table 3: Multivariate association between clinico-pathological characteristics and study cohort (SM-INVIGOR); and between clinico-pathological characteristics and Validation cohort (VAL-INVIGOR).

	Study Cohort		Validation cohort	
Clinico-pathological characteristics	Hazard Ratio (95% Confidence Interval)	P-value	Hazard Ratio (95% Confidence Interval)	P-value
Age (≦ 60 and > 60)	0.987 (0.911-1.074)	0.77	1.007 (0.995-1.017)	0.3241
ER (Negative)	0.837 (0.228 - 2.99)	0.76	1.313 (1.005 - 1.705)	0.0432
Grade 3	3.685 (0.043 - 30.845)	0.23	7.206 (3.608 - 15.221)	<0.001
Grade 2	4.879 (0.614 - 38.703)	0.14	3.721 (1.855 - 7.477)	0.0002

SM-INVIGOR (above)	3.625 (1.015 - 12.945)	0.03	N/A	N/A
VAL-INVIGOR	N/A	N/A	2.053 (1.278 - 3.3117)	0.0031

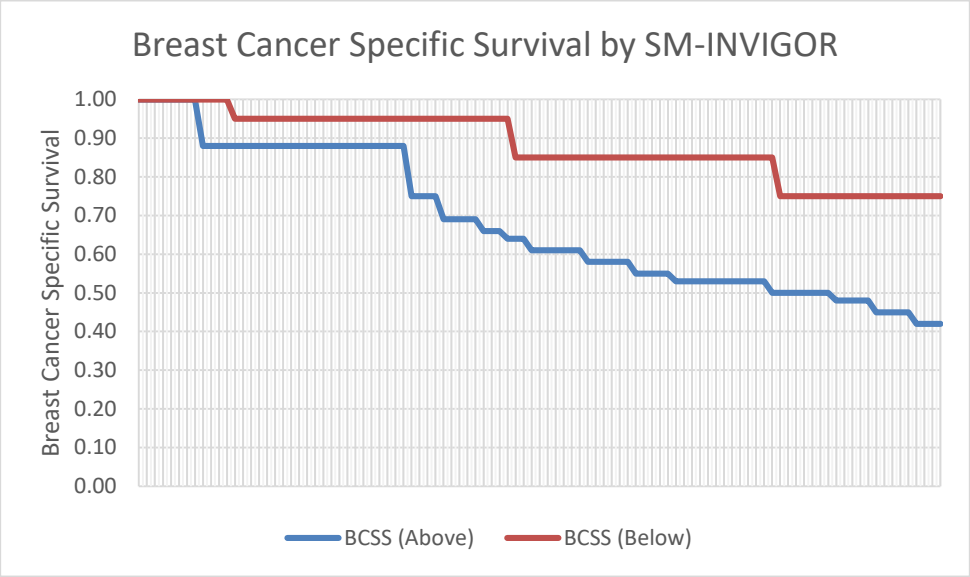

Figure 2: Kaplan-Meier Survival Curve for study cohort group, classified into high and low growth rate (by SM-INVIGOR)

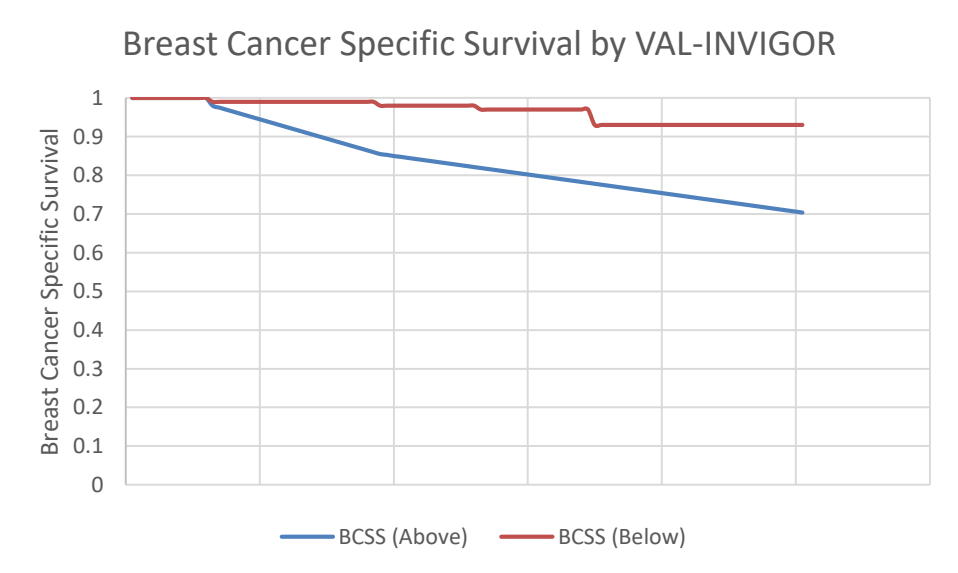

Figure 3: Kaplan-Meier Survival Curve for validation cohort, classified into high and low growth rate (by VAL-INVIGOR)

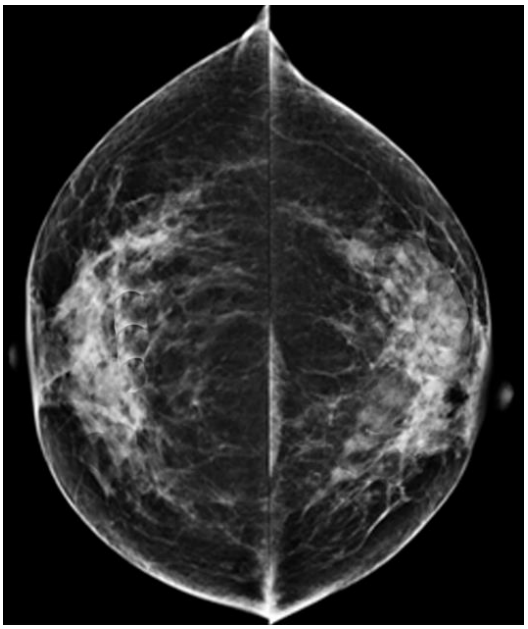

Figure 4: A typical mammogram obtained in this study

The study obtained two mammograms with two different tumour volumes. It has been observed that using SM-INVIGOR makes it difficult to deal with two measurements of in-vivo tumour growth rates. Therefore, the study has developed VAL-INVIGOR, a substitute model for analyzing the in-vivo growth rate of tumours. The newly developed model VAL-INVIGOR considers the mentioned clinico-pathological and other biomarkers for efficient prediction of in-vivo growth. This current study has evaluated seven variables, including tumour size, Nottinham Prognostic Index (NPI), grading of the tumour, mitotic score, Ki-67, molecular subtypes, and histological types, with a p-value less than 0.2 by testing this variable in the newly developed machine learning algorithms by using the method sequential selection.

This study has validated the newly developed VAL-INVIGOR by showing its analytically significant efficacy in the prognostic ability of the tumour. The significance of clinico-pathological variables between the Study and Validation Cohort is shown in Table 2. It has been found that the patients with a faster growth rate of the tumour have lower survival significantly compared to those with a slower rate of tumour growth. This is shown in Kaplan-Meier Survival Curve (Figure 2 and Figure 3).

Discussion

The timely diagnosis of cancer through mammography is critical to the success of breast screening. False-negative mammography is one of the most common causes of BC diagnosis delays [20-22]. Although some authors claim that diagnostic mammography has a high sensitivity (>90%), such results are not uniform [23]. Because the high radiographic density of breasts in young women makes detection difficult, age appears to be one of the key factors behind false-negative reporting [24]. Mammograms can identify tumours as tiny as 2 mm in diameter, translating to 107 cells and approximately 23 tumour doublings [25,26]. Another hotly debated topic is whether tumour spread is caused by delays in identification and therapy or by tumour cells' fundamentally more aggressive nature (i.e., a greater in-vivo tumour growth rate). Breast radiologists have been thrust into the forefront of medicolegal cases due to the relevance of breast imaging in BC diagnosis and the use of mammography in screening.

There are a few cases where screening was missed to classify cancer, but a mammogram confirmed it, but there is a significant number of cases where false-negative mammograms have later been revealed to be Breast Cancer [20,21, 27, 28]. There is a lack of past studies dealing with malignancies like breast cancer and providing large population-driven findings. More studies need to be conducted to gather scientific information on fast-growing tumours. These fast-growing tumours, like breast carcinomas, develop on obtaining nutrition from invading arteries and leaky gaps between endothelium. As part of the management, immediate surgical removal is the guideline for fast-growing tumours and delaying, which may lead the "T" of TNM classification to advance. Studies have shown that this type of tumour has a very poor prognosis and survival rate [29-33].

This current study has employed Artificial Intelligence (AI) as the tool for effective early diagnosis of breast cancer which is expected to contribute to the advanced algorithms for machine learning that can efficiently interfere with and interpret the

mammograms done during screening time. This will help reduce false positives and is expected to improve the breast cancer screening process in the future [33, 34]. Interpreting imaging modalities and pathological reports can be done using the developing AI and may aid in the screening process. Recently developed AI has been successfully shown to improve the screening of metastatic breast cancer diagnosis in reports of sentinel lymph node biopsy [35]. For this purpose, a large-scale population should be considered for developing effective AI programs that can be used in breast cancer. It has been observed that the various statistical analysis-driven AI development and corresponding image capture and interpretation have contributed a lot to AI development in the last few years. Studies have shown that only mammography can reduce mortality rates due to breast cancer [33,35]. This modality (mammography) has been advanced to become breast tomosynthesis (3D rendering of the breast structure). Future research in the development and evaluation of AI needs more qualitative studies to be conducted and the knowledge gaps to be filled. There are many doubts about the research, and it is still under development phases, which also needs several rounds of a clinical trial. Again, there are issues around the world using AI regarding social issues, medical ethics and legal boundaries [33].

Certain changes in laws worldwide will allow institutions and clinicians to confirm the interpretations suggested or shown by the machine (AI) on medical image reports. Many studies also suggested that there is a need to constitute the criteria and basis on which AI will make the diagnosis, and the number of cases of breast cancers should be monitored for any discrepancy in their diagnosis or sudden change in the diagnosis due to the implication of AI. The quality control of the algorithms and the efficiency of the machine hardware should also be considered and should be under strict monitoring by the government and authorities. Auditing and training the clinicians and keeping them up to date with the upgrades of AI algorithms or AI graphical user interface (GUI) is also suggested [36-40]. There are several speculations regarding the full implication of AI in the diagnosis of breast cancer and the impact of the diagnosis and treatment on a country-wide scale.

In conclusion, studies have been considered to advance the diagnosis process of breast cancer by evaluating tomosynthesis images and digital mammography, which is expected to impact breast cancer diagnosis [40,41] substantially. This current study has conducted several statistical analyses, and the results have shown that this method of utilizing AI in screening Breast Cancer is significantly effective compared to the traditional or existing screening method. This can be said because using AI in breast cancer screening effectively reduces false positives. There is also a need to upgrade the algorithms, and finally, if the developing method of AI can be implemented in screening breast cancer, it can revolutionize the screening methods in medical science.

Conclusion

The current study has separately considered and analyzed clinico-pathological characteristics for SM-INVIGOR and validated the newly adopted VAL-INVIGOR to show prognostic significance ($p = 0.0259$). This validates that VAL-INVIGOR can be utilized to determine the tumour's age during the diagnosis. This newly developed method can also be used to assess whether a particular patient has a slow-growing or fast-growing tumour, which can also evidently prove the presence of a tumour and the time for which the tumour is present in that particular patient.

There are several limitations of SM-INVIGOR, especially because it takes time to diagnose the tumour's growth, which may impact the proper management of the tumour. So, this current study involves the development of another prognostic model (VAR-INVIGOR), which can effectively evaluate the in-vivo growth of the tumour, considering various clinico-pathological characteristics of the tumour, using machine learning algorithms. This newly developed model can further differentiate fast-growing tumours from slow-growing tumours; hence, it can suggest the proper management to be adopted at appropriate times. The authors of this current study suggest that immediate surgery should be done in case of a fast-growing tumour which can arrest the tumour from advancing. This new model can be used for follow-up evaluation of the tumour status and also can be used in screening. The study also concluded that the newly developed model could be significantly correlated with the types of BC and tumour growth rate.

Thus, this study has suggested the development of a prognostic model for Breast Cancer patients with the application of machine learning algorithms. However, the author suggests testing the application of this model in the more diversified population of breast cancer patients to document more findings and to run their correlation with the present findings or with the existing models.

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