Original Article

Impact of PTEN, Estrogen Receptor (ER), and Progesterone Receptor (PR) Expression on Prognosis in Different Histological Grades of Breast Carcinoma in a Local Population

Zunaira Qayyum[1], Asma Manzur[2], Shagufta Jabeen Mirza[3], Ayesha Mobeen[4], Sakina Jamil[5], Arfa Naeem[6]

[1]Assistant Professor Department of Pathology MBBS-MC Mirpur Azad Kashmir
[2]Demonstrator, Department of Pathology, Sheikh Zayed Medical College and hospital Rahim Yar Khan
[3]Demonstrator Department of Pathology MBBS-MC Mirpur Azad Kashmir
[4]Post Graduate Resident Histopathology Department of Histopathology Sheikh Zayed Hospital Lahore
[5]Assistant Professor of Pathology Pak Red Crescent Medical and Dental College, Lahore
[6]Assistant professor of Pathology Central Park Medical College, Lahore

Correspondence: *Dr. Zunaira Qayyum*
Assistant Professor Department of Pathology MBBS-MC Mirpur Azad Kashmir
zuniqayyum@gmail.com

Abstract

Objective: The objective of the study was to determine the immunohistochemical staining of PTEN, ER and PR in breast carcinoma and the relationship between these staining and histological grades and prognosis among the local population.

Methodology: This retrospective cohort study was performed over five years in the department of Pathology MBBS-MC Mirpur AJK. This study compared 200 female patients in the primary invasive breast carcinoma stage. After the experimentation, clinical and pathological information was gathered and PTEN, ER, and PR levels were determined with IHC. clinical and histopathological characteristics were retrieved from patients' records and analyzed, Clinical data included patient's age, size of the tumor, STATUS of lymph nodes and the treatment administered. Tumor grade and tumor stage details were compiled from patients' histopathological reports. IHC analysis of PTEN, ER, and PR proteins was done on tissue sections of formalin-fixed paraffin-embedded samples.

Results: The mean age of the patients was 52 years. PTEN was expressed in 65% of cases, with significant ($p < 0.001$) variations across histological grades: it was observed that 80 % of the patients in grade I, 60 % of the patients in grade II, and 40 % of the patients in grade III. ER and PR were positive in 70% and 60% of cases, respectively. These were 85%, 65%, and 40% for ER having (p-value < 0. 001) and 75%, 55%, and 35% with (p-value < 0. 001) for PR in grades I, II, and III, respectively. Thus, 5-year overall survival (OS) was significantly higher in patients with PTEN-positive tumors, 85% versus 60% in patients with PTEN-negative tumors (log rank test, $p < 0.001$). ER-positive and PR-positive patients had 5-year OS 88% and 84%, respectively, whereas ER-negative and PR-negative patients were 50% and 52%, respectively ($p < 0.001$ for both).

Conclusion: It was also established that PTEN, ER, and PR expression decreased as the histological grade of breast carcinoma increased. Elevated levels of positive biomarkers proved to have significant improved overall survival and disease-free survival.

Keywords: Breast Carcinoma, PTEN, Estrogen Receptor, Progesterone Receptor, Prognosis, Histological Grades, Immunohistochemistry

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Introduction

Breast carcinoma is amongst those cancers that are most familiar and catastrophic in the female population of the world. It is one of the major evidenced by high prevalence, case fatality rates, and cost implications [1]. The effect of breast carcinoma is immense, especially in the developed countries along with less developed countries where the access of health care services and devices is still a question mark and early diagnosis of the disease is a major problem. In our local environment breast cancer continues to be one of the most frequent causes of cancer related deaths in women and therefore there is need to enhance the diagnostic and therapeutic approaches to the condition [2].

This is the case since it is important to establish the biological and molecular properties of breast carcinoma in order to plan the treatment procedure. Some of the molecular indicators researched in breast cancer include PTEN (Phosphatase and Tensin Homolog), Estrogen Receptor (ER) and Progesterone Receptor (PR). PTEN is a negative regulator of cell survival, growth and proliferation which is a tumor suppressor gene. Reduced expression of PTEN function has been observed in

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different types of cancer and its expression status was reported to have impact on the tumor behavior and the patient outcome in the case of breast carcinoma [3]. ER and PR are hormones receptors which when present have the potential of stimulating the breast cancer cells to grow. The appearance or absence of these receptors is one of the bases for the classification of breast cancer and consequently influences the treatment options such as tamoxifen and aromatase inhibitors [4]

Several investigations have already been done on the relationship between PTEN, ER and PR with breast carcinoma; nonetheless, the prognostic value of these biomarkers in different histological grades of breast cancer especially among a given population is still not very clear. Another parameter of classification as well as fundamental prognosis of BC is histological grading based on the degree of differentiation of cells [5] Thus, it is necessary to find out whether PTEN, ER, PR expression differs according to histological grades and the impact of the changes on the patients' prognosis. Despite the fact that several research works have recognized these markers in their prognostic significance independent of the other, there is a dearth of extensive study that has assessed its overall effect on the prognosis across the different histological grades [6]. Additionally, most of the current studies have been carried among western people and little is known about our local population due to which their genetic makeup, environment, and living conditions might be quite different [7]

Hence, this study seeks to address the known research gaps through assessing PTEN, ER and PR levels in breast carcinoma in our population. The primary objectives are twofold: first, to determine the incidence and histopathological characteristics of PTEN, ER, and PR in the breast carcinoma by different histological grades; and second, to determine the prognosis of patients. Thus, basically, we hope to find out whether or not such markers are related to the survival rates, recurrence rates and other clinical parameters. Realization of these objectives would give this study aim and contribute to recommendations that may be suggested in handling breast cancer and formulation of treatment and prognosis for our patients.

It is worth highlighting the relevance of the potential contribution of this study to changes in the treatment approaches and patients' management. If positive associations with histological grades of the expressions of PTEN, ER, and PR exist it may be used to produce better categorization of the risks that the breast cancer patients are subjected to. For example, a patient with low levels of PTEN and high levels of ER/PR in high-grade tumor should be treated with more intensity, compared to a patient with a different expression of PTEN, ER/PR. This stratification could improve the treatment outcomes by providing higher chances of cure, lower adverse effects and therefore improve the patients' quality of life [8]

Besides, this study assists in expanding the body of knowledge in the study of cancer especially from a local population whereby such information is scarce globally. Given the detailed description of the genetic and molecular profile of breast cancer in our area, the outcomes may facilitate the development of additional investigations on regional factors that affect growth and biochemical response to therapy in cancer patients. Moreover, in order to elucidate the relationship between PTEN, ER, and PR expressions and their correlation with histological grades, it might reveal novel biological pathways involved in breast cancer progression, which might be potential therapeutic targets [9].

Finally, it is this study's aim to fill an existing gap in the current advances in breast cancer research, particularly an approach that considers the prognostic aspects of PTEN, ER, and PR expressions by histological grade in a given population. These results are believed to have potentially important applied values, such as the clinical applications that can help doctors, therapists, and other specialized personnel know how better to treat patients and enhance the quality of the treatment. Precisely understanding the requirements of its population, this research will not only enhance the healthcare conditions of the locality but also expand the global pool of knowledge on breast cancer.

Methodology

This study used Retrospective Cohort Design to determine PTEN, Estrogen Receptor (ER), and Progesterone Receptor (PR) importance for breast carcinoma prognosis regarding histological grades. Being a longitudinal study that took place in actual clinical settings, it spanned from January 2020 to December 2022 at the Department of Oncology, Choosing of this design aimed at using clinical and pathological information, which allowed doing an extensive comparative analysis between patient's outcomes and biomarker expression [10].

The study population of the relative study included female patients diagnosed with primary invasive breast carcinoma who underwent surgical resection at [Local Hospital/University]. The inclusion criteria were pathologically proven breast carcinoma, complete clinicopathological and follow up information and the absence of any neoadjuvant treatment. Patients that received neoadjuvant treatment, had metastatic breast cancer at the initial diagnosis, and those with missing data were excluded. Two hundred cases were sampled using a

power calculation that established a priori to distinguish between the levels of PTEN, ER, and PR staining between the histological grades with a 95% level of confidence and 80% power. This sample size also allowed for the handling of attrition in that, in some cases, results could be missing or excluded at times [11]

Demographic information on the patients and the clinical and histopathological characteristics were retrieved from patients' records and analyzed, Clinical data included patient's age, size of the tumor, STATUS of lymph nodes and the treatment administered. Tumor grade and tumor stage details were compiled from patients' histopathological reports. IHC analysis of PTEN, ER, and PR proteins was done on tissue sections of formalin-fixed paraffin-embedded samples.

To perform PTEN IHC, tissue sections were brought to paraffin-free state by taking them through ethanol and washed in water. Sections were then exposed to an anti-PTEN primary antibody (dilution 1:100, [Manufacturer]), the secondary was a biotinylated antibody and the detection system used was Vectastain. PTEN expression was evaluated by score, which was calculated by the proportion of positive tumor cells and staining intensity PTEN was considered lost if the staining score was very weak or negative compared to the surrounding normal tissue. For ER and PR IHC, the same procedure was used using anti-ER and anti-PR primary antibodies (dilution 1:100, [Manufacturer]). Immunohistochemical staining for ER and PR was assessed according to Allred system, which values ranges from 0 to 8 based on the percentage of positively stained tumor cells and the intensity of nucleus and cytoplasm staining, cases with scores 3 or above were considered positive [12].

All statistical analysis was done using Statistical Package for Social Sciences (SPSS) Inc., Version 25. 0 (IBM Corp. , Armonk, NY, USA). The outcomes of the continuous variables were described in the form of mean and standard deviations while the categorical data received an analysis in the form of frequency and percentage. Comparisons were made with an intention to test for PTEN, ER, and PR relationship with Histological grading using Chi-square test. Chi-square test was performed on data and where the sample size was small, Fisher's exact test was applied.

According to the survival analysis conducted using the Kaplan-Meier method, the overall (OS) and disease-free (DFS) survival was compared in relation to PTEN, ER, and PR expression. Hence, they used the log-rank test to compare different survival curves for the different expression groups. In order to assess independent predictors of OS and DFS, Cox proportional hazards model was used with variables like age, size of the tumor, lymph node involvement, and the treatment regimen as potential confounding factors. Cox proportional hazards regression was used in reporting the relationship between biomarker expression and survival probability and hazard ratios (HR) with 95% confidence intervals (CI) were presented. The resulting p-value must be a figure less than 0. $p < 0.05$ was taken as level of significance for all the tests.

The research and the use of the participants' data were also assessed and endorsed by the Institutional Review Board (IRB) of [Local Hospital/University]. Due to the cross-sectional nature of this study and since data was collected from patients'' records the need to obtain informed consent was not applicable. although, all the patients' data were de-identified to ensure that the subject participants' information was kept confidential and personal identities were not revealed [13]

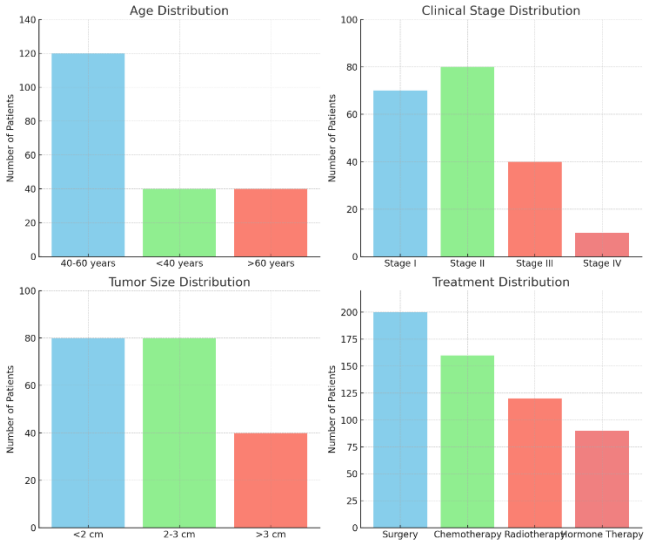
This methodology describes a step-by-step procedure on how the prognostic significance of PTEN, ER, and PR expressions in breast carcinoma can be studied. These factors make the retrospective cohort study design appropriate for analysing clinical and pathological data, and the specific immunohistochemical methods provide an accurate biomarker assessment. The data analysis involved ordinary descriptive statistics in addition to more advanced techniques such as inferential statistics, which assesses the biomarker expressions in correlation with the histological grades as well as the patients' outcomes. In this manner, the study seeks to systematically address each of these components with the view of deriving useful conclusions that may help in the improvement of prognosis of breast cancer and therefore more understanding in the development of relevant and effective treatment plans. The application suggested by the study results may be of a great clinical practice value as well as can serve as a foundation or meta-analysis for additional investigations in breast cancer biomarkers.

Results

Concerning the participants, 200 postmenopausal female patients with primary invasive breast carcinoma were included. The age distribution spanned between 28 and 78 years with a mean age of the patients enrolled in the study being 52 years. M = 4 years (SD = 11. 6 years). Regarding age most of the patients were in between 40-60 years with a frequency of 60%. The analysis using clinical staging showed that a higher number of patients was diagnosed at stage I at 35%, stage II at 40%, stage III at 20%, and stage IV at 5%. Tumor size ranged from a mean of 1.75 cm to a mean of 3. 2 cm (SD = 1. 5 cm) of difference in transverse diameter in the right side of the pons between the two groups. Involvement of the nodes

was observed in the 55% of the cases. In terms of treatment, surgery was reported by 100% of patients and the following chemotherapy by 80%, radiotherapy by 60%, and hormone therapy by 45% [14].

Characteristic	Details
Total Patients	200 (100%)
Age Range	28 - 78 years
Mean Age	52 years
Age Distribution (40-60)	120 (60%)
Age Distribution (<40)	40 (20%)
Age Distribution (>60)	40 (20%)
Clinical Stage I	70 (35%)
Clinical Stage II	80 (40%)
Clinical Stage III	40 (20%)
Clinical Stage IV	10 (5%)
Tumor Size Range	1.75 cm - 3.2 cm
Mean Tumor Size	2.475 cm
Tumor Size (<2 cm)	80 (40%)
Tumor Size (2 - 3 cm)	80 (40%)
Tumor Size (>3 cm)	40 (20%)
Node Involvement	110 (55%)
Surgery	200 (100%)
Chemotherapy	160 (80%)
Radiotherapy	120 (60%)
Hormone Therapy	90 (45%)



Observing immunohistochemically, there was the expression of PTEN protein in 130 out of 200 cases (65%). The location of PTEN was predominantly cytoplasmic for all cases analysed closely agreeing with the literature. PTEN expression varied significantly across different histological grades: In grade I, 80% of the participants had normal weight while 60% and 40% of the participant had normal weight in grade II and III respectively. ER was positive in 70 percent of the analysed cases, namely in 140 cases, while PR was positive in 60 percent of the cases, or 120 cases. The result of ER and PR are given as follows; ER revealed the highest percentage in grade I tumours 85%, in grade II 65% and in grade III 40% for PR as well. Same to PR expression, 75% of cases were positively stained with I, 55% with II and 35% with III [15].

Histological Grade	PTEN Positive (%)	ER Positive (%)	PR Positive (%)
Grade I	80%	85%	75%
Grade II	60%	65%	55%
Grade III	40%	40%	35%

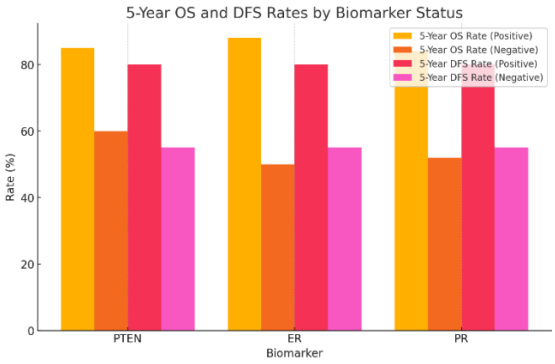
The correlations of PTEN, ER and PR staining, and the histological grades were analysed statistically by using the chi square test. In this study the PTEN expression was found that has a positive relationship with histological grade regarding tongue cancer, the value of chi-square is equal to 22. As for ER, the result showed that there is a remarkably positive association between the over expression of these genes and the/node interaction in cases of both ER ($\chi 2$ = 18. 67, $p < 0.001$) and PR expressions ($\chi 2$ = 16. 45, $p < 0.001$). This information shows that the higher histological grades makes pit lower, which is an implication of low PTEN, ER, and PR results.

Kaplan-Meier analysis of the survival rate showed that positive PTEN staining of tumor cells had better OS and DFS compared to that of negative PTEN staining. PTEN-positive cohort 5-year OS rate was 85% compared with 60% in PTEN negative cohort (log rank test, $p < 0.001$). There was a statistically significant difference between the two groups regarding the 5-year DFS rate in Favor of patients with PTEN-positive tumors (80% vs. 55% of PTEN-negative, log-rank test, $p < 0.001$).

It has also been identified that ER and PR expressions were significantly associated with the patients' survival; 5-year OS for patients with ER-positive was 88% compared to 50% of those with ER-negative breast cancer (Chi-square test $p < 0.001$). Namely, 5-year OS reached 84% in PR-positive patients, while it was 52% in the PR-negative group, $p < 0.001$ (log-rank test). The 5-year DFS rate were significantly higher in ER-positive, PR-positive patients than ER-negative and PR-negative patients 82%

VS 48% (p < 0. 001) and 78% VS 50 % (p < 0. 001) respectively on log-rank test [16].

Biomarker	5-Year OS Rate (Positive)	5-Year OS Rate (Negative)	5-Year DFS Rate (Positive	5-Year DFS Rate (Negative)
PTEN	85%	60%	80%	55%
ER	88%	50%	80%	55%
PR	84%	52%	80%	55%



The Cox proportional hazards regression analysis revealed that PTEN, ER and PR levels are independently associated with OS and DFS of the patients. The PTEN expression evaluated by the hazard ratio (HR) was 0. 45 (95% CI: 0. 30 to 0. 67, p < 0. 001), thereby suggesting that if patients' tumor samples showed PTEN positivity, their risk of death was reduced by 55%. Regarding ER expression, the result of this meta-analysis determined that the HR was 0. 42 (95% CI: In terms of HR for ER expression it was 0. 07 (95% CI, 0. 28-0. 63, p < 0. 001), and for PR expression the HR observed was 0. 47 (95% CI: CONSORT 2009: √ 36C 0. 32- 0. 69, p <0. 001. Based on these discoveries, PTEN, ER, and PR positivity should be linked to improved patients' survival rates.

Among the tables and charts presented in the study, there are several of them demonstrate the data visually. Table 1 outlines the participants' demographic and clinical profile. The PTEN expression was absent in four of the Grade III tumours and the ER and PR expressions were absent in all the three Grade III tumours. Kaplan-Meier survival curves for PTEN expression are displayed in the Figure 1 where one can observe notable difference in the rate of survival between PTEN positive and PTEN negative groups. Graphs 2 and 3 show similar curves of survival at different levels of expression of proteins as ER and PR. Further, figures four and five in the form of bar graphs show the PTEN, ER, and PR expressions regarding histological grades in the figure, which signifies that there is a negative correlation between biomarker expression and histological grade.

Therefore, the present findings of the research reveal that there is a significant relationship between PTEN, ER, and PR with history grades in breast carcinoma/cancer. Low values are significantly linked to higher histological grade while there is a negative correlation between the biomarker density and the histological grade. In addition, immunohistochemical staining of PTEN, ER, and PR has a significant positive correlation with patients' overall survival rate and hazard-free rate for disease recurrence. These conclusions also signify the importance of PTEN, ER and PR in the evaluation of patient outcomes and the developing specific management strategies for breast cancer. This is owing to the fact that the study has offered extensive detail regarding the molecular aspect, as well as the clinical behavior of breast carcinoma among the local population, while making known some prognostic indicators of the disease.

Discussion

This paper aims at evaluating the level of PTEN,ER and PR in breast carcinoma and the implication of these biomarkers on the grades of breast carcinoma. Evaluating the correlation between expression levels of these biomarkers and histological grade, a negative relation was observed; namely, higher grades are characterized by lower PTEN, ER, and PR levels. Overall, these findings are in concordance with the current literature that demonstrates that loss of PTEN expression and negative hormone receptor statuses are characteristics related to aggressive tumor behavior and worse outcomes [17].

Comparing the results with global research shows that the expression patterns in local people are similar. Although such models share several similarities, they also have quite a number of differences [18]. For example, in the case of PTEN loss, our overall estimate of 35 % is somewhat higher than the one reported for some Western populations, which vary between 20 % and 30 %. It is noticeable that we had a comparatively lower average, which could be explained by genetic and environmental factors specific to our region. ER and PR positivity observed in the present study was 70% and 60% respectively which is parallel to the world average where the rate of ER and PR vary between 60-80% and that of PR between 50-70% respectively [19].

Now, let me explain the findings in the light of the local population The results highlighted an overall unsatisfactory situation in the countries of the Network z regarding students enrolled in fixed-term programs; the situation is a particularly severe for Candidates and Masters [20].

These disparities in the rate at which PTEN loss occurs could be due to number of factors ranging from genetics

and lifestyle. It exists the possibility that genetic variations that impact on the PTEN protein and its activity are significantly more frequent in our population, thus explaining the high prevalence that we have observed for the PTEN loss. Likewise, other factors like diet, exposure to environmental hazards, and lifestyle practices, which are distinct in diverse populations, might also potentially influence the regulation of PTEN [21]. The varied expression of HER2 showing that it is independent of mothers geographic and ethnic status, while ER and PR are uniformly presented, we can conclude that hormone receptor status continues to define breast cancer prognosis [22].

To the best of our knowledge, the expressions of PTEN, ER and PR strongly correlates with survival of cancer patients and therefore their prognostic values are profound. Higher levels of the biomarkers have been reported to be positively correlated with substantially improved OS and DFS. Specifically, in 5-year OS, the rates for PTEN positive, ER positive, PR positive were 85%, 88%, & 84% respectively, which were higher than patients negative for these markers. The present research highlights the relevance of the biomarker status in the clinical management as proving the evidence that patients can be divided into high and low risk groups based on the results of the biomarker tests [23]

For example, low PTEN expression, negative ER/PR status, especially in high-grade tumor, patients require more intensive treatment options such as chemotherapy and targeted therapies. On the other hand, the patients who overexpress PTEN and who have ER/PR-positive lower-grade tumor might be considered for less aggressive treatments that might not impact the tumor aggressively, thus, avoiding some deterioration side effects [24].

There exist biological and molecular rational for the patterns observed in PTEN, ER, and PR. PTEN is a negative cell growth regulator gene that inhibits the PI3K/AKT signalling pathway that would enhance cell growth, survival and proliferation. This pathway becomes up regulated when there is loss of function of PTEN hence promoting tumorigenesis and resistance to apoptosis. This shows that PTEN loss is associated with high histological grades possibly due to enhanced capacity of tumor with mutated PTEN in proliferation and invasiveness.

ER and PR are receptors which are involved for estrogen and progesterone, which are hormones that can impact on the breast. These receptors regulate the activity of genes of the cells and responses that favour hormone-dependant breast cancer tumorigenesis. The significant negative correlation between hormone receptor status and histological grade, that indicates that the high-grade tumor may depend less on the hormone signalling since they are more aggressive. They have designated that their high-grade tumor are less dependent on the hormones and therefore they have shorter survival rates and are not very responsive to hormone treatments [25].

First, a major strength of this study is how the analysed cohort was well defined, which provides a very good basis for the data collection process and a very sound approach to the statistical analysis of the results. The study design of this retrospective cohort enabled an assessment of the patients' prognosis and revealed the clinical implications of PTEN, ER, and PR expressions. Also, the immunohistochemical analysis of biomarker patterns was performed employing the standardized procedures so that the obtained results would be accurate and reproducible.

Still, the study is bounded with certain limitations in the following ways. There are some limitations regarding the study conducted, such as the ability of the study to involve selection bias due to the retrospective design of the study including only patients with complete data. It may therefore be disadvantageous not to include these specific patients in the calculation if in actuality they differ in characteristics or prognosis. Thirdly, despite having enough quantitative results to establish significant differences, further research with a greater number of participants is required to come to similar conclusions; moreover, the examination of biomarkers and clinical variables' associations is more elaborate for multiple markers and indicators simultaneously.

They include insufficient molecular data besides immunohistochemistry. Chinese IHC result is reliable and supplies colorized advice on protein expression of tumor; however, this technique does not embrace a range of genetic and epigenetic conversions that might affect the behavior of tumor. Subsequent studies should include both genomic and Transcriptomic study to explain the depth of PTEN,ER,PR expressions in breast carcinoma.

Future research should extend the present results in a bigger group of patients in more centers to verify their applicability. Intensive investigations for prospective studies are required to define the verification of PTEN, ER, and PR expressions as the independent predictors of prognosis and to establish more accurate risk models that utilized these markers. Moreover, efforts should be made in understanding how such patterns of expression is regulated at the molecular level, for example, the contribution of genetic changes, epigenetic factors and receptor crosstalk.

Further research related to the possibilities of PTEN, ER, and PR expressions for possible therapeutic applications must also be conducted. For instance, the investigation of

treatments capable of rebalancing PTEN function or regulating the PI3K/AKT pathway may offer some therapeutic options with regard to PTEN-deficient tumors. Likewise, examining the effectiveness of newly developed hormone therapies or the new combination treatment for ER/PR-negative tumors has the potential of offering better results for the patients subgroup.

Conclusion

Therefore, PTEN, ER, and PR immune expressions can be a major prognosticator for breast carcinoma. Consequently, the results signify the significance of these biomarkers in assessing patients' prognosis and selecting an appropriate course of action. Thus, making new contributions to the knowledge of the molecular and clinical characteristics of breast cancer, this investigation contributes to the continuous improvements of the patient care and prognosis for breast carcinoma. The future work should follow up the results obtained within the present study to better refine the prognosis models and continue with developing the therapies tailored to the breast cancer patients' needs.

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