Section: Pathology

Original Research Article

ANDROGEN RECEPTOR (AR) EXPRESSION IN TRIPLE NEGATIVE BREAST CANCER: AN INSTITUTIONAL EXPERIENCE

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Received *: 12/03/2026*
Received in revised form *: 20/04/2026*
Accepted *: 04/05/2026*

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DOI: 10.70034/ijmedph.2026.2.653

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (2); 3973-3978

ABSTRACT

Background: Triple-negative breast carcinoma (TNBC) is known for its aggressive nature and poor prognosis. Androgen receptor (AR) expression has been identified in a subset of TNBC and may define a biologically distinct subgroup with potential therapeutic relevance. **Aim:** This study aimed to evaluate the immunohistochemical expression of AR in triple-negative breast carcinoma and its association with clinicopathological parameters.

Materials and Methods: A retrospective analysis of 77 cases of TNBC was performed. An immunohistochemical assessment of AR expression was carried out, with tumours showing at least 1% nuclear expression being considered as AR-positive. Statistical analysis was performed to assess the association of AR expression with various clinicopathological parameters like age, tumour grade, staging of tumour and lymphovascular invasion, and Ki-67 proliferation index.

Results: AR expression in TNBC showed a significant association with lower histological grade (Grade I–II vs. Grade III; $p = 0.024$), lymphovascular invasion ($p = 0.0016$), and older patient age ($p = 0.038$). AR expression in TNBC did not show statistically significant associations between AR expression and tumour stage ($p = 0.31$) or the Ki-67 proliferative index ($p = 0.201$).

Conclusions: AR expression was observed in nearly 25% of cases of triple-negative breast cancer (TNBC). There was a statistically significant correlation with a lower histological grade and lymphovascular invasion; however, no statistically significant association was found with tumour staging and the Ki-67 proliferation index. These findings support the existence of an AR-positive subset of TNBC and may have therapeutic implications.

Keywords: Triple-negative breast carcinoma; androgen receptor; immunohistochemistry; lymphovascular invasion; tumour grade; and Ki-67 index.

INTRODUCTION

Triple-negative breast carcinoma (TNBC), is defined by the absence of estrogen receptor, progesterone receptor, and HER2/neu expression, accounts for approximately 15–20% of breast cancers and is associated with aggressive clinical behaviour and limited therapeutic options.[1]

Despite being classified as a single entity, TNBC is biologically heterogeneous and comprises multiple molecular subtypes with distinct prognostic and therapeutic implications.[2] As reported by Lehmann et al., TNBC can be further classified into four molecular subtypes [basal-like1, basal-like2, mesenchymal, and luminal androgen receptor (LAR)]. Each type is characterized by distinct clinicopathologic features and driver signalling pharmacologically actionable pathways. In another study, Jézéquel et al. demonstrated three molecular subtypes (basal with low immune response, basal with high immune response, and LAR).[3] Subsequently, other groups have confirmed LAR as a distinct subtype of TNBC characterized by high AR expression and enrichment of hormonally regulated pathways that are important in steroid synthesis,

porphyrin metabolism, and androgen/estrogen metabolism despite the absence of ER.[4,5]

AR is a nuclear hormone receptor involved in cellular proliferation and differentiation and has been reported in 10–35% of TNBC cases.[6] Several studies have demonstrated the associations between AR expression and clinicopathological features such as older age and lower histological grade.[7] However, its prognostic significance remains controversial, with variable results reported across studies.[8] Emerging evidence suggests that AR may represent a potential therapeutic target in TNBC, with anti-androgen therapies showing clinical benefit in selected patients.[9]

The present study was undertaken to evaluate AR expression in TNBC and to analyse its association with clinicopathological parameters including age, tumour grade, lymphovascular invasion, tumour stage, and Ki-67 index.

Aims and Objectives

1. To evaluate the androgen receptor (AR) expression in triple-negative breast cancer (TNBC).
2. To analyse AR-positive TNBC and its association with various clinicopathological parameters such as age, tumour grade, tumour staging, and lymphovascular invasion status.

MATERIALS AND METHODS

Study Design: Retrospective study

Study Center: Department of Pathology

Study Sample: Paraffin-embedded tissue blocks of cases diagnosed as triple-negative breast cancer during the years September 2024 to August 2025 in the Department of Pathology were archived.

Study Duration: September 2024 to August 2025

Inclusion Criteria

1. Histologically verified cases of breast carcinoma.
2. Breast carcinoma cases lacking estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth receptor 2 (HER2/neu) expression, as validated by IHC.

Exclusion Criteria

1. Patients having incomplete IHC or clinical data.
2. Inadequate tissue samples

Study Procedure

This study was initiated after getting approval from the institutional ethics committee. The demographic details of the patients, laterality and site of tumour, and procedure performed were recorded. Paraffin-embedded tissue blocks with tumours were evaluated for ER, PR, and HER2/neu. The triple-negative breast cancer was studied further for immunohistochemical marker - AR. All H&E slides and IHC slides were independently evaluated by two pathologists blinded to clinicopathological data.

Evaluation of AR staining

Immunohistochemical staining of AR was evaluated in tumour cells for nuclear staining, which was examined under high-power magnification (×400) fields. AR staining was interpreted manually, and samples with at least 1% nuclear staining were considered to be positive, as in ER and PR scoring according to ASCO/CAP guidelines [10].

Cases were classified into two categories:

Positive ≥1%

Negative <1%

Evaluation of the Ki-67 Index

The Ki-67 labelling index was assessed by calculating the percentage of nuclei with positive staining in the tumour cells. The Ki-67 index was assessed in the hotspot area (the proliferative area of the tumour) at ×400 magnification, and at least 500 cells were counted for each case. A Ki-67 proliferative index of ≥15% was taken as high and <15% was taken as low [11].

Statistical Analysis

Statistical analysis was performed using appropriate statistical software. Categorical variables were analysed using the chi-square test or Fisher's exact test. Age was analysed as a continuous variable using an independent samples t-test. A p value < 0.05 was considered statistically significant.

RESULTS

Patient and Tumour Characteristics

A total of 77 cases of triple-negative breast carcinoma (TNBC) were included in this study. Androgen receptor (AR) expression was observed in 18 cases (23.4%) as shown in Figure 1, while 59 cases (76.6%) were AR-negative as shown in Figure 2, which was summarized in Table 1.

Table 1: Androgen receptor expression in triple-negative breast carcinoma (n = 77)

AR Expression	Number of Cases	Percentage (%)
AR Positive	18	23.4
AR Negative	59	76.6
Total	**77**	**100**

Association Between Patient Age and Androgen Receptor Expression

The mean age of patients with AR-positive tumours was 58.7 ± 10.9 years, which was significantly higher than that of patients with AR-negative tumours (52.4 ± 9.6 years), as shown in Table 2. Independent samples t-test confirmed a statistically significant difference between the two groups ($p = 0.038$). These findings indicate that AR-positive TNBC occurred more frequently in older patients.

Table 2: Association between androgen receptor expression and patient age

AR Expression	Mean Age (Years) ± SD	P Value
AR Positive (n = 18)	58.7 ± 10.9	0.038*
AR Negative (n = 59)	52.4 ± 9.6	

***Independent samples t-test (statistically significant).**

Association Between AR Expression and Histological Grade

The distribution of AR expression across histological grades is shown in Table 3. AR positivity was identified in 2 of 7 Grade I tumours (28.6%), 13 of 38 Grade II tumours (34.2%), and 3 of 32 Grade III tumours (9.4%). For statistical analysis, tumours were grouped into Grade I–II (low and intermediate grade) and Grade III (high grade) categories. AR expression was significantly higher in Grade I–II tumours compared to Grade III tumours (33.3% vs. 9.4%). Chi-square analysis showed a statistically significant association between AR expression and histological grade ($\chi^2 = 5.12$, $p = 0.024$). AR positivity was 4.83 times more likely in low- and intermediate-grade tumours compared to high-grade tumours (OR = 4.83; 95% CI: 1.28–18.21).

Table 3: Association between androgen receptor expression and histological grade

Histological Grade	AR Positive	AR Negative	Total	P Value
Grade I	2	5	7	0.024*
Grade II	13	25	38	
Grade III	3	29	32	
Grade Group	**AR Positive**	**AR Negative**	**Total**	**P Value**
Grade I–II	15	30	45	0.024*
Grade III	3	29	32	

Chi-square test. Odds ratio: 4.83 (95% CI: 1.28–18.21).

Association Between AR Expression and Lymphovascular Invasion (LVI)

Lymphovascular invasion was identified in 31 cases (40.3%) and was absent in 46 cases (59.7%). Among LVI-positive tumours, AR expression was observed in 13 cases (41.9%), compared with only 5 cases (10.9%) among LVI-negative tumours, as shown in Table 4. A statistically significant association was identified between AR expression and lymphovascular invasion ($\chi^2 = 9.93$, $p = 0.0016$). AR-positive tumours were 5.9 times more likely to exhibit lymphovascular invasion compared with AR-negative tumours (OR = 5.9; 95% CI: 1.82–18.9).

Table 4: Association between androgen receptor expression and lymphovascular invasion

Lymphovascular Invasion	AR Positive	AR Negative	Total	P Value
Present	13	18	31	0.0016**
Absent	5	41	46	

Chi-square test (statistically highly significant). Odds ratio: 5.9 (95% CI: 1.82–18.9).

Association Between AR Expression and Tumour Stage

Tumour staging revealed 1 case in Stage I, 41 cases in Stage II, 32 cases in Stage III, and 1 case in Stage IV, as shown in Table 5. AR positivity was observed in 1 Stage I case, 11 Stage II cases, and 6 Stage III cases; the single Stage IV case was AR negative. Given the very small numbers in Stage I and Stage IV (n = 1 each), tumours were grouped into early stage (Stage I–II) and advanced stage (Stage III–IV) for statistical analysis. AR expression was observed more frequently in early-stage tumours compared with advanced-stage tumours (28.6% vs. 17.1%); however, this difference did not reach statistical significance ($\chi^2 = 1.01$, $p = 0.31$; OR = 1.93; 95% CI: 0.66–5.63).

Table 5: Association between androgen receptor expression and tumour stage

Tumour Stage	AR Positive	AR Negative	Total	P Value
Stage I	1	0	1	
Stage II	11	30	41	
Stage III	6	26	32	
Stage IV	0	1	1	
Stage Group	**AR Positive**	**AR Negative**	**Total**	**P Value**
Early Stage (I–II)	12	30	42	0.31
Advanced Stage (III–IV)	6	29	35	

Chi-square test — not statistically significant. Odds ratio: 1.93 (95% CI: 0.66–5.63).

Association Between Androgen Receptor Expression and Ki-67 Proliferative Index

Among the 18 AR-positive cases, 4 (22.2%) demonstrated a Ki-67 labelling index of <15%, while 14 (77.8%) showed a Ki-67 index of ≥15%. Among the 59 AR-negative cases, 5 (8.5%) demonstrated a Ki-67 index of <15%, while 54 (91.5%) showed a Ki-67 index of ≥15%, as shown in Table 6. Fisher's exact test demonstrated no statistically significant association between AR expression and Ki-67

proliferative index (p = 0.201). Although AR-positive tumours were approximately three times more likely to demonstrate a low Ki-67 index (<15%) compared with AR-negative tumours (OR = 3.09), this association did not reach statistical significance. Phi coefficient analysis (φ = +0.13) demonstrated a weak positive correlation, suggesting a trend toward lower Ki-67 values in AR-positive tumours; however, this correlation was not statistically significant.

Table 6: Association between androgen receptor expression and Ki-67 proliferative index

AR Status	Ki-67 <15%	Ki-67 ≥15%	Total	Odds Ratio
AR Positive	4	14	18	3.09
AR Negative	5	54	59	
Total	**9**	**68**	**77**	

Fisher's exact test; p = 0.201 (not statistically significant). Odds ratio: 3.09. Phi coefficient (φ): +0.13 (weak positive correlation).

Summary of Findings

In summary, AR expression in TNBC showed significant association with lower histological grade (Grade I–II vs. Grade III; p = 0.024), lymphovascular invasion (p = 0.0016), and older patient age (p = 0.038). AR expression in TNBC did not show statistically significant associations between AR expression and tumour stage (p = 0.31) or Ki-67 proliferative index (p = 0.201), though the latter revealed a trend toward lower proliferative activity in AR-positive tumours that warrants further investigation in larger cohorts.

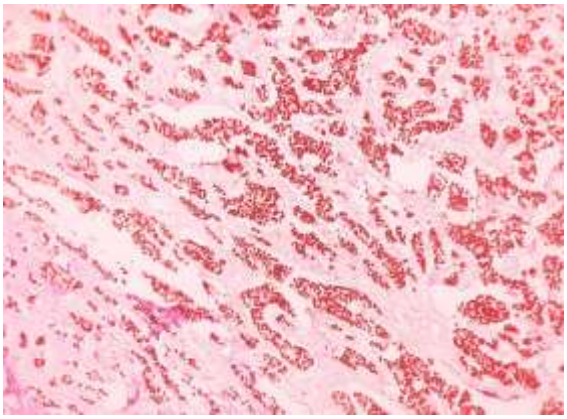

Figure 1: Triple-negative breast carcinoma showing strong nuclear positivity for Androgen Receptor (AR) in tumour cells. Note the brown nuclear staining pattern consistent with AR expression (IHC, ×400)

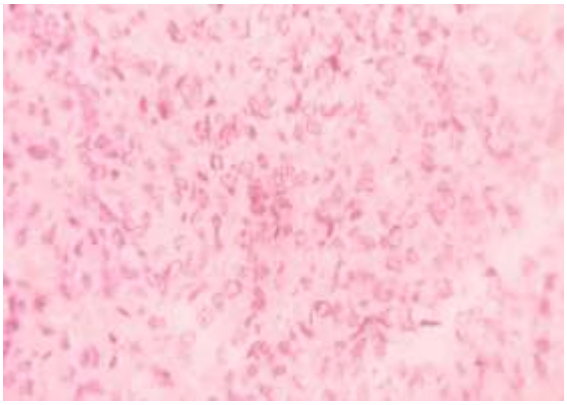

Figure 2: Triple-negative breast carcinoma showing androgen receptor (AR) negativity. No nuclear staining is observed in tumour cells, indicating lack of AR expression (IHC, ×400)

DISCUSSION

Triple-negative breast cancer (TNBC) is one of the therapeutically challenging subtypes of breast carcinoma, owing to the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu). In this context, the androgen receptor (AR) has emerged as a biologically relevant and actionable molecular marker within the TNBC subtypes. The present study evaluated AR expression by immunohistochemistry in 77 cases of TNBC and correlated the findings with key clinicopathological parameters including histological grade, lymphovascular invasion (LVI), tumour stage, patient age, and Ki-67 proliferative index. The results yielded several significant associations that are consistent with, and to some extent extend, the existing literature.

In the present study, AR expression was noted in 23.4% of TNBC cases, which is consistent with previously reported prevalence rates ranging from 15% to 35%.[7,12] The AR expression in TNBC across various studies showed the differences in immunohistochemical protocols, antibody clones, scoring cutoffs, and patient demographics.

A significant observation made from this study was that a higher frequency of AR expression was noted in Grade I–II tumours compared to Grade III tumours, suggesting that AR-positive TNBC represents a biologically distinct and relatively more differentiated subgroup. Similar findings have been reported by Dogra et al., who demonstrated an association between AR expression, lower histological grade, and older patient age.[7] These observations support the existence of a luminal androgen receptor–driven subset within TNBC, with hormone-related signalling pathways despite the absence of estrogen and progesterone receptor expression.[2,8]

Another noteworthy observation in the present study was the association between AR positivity and lymphovascular invasion (LVI). LVI is considered an adverse histopathological feature, and indicating its invasive potential and a higher risk of metastatic spread. The coexistence of AR positivity with LVI highlights the heterogeneous nature of AR biology in TNBC. While AR positivity has been associated with favourable histopathological features like lower histological grade, its concurrent association with

LVI highlights the complex nature of AR signalling. Similar inconsistencies have been reported in the literature, implying that AR signalling may influence tumour behaviour in a context-dependent manner rather than serving as a straightforward prognostic marker.[13]

This study also demonstrated a significant association between AR positivity and older age, which further supports that AR-positive TNBC is more frequently seen in postmenopausal women. A similar age association was reported by Dogra et al., suggesting a potential influence of hormonal milieu on AR expression.[7] Further investigation is essential to elucidate the influence of age-related hormonal changes on AR expression.

In contrast, no statistically significant association was seen between AR expression and tumour stage in the present study. This finding implies that AR status may reflect intrinsic tumour biology rather than the anatomical extent of disease. This finding is consistent with the observations of Hedjem et al., who did not find a significant association between AR expression and tumour stage or survival in early-stage TNBC.[14] However, the lack of association should be interpreted with caution because of the limited sample size and the small number of cases in certain stage categories.

Although AR-positive TNBCs expressed a higher proportion of tumours with a low Ki-67 proliferative index compared to AR-negative cases, this association was not statistically significant. Correlation analysis showed a weak inverse relationship between AR expression and Ki-67 index. These findings suggest a less proliferative phenotype in AR-positive TNBC, but the limited number of AR-positive cases may have reduced the statistical power. Larger studies are required to validate the prognostic relevance of AR-Ki-67 interaction in TNBC.[15]

Overall, the observations of this current study emphasize the fact that AR-positive TNBC represents a heterogeneous subgroup with distinct clinicopathological characteristics. Identification of AR expression in TNBC is clinically relevant in the context of emerging anti-androgen therapies, and further large-scale prospective studies are warranted to clarify the prognostic and predictive significance of AR expression.[9]

Limitations

The limitations of this study include its retrospective design, single-institution setting, lack of survival data, and absence of molecular subclassification.

CONCLUSION

About 25% of TNBC cases have AR expression, suggesting the existence of an AR-positive subgroup. AR positivity was significantly correlated with older age, lymphovascular invasion, and lower histological grade, but not with tumour stage. The inverse relationship observed between AR expression and Ki-67 index suggests biological heterogeneity within TNBC, despite a lack of statistical significance. The paradoxical co-occurrence of lower tumour grade and higher LVI rates in AR-positive tumours signifies the complexity of androgen receptor biology and warrants further investigation. Given the emerging role of AR as a therapeutic target in TNBC, routine immunohistochemical assessment of AR expression in TNBC specimens is recommended, as it may guide patient selection for anti-androgen-based therapies. These results imply that rather than being a reliable indicator of prognosis, AR represents a unique biological subgroup. To elucidate its prognostic and therapeutic importance, larger prospective investigations using molecular profiling and survival analysis are needed.

Ethical Considerations

This study was conducted in accordance with institutional ethical guidelines. Institutional Ethics Committee approval was obtained before the procedure was initiated. As this was a retrospective study that utilized archival records, only non-identifiable patient data were used. Personal identifiers such as name, hospital number, or any information that could reveal patient identity were not included in the study. Therefore, a waiver of informed consent was requested. All collected data were kept confidential and were used solely for academic and research purposes.

Conflict of Interest: None declared.

Financial Support and Sponsorship: Nil.

Author Contributions

All authors contributed to study conception, data collection, analysis, and manuscript preparation.

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