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Original Research

Role Of PDL1 And AR In Cases Of Malignant Tumor Of Breast With Clinico-Histopathological Correlation

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ABSTRACT

INTRODUCTION: Breast cancer (BC) is the most common cancer among women worldwide, with 1.7 million new cases annually and a high mortality rate, particularly in India. Risk factors include age, hormonal factors, obesity, and family history is a heterogeneous disease with four subtypes based on estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. Advances in molecular biology have improved treatment, but additional biomarkers are needed for better prognosis. Androgen receptor (AR) and programmed death-ligand 1 (PD-L1) are emerging markers, with PD-L1 aiding immune evasion in tumors and correlating with high-grade BC, especially in Triple Negative Breast Cancer (TNBC) cases.

AIM AND OBJECTIVES: This study aimed to evaluate AR and PD-L1 expression in malignant breast tumors and correlate these markers with clinical and histopathological findings, focusing on NMBR grading and WHO classification.

MATERIAL AND METHOD: This was a hospital-based, prospective cross-sectional study conducted over two years (February 2023 - August 2024) at Subharti Medical College, Swami Vivekanand SubhartiUniversity,Meerut, with a sample of 60 cases. Immunohistochemistry (IHC) was used to assess AR and PD-L1 expression, and findings were correlated with clinicopathological features.

RESULTS: The study found an average patient age of 51 years, predominantly female cases (98.33%). Right-sided tumors were slightly more common (56.67%), with invasive ductal carcinoma being the most prevalent subtype (75%). Of 23 cases analyzed for molecular subtype, 43.48% were Luminal A, 4.35% Luminal B, 13.04% HER2 enriched, and 39.13% TNBC. PDL1 positivity was higher in TNBC (66.67%), and AR positivity was higher in Luminal A (80%).

PD-L1 expression was positive in 30% and AR in 41.67% of cases, with both markers correlating with higher tumor grades, particularly in invasive ductal carcinoma.

DISCUSSION AND CONCLUSION: The study concluded that PD-L1 and AR expression in breast cancers is associated with higher tumor grades and is most common in invasive ductal carcinoma. These markers show potential astargeted treatment.

INTRODUCTION

Breast cancer (BC) is the most common cancer among women globally, with 1.7 million new cases annually, and accounts for a significant mortality rate. It is particularly prevalent in India, which has one of the highest global rates of BC fatalities.[1] BC risk factors include age, early menarche, delayed menopause, nulliparity, short lactation, obesity, hormone replacement therapy, birth control pill use, and family history.[2] Passive smoking and hormone therapy with estrogen and progesterone also elevate BC risk.[1]

BC is a heterogeneous disease with four subtypes—HER2-enriched, basal-like, luminal A, and luminal B—identified by gene expression profiling based on three receptors: estrogen receptor α (ER α), progesterone receptor (PR), and HER2.3 Luminal A and B subtypes are hormone-receptor-positive, while HER2-enriched is hormone-receptor-negative.[3]

Advancements in BC molecular biology have led to targeted therapies, but new biomarkers are needed to improve prognosis and survival rates. Histologically, BC varies widely, from slow-growing tumors with good outcomes to aggressive types.[4] However, traditional markers like CEA, CA15.3, and CA27.29 have limited sensitivity and specificity for BC detection.[4]

The androgen receptor (AR) is a new biomarker with structural similarities to ER and PR, expressed in

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many BCs and influencing cell motility and metastasis.[3]AR expression has been studied in various BC subtypes, showing potential as a prognostic marker.[5] Another key marker, PD-L1, aids immune evasion in tumors and correlates with high-grade BC, particularly in Triple Negative Breast Cancer (TNBC) cases.[6]

This study aims to explore the clinico-histopathological association between AR and PD-L1 in malignant BC, with implications for immunotherapy and targeted treatment.

METHODOLOGY

Hospital-based, prospective cross-sectional study was done for a duration of2 years (February 2023 - August 2024) in the Department of Pathology, Subharti Medical College, and affiliated Chhatrapati Shivaji Hospital, Meerut, Uttar Pradesh on a sample size of 60.

Paraffin-embedded tissue sections from diagnosed cases of malignant breast tumors were included in the study.

Exclusion Criteria was inadequate biopsy area, autolysed tissue and history of presurgical neoadjuvant therapy.

Tumor sections were graded and subtyped, with immunohistochemistry (IHC) performed for AR and PD-L1 using antibodies. Clinical and pathological factors (age, tumor size, type, hormone receptor status, clinical stage, grade, and lymph node status) were correlated with AR and PD-L1 expression. PD-L1 expression was scored using Combined Positive Score (CPS):

CPS <10: No PD-L1 expression

CPS ≥10: PD-L1 expression

Sections were examined at 4x, 10x, and 40x magnifications. Images captured with Moticam Lite digital.

Breast cancer grade and type wasdetermined by WHO Classification of Breast Tumors (2019; 5th ed.) and Nottingham Modified Bloom Richardson (NMBR) grading.

Categorical variables presented as numbers/percentages; quantitative data as mean ± SD or median (IQR). Qualitative associations analyzed with Chi-Square or Fisher's exact test (if expected value <5). Data entered in Microsoft Excel; analyzed using SPSS software, ver 25.0. Significance threshold set at $p < 0.05$.

RESULTS

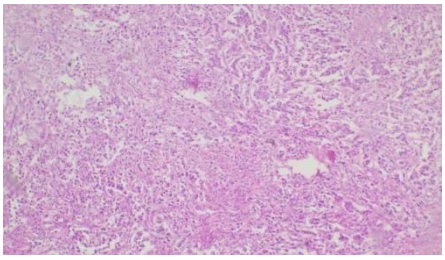
In our study, the average age of participants was 51.43 years, with 82% being postmenopausal. Patients aged 41–50 years made up the largest group (40%).

Females comprised 98.33% of cases, with only one male case (1.67%).

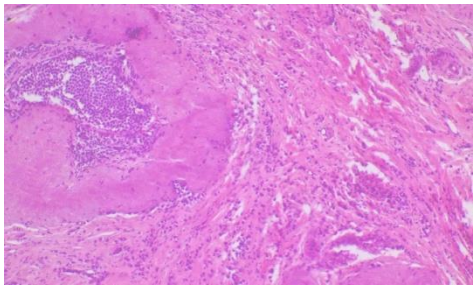
Right-sided tumors were most common (56.67%), followed by left-sided (38.33%), and one case of bilateral involvement. Laterality details were unavailable for two cases.

Core biopsies were the most frequent (40%), followed by modified radical mastectomy (MRM) specimens (20%).

Invasive ductal carcinoma (NST) was the most prevalent subtype (75%). Other types included lobular carcinoma (5%), mixed carcinoma (1.67%), DCIS (3.33%), and phyllodes tumors (6.67%).



Histopathology Section of Breast Tissue Showing Invasive Carcinoma NST(Ductal)((H&E,100X); NMBR Grade 2[H/18/24]



Histopathology Section of Breast Tissue Showing Invasive Lobular Carcinoma (ILC)(H&E,100X) [H/2674/22]

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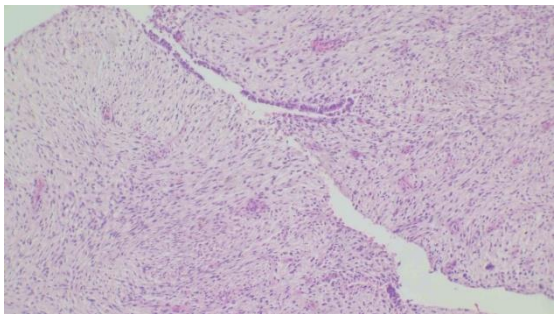


Histopathology section of Breast Tissue showing Borderline Phyllodes Tumor(H&E,100X) [H/2681/22]

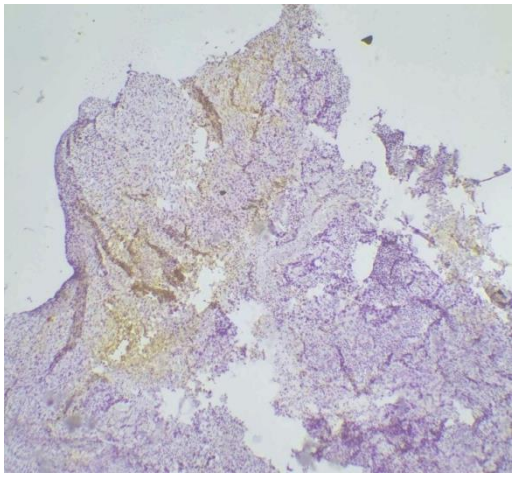
Most participants presented with painful breast lumps. Histopathology confirmed malignancy in cases initially suspected as breast cancer or lumps.

Of the 54 cases graded, 33.33% were grade 1, 50% were grade 2, and 16.67% were grade 3. Six cases were ungraded due to tissue insufficiency or irrelevant grading (e.g., phyllodes tumors).

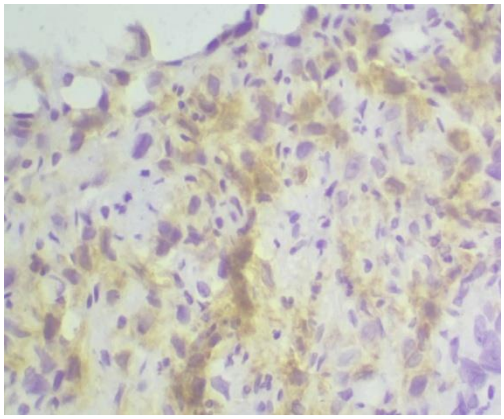
Of 23 cases analyzed for molecular subtype, 43.48% were Luminal A, 4.35% Luminal B, 13.04% HER2 enriched, and 39.13% TNBC. PDL1 positivity was higher in TNBC (66.67%), and AR positivity was higher in Luminal A (80%).

Overall, 30% of cases showed positive PDL1 expression, while 41.67% were positive for AR.

PDL1 expression was seen in 40% of ductal carcinoma cases but absent in other subtypes. AR expression was highest in ductal carcinoma (48.89%) and associated with higher histological grades (grades 2 and 3).



Immunohistochemical expression of PDL1 Receptors(IHC,40X)



Immunohistochemical expression of PDL1 Receptors(IHC,100X)

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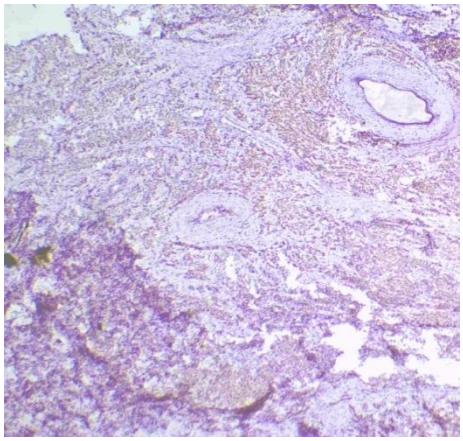
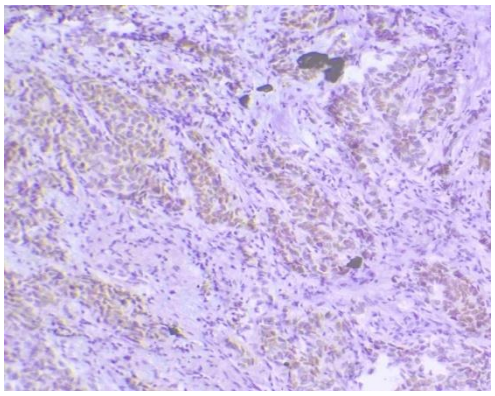


Immunohistochemical expression of Androgen Receptors(IHC,40X)



Immunohistochemical expression of Androgen Receptors(IHC,100X)

In conclusion, PDL1 and AR expression were more frequent in invasive ductal carcinoma and correlated with higher NMBR grades, suggesting potential prognostic and therapeutic relevance in breast cancer.

Table1: -Association of PDL1 with molecular subtype.

PDL1	Her 2 neu enriched(n=3)	Luminal A(n=10)	Luminal B(n=1)	TNBC(n=9)	Total	P value
Negative	2 (66.67%)	8 (80%)	1 (100%)	3 (33.33%)	14 (60.87%)	0.138*
Positive	1 (33.33%)	2 (20%)	0 (0%)	6 (66.67%)	9 (39.13%)	
Total	3 (100%)	10 (100%)	1 (100%)	9 (100%)	23 (100%)	

* **Fisher's exact test**

Table 2: -Association of PDL1 with histopathological subtype.

PDL1	Ductal carcinoma-NST(n=45)	Lobular carcinoma (n=3)	Mixed (Ductal+ Lobular) (n=1)	Others types(n=5)	DCIS (n=2)	Phyllodes tumor (n=4)	Total	P value
Negative	**27 (60%)**	**3 (100%)**	**1 (100%)**	**5 (100%)**	**2 (100%)**	**4 (100%)**	**42 (70%)**	**0.149***
Positive	**18 (40%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**	**18 (30%)**	
Total	**45 (100%)**	**3 (100%)**	**1 (100%)**	**5 (100%)**	**2 (100%)**	**4 (100%)**	**60 (100%)**	

* **Fisher's exact test**

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AR expression was 41.67% in our study. This rate falls within the range reported in studies by Park et al., Ricciardelli et al., and others, which documented AR expression in ER-positive cancers and its prognostic significance. [16,17]

Table 3: -Association of AR with molecular subtype.

AR	Her 2 neu enriched(n=3)	Luminal A(n=10)	Luminal B(n=1)	TNBC(n=9)	Total	P value
Negative	**3 (100%)**	**2 (20%)**	**1 (100%)**	**5 (55.56%)**	**11 (47.83%)**	**0.036***
Positive	**0 (0%)**	**8 (80%)**	**0 (0%)**	**4 (44.44%)**	**12 (52.17%)**	
Total	**3 (100%)**	**10 (100%)**	**1 (100%)**	**9 (100%)**	**23 (100%)**	

*** Fisher's exact test**

Table 4: -Association of AR with histopathological subtype.

AR	Ductal carcinoma-NST(n=45)	Lobular carcinoma (n=3)	Mixed (Ductal+ Lobular) (n=1)	Others types (n=5)	DCIS (n=2)	Phyllodes tumor (n=4)	Total	P value
Negative	23 (51.11%)	1 (33.33%)	0 (0%)	5 (100%)	2 (100%)	4 (100%)	35 (58.33%)	0.022*
Positive	22 (48.89%)	2 (66.67%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	25 (41.67%)	
Total	45 (100%)	3 (100%)	1 (100%)	5 (100%)	2 (100%)	4 (100%)	60 (100%)	

DISCUSSION

Breast cancer (BC) is the most common malignant neoplasm in women and a leading cause of cancer mortality.[7] Biomarkers like estrogen/progesterone receptors and HER2 are widely used in BC management. [7]

The mean age in various studies ranged from 48.21 to 56.39 years, with our study showing a mean age of 51 years. This is in line with studies by Khadilkar et al., Zangouri et al., Wijesinghe et al., and Sofi et al., which documented similar age patterns. [1,8,9,10]

BC predominantly affects women due to hormone sensitivity. This finding aligns with studies by Łukasiewicz et al. (2021) and Sofi et al. (2012), who reported a female predominance. [11,10]

Core biopsy (24/60) was the most common specimen in our study, similar to the pattern observed by Sofi et al., who mostly studied modified radical mastectomies.[10]

Our study found a predominance of right-sided BC, differing from Sofi et al. and Al Saad et al., where the left side was more commonly affected. [12,10]

Invasive ductal carcinoma (IDC) was the predominant subtype in our study, consistent with findings by Sofi et al., Punhani et al., and Łukasiewicz et al. [10,6,11]

Grade 2 was the predominant grade in our study, which aligns with previous studies by Sofi et al. and Punhani et al., where grade 2 was most common. [10,6]

PD-L1 was expressed in 30% of cases in our study, close to other findings, with PD-L1 expression ranging from 10.4% to 74% in different studies, including those by Zhou et al., Noske et al., and Constantinou et al. [13,14,15]

*** Fisher's exact test**

Our study found that PD-L1 and AR receptor expression in breast cancers tends to increase with tumor grade, predominantly in invasive ductal carcinoma. Further patient monitoring is essential to optimize targeted treatment effectiveness using these markers, as many studies have shown a positive correlation between AR expression and favorable clinicopathological characteristics.

CONCLUSION

This study observed that both PD-L1 and AR expression levels increased with higher tumor grades and were primarily associated with invasive ductal carcinoma. These findings align with other research, which has noted a positive association between AR expression and favorableclinicopathological characteristics. However, continued patient monitoring and follow-up are essential to optimize the impact of treatments targeting these markers. In particular, this study found that high-grade invasive ductal carcinomas showed higher PD-L1 expression (39.13%) and AR expression (47.83%), both of which increased with rising NMBR grading.

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