

IMMUNOHISTOCHEMICAL EXPRESSION OF ANDROGEN RECEPTOR IN TRIPLE-NEGATIVE BREAST CARCINOMA

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ABSTRACT

Objective: To evaluate Androgen Receptor (AR) expression in triple-negative breast cancers and correlate it with tumor grade and stage.

Methods: This cross-sectional study was conducted at the Department of Histopathology, Rehman Medical Institute, Peshawar, from June 2022 to June 2023. A total of 44 biopsy specimens from patients diagnosed with triple-negative breast cancer underwent immunohistochemical analysis for androgen receptor (AR) expression, and clinicopathological correlations were assessed.

Results: All participants were female. The mean age of the participants was 49.75 ± 11.74 years. Grade and Tumor Size had a moderate positive correlation ($r = 0.492$, $p < 0.01$). Grade and Laterality had a weak negative correlation ($r = -0.166$). A weak negative correlation was observed between tumor grade and AR expression ($r = -0.223$). Tumor Size and Laterality exhibited a correlation coefficient close to zero (0.028). Tumor Size and AR expression showed a moderate negative correlation (-0.475 ; $p < 0.01$).

Conclusion: Our study shows a weak association between AR expression and the aforementioned factors. Further studies with larger samples are required to evaluate the impact of AR status on patient outcomes and the use of targeted AR-based hormonal therapies in TNBC patients.

Keywords: Expression, Immunohistochemistry, Androgen receptors, Triple-negative breast cancers

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INTRODUCTION

Breast carcinoma is amongst the most common cancers, affecting 25% of women during their lifetime.¹ Data show that 2.3 million women were diagnosed with breast carcinoma in the year 2020, with a mortality of 685,000. Among Asian countries, the highest incidence of breast cancer is in Pakistan, with the risk of every ninth woman being diagnosed with breast cancer. In 2018, a report published by the International Agency for Research on Cancer Revealed that the incidence of breast cancer was 34,066 in Pakistani women.² According to the St. Gallen Consensus 2011, Breast cancer is categorized into 3 major molecular subtypes based on the status of molecular markers. Luminal subtype accounts for the majority of the cases (70%) and is defined as tumors expressing hormone receptors i.e estrogen (ER) and progesterone receptors (PR); HER2-overexpressions of human epidermal

growth factor receptor 2 (ER-/PR-/HER2+), accounting for 15-20% cases and, with 15 % cancers lacking all the three molecular markers are categorized as triple-negative breast cancers /TNBCs (ER-/PR-/HER2-).³ Ki 67, a marker of tumor proliferation and aggressiveness, is used to subclassify luminal type into luminal A (ER+/PR+/HER2-/lowKi-67) and Luminal B (ER+/PR+/HER2-/high Ki-67). Targeted therapies are available for those cancers that express ER, PR, or HER2-neu, which are directed against these receptors; however, traditional chemotherapeutic agents are used to treat TNBC, leading to relapse, an aggressive nature, poor therapeutic response, and high invasiveness. Differentiating TNBC subtypes is important for developing targeted therapies for this group of tumors.⁴

Many researchers further subclassify TNBC. Cluster analysis classified TNBC into six subtypes, which include 2 basal-like (BL1 and BL2), luminal androgen receptor (LAR), mesenchymal (M), mesenchymal (M), immunomodulatory (IM), and mesenchymal stem-like subtype. AR expression in TNBC varies widely, with the literature reporting values from 6.6% to 75%. Quadruple-negative breast cancer (QNBC) is a subtype of TNBC that is AR-negative; it currently lacks a definite targetable pathway and predominantly shows a basal-like molecular subtype. AR expression in TNBC has important prognostic and predictive significance. It plays a role in tumorigenesis

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and may inform future targeted therapies against AR and its downstream signaling pathways. Our study aimed to measure AR expression in triple-negative breast cancers. We also correlated tumor grade and stage with AR expression.

MATERIALS AND METHODS

After approval by the hospital ethical review committee, we conducted a cross-sectional analytical study in the Department of Histopathology at Rehman Medical Institute, Peshawar, from June 2022 to June 2023. A total of 44 cases were included, selected using a nonprobability convenience sampling technique. All female patients diagnosed with triple-negative breast carcinoma (TNBC) during the study period were eligible for inclusion. Patients with a history of neoadjuvant therapy, chemotherapy, radiotherapy, or hormonal therapy were excluded. Mastectomy specimens from patients with a prior histological diagnosis of TNBC were received in the histopathology laboratory. Demographic variables were recorded, and specimens were grossly examined per the College of American Pathologists (CAP) protocol. Standard tissue processing and hematoxylin and eosin (H&E) staining were performed. Diagnosis was confirmed, and tumor grade and stage were determined. Immunohistochemical staining for androgen receptor (AR) was performed on 0.4 cm tissue blocks using a monoclonal antibody (clone F39.4.1, Biogenex) at a 1:100 dilution, with incubation at room temperature for 45 minutes. The proportion of tumor cell nuclei showing staining was recorded, and AR expression was classified as positive or negative. Tumors with $\geq 1\%$ nuclear staining were considered positive. Two histopathologists independently reviewed all cases, and the results were recorded. Data were analyzed using SPSS version 23. Descriptive statistics were computed, with means and standard deviations for continuous variables and frequencies and percentages for categorical variables. We assessed associations between AR expression and clinicopathological parameters using chi-square tests for categorical data. Tumor size, treated as a continuous variable, was evaluated in relation to AR status using Spearman's rank correlation coefficient. A p -value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 44 female patients with triple-negative breast carcinoma (TNBC) were included in this study. The mean age at diagnosis was 49.7 years (SD 11.7; range 31–77 years). The mean tumor size was 5.9 cm (SD 3.19; range 0.8–15.5 cm), indicating considerable variation in disease burden at presentation. Histologically, most tumors were high grade, with 29 (66%) classified as Grade 3, 12 (27%) as Grade 2, and 2 (5%) as Grade 1. Immunohistochemical analysis revealed that 26 tumors (60%) were androgen receptor (AR) positive, while 14 (33%) were AR negative. Tumor laterality was nearly balanced, with 18 (41%) tumors arising in the left breast and 25 (57%) in the right (Table 1). To assess associations between AR expression and clinicopathological parameters, we con-

ducted several statistical tests (Table 2). No significant association was observed between AR status and tumor laterality (χ^2 , $p = 0.613$) or tumor grade (Spearman's $\rho = 0.06$, $p = 0.714$). In contrast, tumor size showed a moderate positive correlation with AR expression (Spearman's $\rho = 0.45$, $p = 0.003$), indicating that AR-positive tumors tended to be larger. Further analysis of tumor staging revealed a significant association between higher T-stage and AR positivity (χ^2 , $p = 0.022$). AR expression was more frequent in tumors staged as pT3–pT4, whereas AR-negative cases were more commonly associated with lower T-stages (pT1–pT2). Overall, these findings suggest that AR expression is not related to tumor grade or laterality, but is significantly associated with larger tumor size and higher T-stage, raising the possibility of its role as a marker of tumor progression in TNBC.

DISCUSSION

In this study, we evaluated immunohistochemical androgen receptor (AR) expression in a cohort of patients with triple-negative breast carcinoma (TNBC) and examined its association with clinicopathological parameters. AR positivity was observed in nearly half of cases (49%), consistent with previously reported prevalence rates of 20–55% in TNBC across different populations.^{6–8} This finding highlights the biological heterogeneity within TNBC and suggests that AR may define a distinct molecular subset with potential clinical relevance. Our findings demonstrated a statistically significant positive correlation between AR expression and tumor size, as well as a significant association with higher T-stage. Specifically, AR positivity was more common in tumors staged as pT3 and pT4, whereas AR-negative tumors were more frequently associated with lower T-stages. These results suggest

Table No 1: Descriptive characteristics of the study cohort

Variable	Value
Age (years), mean (SD)	49.7 (11.7)
Tumor size (cm), mean (SD)	5.9 (3.19)
Grade 1	2 (5%)
Grade 2	12 (27%)
Grade 3	29 (66%)
AR positive	26 (60%)
AR negative	14 (33%)
Left-sided tumors	18 (41%)
Right-sided tumors	25 (57%)

Table No 2. Associations between AR expression and clinicopathological parameters

Comparison	Test used	Statistic / coefficient	p-value
Laterality vs. AR	Chi-square	χ^2	0.613
Grade vs. AR	Spearman's ρ	$\rho = 0.06$	0.714
Tumor size vs. AR	Spearman's ρ	$\rho = 0.45$	0.003
T-stage vs. AR	Chi-square	χ^2	0.022

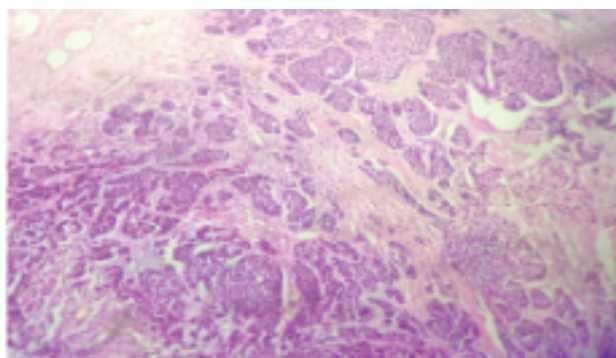


Fig-1: Invasive ductal carcinoma of no special type showing high grade features

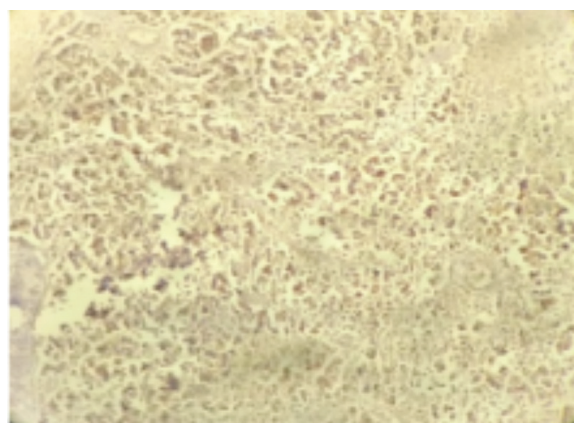


Fig-2: Nuclear expression of AR in invasive ductal carcinoma of no special type

that AR expression may be linked to more advanced local disease at presentation. Previous studies have reported conflicting evidence regarding the prognostic role of AR in TNBC, with some associating AR positivity with better outcomes, and others with more aggressive behavior.⁹⁻¹² Our results support the notion that AR may be associated with disease progression in certain patient subsets. The observed relationship with tumor size and T-stage raises the possibility that AR-driven signaling could contribute to tumor growth or confer selective advantages in advanced disease. Interestingly, AR expression in our cohort did not show any significant association with tumor grade. This is consistent with some reports that have found no relationship between AR status and histological differentiation, although other studies have described lower-grade tumors as more likely to express AR.^{13,14} Similarly, no association was identified between tumor laterality and AR expression, supporting the idea that AR positivity is not influenced by breast side and is more likely to be determined by underlying tumor biology. These findings have potential clinical implications. TNBC lacks targeted therapeutic options, and standard treatment relies largely on cytotoxic chemotherapy.¹⁵ The identification of AR as a biomarker of disease progression suggests that AR-directed therapies, such as anti-androgens, may benefit this subgroup. Several clinical trials have evaluated AR antagonists (e.g., bicalutamide, enzalutamide) in AR-positive TNBC, showing encouraging activity in selected patients.^{16,17} If validated in

larger cohorts, the association between AR positivity and higher tumor stage observed in our study could further support integrating AR-targeted approaches into TNBC management, particularly for patients presenting with bulky or advanced tumors. The present study has some limitations. The sample size was relatively small, which may limit the generalizability of the findings. Furthermore, we did not evaluate survival outcomes, which would be necessary to establish the true prognostic impact of AR expression. Additional research in larger, multicenter cohorts, ideally incorporating molecular profiling and survival analyses, will be essential to clarify AR's role as a prognostic and predictive biomarker in TNBC.¹⁸

CONCLUSION

In conclusion, our results demonstrate that AR expression in TNBC is significantly associated with larger tumor size and higher T-stage but not with tumor grade or laterality. These findings support the hypothesis that AR may serve as a marker of tumor progression in TNBC and highlight the need for further investigation into its prognostic significance and therapeutic potential. Acknowledgments: We are grateful to our consultants for their continuous support. We are also thankful to our technical staff for their help with all technical work in this study.

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Authors Contribution:

Following authors have made substantial contributions to the manuscript as under

Authors	Conceived & designed the analysis	Collected the data	Contributed data or analysis tools	Performed the analysis	Wrote the paper	Other contribution
Sajjad A	✓	✓	✗	✗	✓	✗
Javed F	✓	✗	✓	✓	✓	✗
Basharat S	✓	✓	✗	✗	✗	✓
Khan M	✓	✗	✓	✓	✓	✗
Nisar Z	✓	✗	✓	✓	✓	✗
Khattak MT	✓	✓	✗	✗	✗	✓
Khan IM	✓	✗	✓	✓	✓	✗

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical Approval:

This Manuscript was approved by the Ethical Review Board of Rehman Medical Institute, Peshawar. Vide No. RMI/RMI-REC/Article Approval/32. Dated: 12 05 2022



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