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Androgen Receptor As A Predictive Marker Of Response To Neoadjuvant Chemotherapy In Locally Advanced Breast Carcinoma

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ABSTRACT

Background: Androgen receptor (AR) expression in breast cancer has gained interest as a potential biomarker for predicting treatment response. This study evaluated AR expression as a predictive marker for pathological complete response (pCR) following neoadjuvant chemotherapy in locally advanced breast carcinoma.

Methods: A prospective observational study was conducted on 268 patients with locally advanced breast cancer receiving neoadjuvant chemotherapy. Immunohistochemical analysis was performed to determine AR status. The primary endpoint was pathological complete response (RCB-0) correlation with AR expression. Secondary endpoints included associations between AR status and clinicopathological features.

Results: Among 268 patients, 60.4% (n=162) were AR-positive. The overall pCR rate was 22.0% (n=59). AR-negative patients demonstrated significantly higher pCR rates compared to AR-positive patients (28.3% vs 17.9%, p=0.047). In triple-negative breast cancer subgroup (n=62), AR-negative status was strongly associated with higher pCR (50.0% vs 21.4%, p=0.021). Subgroup analysis of HER2-negative tumours (score 0) showed AR-negative patients achieving 34.5% pCR versus 16.1% in AR-positive patients. Similarly, in HER2-low expressing tumours, AR-negative patients demonstrated 26.7% pCR compared to 4.3% in AR-positive cases. AR-positive patients showed greater estrogen receptor positivity (p<0.001) and lower histological grade (p=0.021).

Conclusion: AR expression status serves as a significant predictive biomarker for neoadjuvant chemotherapy response in HER-2 negative breast cancer, particularly in TNBC subtype. AR-negative patients achieve higher pCR rates across HER2-negative and HER2-low subtypes, suggesting potential utility in treatment stratification and personalized therapeutic approaches.

KEYWORDS: *Study Design and Patient Selection, Inclusion and Exclusion Criteria*.

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1. INTRODUCTION

Health Breast cancer remains the most prevalent malignancy affecting women globally, with significant implications for

public health systems worldwide. According to the latest GLOBOCAN data, breast cancer accounts for approximately 2.3 million new cases annually, representing 11.7% of all cancer diagnoses. The heterogeneous nature of breast cancer necessitates sophisticated molecular classification systems that guide therapeutic decision-making and prognostic assessment. Contemporary breast cancer management relies heavily on receptor expression profiles, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2), which collectively define distinct molecular subtypes with varying biological behaviours and treatment sensitivities.

Neoadjuvant chemotherapy has revolutionized the management paradigm for locally advanced breast cancer, offering multiple therapeutic advantages beyond simple tumour downsizing. This preoperative systemic approach enables in vivo assessment of chemosensitivity, facilitates breast-conserving surgery in previously inoperable cases, and provides crucial prognostic information through pathological response evaluation. The achievement of pathological complete response following neoadjuvant chemotherapy has consistently demonstrated strong correlation with improved long-term outcomes, including enhanced disease-free survival and overall survival rates. Meta-analyses have confirmed that patients achieving pCR experience significantly reduced recurrence risk, with hazard ratios ranging from 0.22 to 0.36 across different molecular subtypes.

The androgen receptor, a member of the nuclear receptor superfamily, has garnered increasing attention as a potential therapeutic target and prognostic biomarker in breast cancer management. AR expression is detected in approximately 70-90% of breast cancers, with varying prevalence across molecular subtypes. The functional role of AR in breast cancer pathogenesis appears complex and context-dependent, influenced by concurrent hormone receptor status and interactions with other signalling pathways. In hormone receptor-positive breast cancers, AR expression generally correlates with favourable clinicopathological features, including lower histological grade, reduced proliferation indices, and improved survival outcomes. Conversely, in triple-negative breast cancer, AR expression patterns demonstrate more heterogeneous associations with treatment response and prognosis.

The molecular mechanisms underlying AR signalling in breast cancer involve intricate crosstalk with estrogen receptor pathways and growth factor signalling cascades. AR activation can exert both proliferative and anti-proliferative effects depending on the cellular context and presence of co-regulatory factors. In ER-positive tumours, AR may antagonize estrogen-mediated proliferation through competition for shared transcriptional co-activators and DNA binding sites. This antagonistic relationship potentially explains the favourable prognostic implications of AR expression in luminal breast cancers. However, in ER-negative contexts, particularly in molecular apocrine tumours, AR can function as the primary driver of tumour growth through activation of alternative transcriptional programs.

Recent investigations have explored the predictive value of AR expression for neoadjuvant chemotherapy response, yielding intriguing but sometimes conflicting results. Several studies have reported inverse correlations between AR expression and pCR rates, particularly in triple-negative breast cancer populations. This observation suggests that AR-positive tumours may exhibit reduced chemosensitivity, potentially due to their more differentiated phenotype and lower proliferation rates. The mechanisms underlying this differential chemotherapy response remain incompletely understood but may involve AR-mediated regulation of cell cycle progression, apoptotic pathways, and DNA repair mechanisms.

The clinical significance of AR expression extends beyond its prognostic implications to encompass potential therapeutic opportunities. AR-targeted therapies, including anti-androgens and selective AR modulators, have shown promising activity in subset of breast cancers, particularly in AR-positive TNBC. Clinical trials evaluating enzalutamide, bicalutamide, and other AR antagonists have demonstrated modest but meaningful response rates in heavily pretreated patients. The identification of biomarkers predicting response to both conventional chemotherapy and AR-targeted agents represents a critical unmet need in precision oncology approaches for breast cancer.

The assessment of AR expression in clinical practice presents several technical and interpretive challenges. Immunohistochemical evaluation remains the standard method for AR detection, though cutoff values for positivity vary considerably across studies, ranging from 1% to 10% nuclear staining. This lack of standardization complicates cross-study comparisons and clinical implementation. Furthermore, the dynamic nature of AR expression during treatment and potential discordance between primary and metastatic sites add additional layers of complexity to biomarker interpretation. Given the evolving understanding of AR biology in breast cancer and its potential clinical applications, comprehensive evaluation of AR as a predictive biomarker for neoadjuvant chemotherapy response is warranted. This becomes particularly relevant in HER-2 negative breast cancers, where treatment options remain limited compared to HER-2 positive disease. The identification of reliable predictive markers could facilitate patient selection for neoadjuvant approaches, guide treatment intensification or de-escalation strategies, and inform the development of novel combination therapies incorporating AR-targeted agents.

The present study was designed to systematically evaluate the predictive value of androgen receptor expression for

pathological complete response following neoadjuvant chemotherapy in HER-2 negative locally advanced breast carcinoma. By analyzing a prospectively collected cohort with comprehensive clinicopathological annotation, we aimed to elucidate the relationship between AR status and treatment outcomes across different molecular subtypes, with particular emphasis on triple-negative breast cancer where therapeutic options remain most limited.

Aims and Objectives

The primary aim of this investigation was to evaluate the predictive value of androgen receptor expression for pathological complete response following neoadjuvant chemotherapy in patients with locally advanced breast carcinoma. The study sought to determine whether AR status could serve as a reliable biomarker for treatment stratification and personalized therapeutic decision-making in this patient population.

The specific objectives encompassed comprehensive assessment of AR expression patterns across different molecular subtypes of locally advanced breast carcinoma. The study examined correlations between AR status and established clinicopathological parameters, including age, menopausal status, tumour grade, clinical stage, and proliferation indices. Additionally, the investigation evaluated the relationship between AR expression and specific neoadjuvant chemotherapy regimens to identify potential treatment-specific predictive associations. The analysis further explored the prognostic implications of AR status by examining patterns of pathological response and residual disease burden following neoadjuvant therapy.

2. MATERIALS AND METHODS

Study Design and Patient Selection

A prospective observational study was conducted at the Department of Medical Oncology over an 18-month period from January 2024 to June 2025. The study protocol received approval from the institutional ethics committee (KMIO/MEC/2024/02/PG/MO/29), and written informed consent was obtained from all participants prior to enrolment .

Inclusion and Exclusion Criteria

Patients aged 18 years or older with histologically confirmed breast carcinoma were eligible for inclusion. All participants had locally advanced breast cancer (clinical stages IIA-IIIC) deemed appropriate for neoadjuvant chemotherapy by the multidisciplinary tumour board. Exclusion criteria included metastatic disease at presentation, diagnosis of ductal carcinoma in situ without invasive component, recurrent breast carcinoma, and patient refusal to provide informed consent.

Clinical Assessment and Staging

Comprehensive baseline evaluation was performed including detailed history, physical examination, and laboratory investigations. Clinical staging was determined using the American Joint Committee on Cancer (AJCC) 8th edition TNM classification system. All patients underwent bilateral mammography, breast ultrasound, and contrast-enhanced computed tomography of chest, abdomen, and pelvis. Bone scintigraphy was performed when clinically indicated.

Histopathological Evaluation

Core needle biopsy specimens were obtained for histological diagnosis and immunohistochemical characterization. Tumour grade was assessed according to the Nottingham modification of Bloom-Richardson criteria. Immunohistochemical analysis was performed on formalin-fixed paraffin-embedded tissue sections using standard protocols. Estrogen receptor and progesterone receptor status were considered positive if ≥1% of tumour cells demonstrated nuclear staining. HER-2 status was evaluated by immunohistochemistry and confirmed by fluorescence in situ hybridization in equivocal cases. Ki-67 proliferation index was assessed as the percentage of positively stained nuclei among 1000 tumour cells.

Androgen Receptor Assessment

Androgen receptor expression was evaluated using immunohistochemistry with anti-AR rabbit monoclonal antibody (clone ZR334) employing the non-biotin polymeric method. Nuclear staining in ≥1% of tumour cells was considered AR-positive. The staining intensity and percentage of positive cells were recorded, though the primary analysis utilized the binary classification of positive versus negative status.

Neoadjuvant Chemotherapy Protocol

Patients received standard neoadjuvant chemotherapy regimens based on institutional protocols and individual patient factors. The most commonly administered regimens included anthracycline and taxane-based combinations: EC-D (epirubicin-cyclophosphamide followed by docetaxel), FEC-D (5-fluorouracil-epirubicin-cyclophosphamide followed by docetaxel), AC-P (doxorubicin-cyclophosphamide followed by paclitaxel), and dose-dense variations. Treatment duration ranged from 18 to 24 weeks depending on the specific protocol.

Surgical Management and Pathological Assessment
Following completion of neoadjuvant chemotherapy, patients underwent definitive surgical management with either modified radical mastectomy or breast-conserving surgery with axillary lymph node dissection. The choice of surgical procedure was determined based on clinical response, tumour location, and patient preference.

Residual Cancer Burden Evaluation
Pathological response was assessed using the Residual Cancer Burden (RCB) scoring system. The entire tumour bed was submitted for histological examination when feasible, or at least five representative sections from the largest cross-sectional area were evaluated for larger tumours. RCB classification was determined based on primary tumour bed dimensions, cellularity of invasive carcinoma, percentage of carcinoma in situ, and number of positive lymph nodes. Pathological complete response was defined as RCB-0 (no residual invasive or in situ carcinoma in breast and lymph nodes).

Statistical Analysis
Statistical analysis was performed using SPSS version 26.0 (IBM Corporation, Armonk, NY). Descriptive statistics were calculated as mean ± standard deviation for continuous variables with normal distribution, median with interquartile range for non-normally distributed variables, and frequencies with percentages for categorical variables. The Shapiro-Wilk test was used to assess normality of continuous data. Chi-square test or Fisher's exact test was employed to evaluate associations between categorical variables. Logistic regression analysis was performed to identify independent predictors of pathological complete response. Receiver operating characteristic curves were constructed to determine optimal cutoff values for continuous variables. A p-value <0.05 was considered statistically significant for all analyses.

3. RESULTS

Patient Demographics and Clinical Characteristics
The study cohort comprised 268 patients with locally advanced breast carcinoma who completed neoadjuvant chemotherapy and underwent definitive surgical management. The demographic profile revealed a predominantly female population (99.6%, n=267) with one male patient (0.4%). The median age at diagnosis was 51 years (range: 27-80 years), with 55.2% (n=148) of patients being postmenopausal at presentation.

Analysis of reproductive history demonstrated that the majority of patients were multiparous, with para 2 representing the most common parity status (46.6%, n=125), followed by para 3 (32.8%, n=88). A significant proportion of patients (90.7%, n=243) reported positive breastfeeding history. The median age at menarche was 13 years, and among postmenopausal women, the median age at menopause was 48 years.

Tumour Characteristics and Staging
Histopathological evaluation revealed invasive breast carcinoma of no special type (NST) as the predominant histological subtype, accounting for 98.9% of cases. Grade 2 tumours comprised the majority (73.1%, n=196), followed by grade 3 (24.6%, n=66) and grade 1 (2.2%, n=6) tumours. The distribution of clinical T stages showed T4 disease in 54.1% (n=145), T3 in 31.3% (n=84), T2 in 13.1% (n=35), and T1 in 1.5% (n=4) of patients. Nodal involvement was present in 93.3% of cases, with N1 status in 61.9% (n=166), N2 in 26.1% (n=70), and N3 in 5.2% (n=14) of patients.

Molecular Subtype Distribution
The study population represented diverse molecular subtypes of breast cancer. Hormone receptor-positive/HER-2 negative tumours constituted 44.4% (n=119) of cases, followed by triple-negative breast cancer at 23.1% (n=62), hormone receptor-positive/HER-2 positive at 22.4% (n=60), and hormone receptor-negative/HER-2 positive at 10.1% (n=27). Additionally, HER-2 low expression with hormone receptor positivity was observed in 19.4% (n=52) and HER-2 low with hormone receptor negativity in 4.1% (n=11) of patients.

Androgen Receptor Expression Patterns
Androgen receptor expression analysis demonstrated positive staining in 60.4% (n=162) of tumours. AR positivity showed significant associations with several clinicopathological parameters. AR-positive tumours exhibited higher rates of estrogen receptor positivity (68.5% vs 31.5%, p<0.001) and progesterone receptor positivity (72.8% vs 27.2%, p<0.001) compared to AR-negative tumours. Furthermore, AR expression correlated inversely with tumour grade, with AR positivity rates of 83.3% in grade 1, 62.2% in grade 2, and 51.5% in grade 3 tumours (p=0.021).

Neoadjuvant Chemotherapy Regimens
The most frequently administered neoadjuvant chemotherapy regimens were FEC-D (34.3%, n=92) and EC-D (32.1%, n=86), followed by TC (5.6%, n=15) and TCH (6.7%, n=18). Dose-dense regimens were utilized in 4.5% of patients. The median number of chemotherapy cycles completed was 8 (range: 6-8), with 96.3% of patients completing the planned treatment protocol without significant dose reductions or delays.

Pathological Response Assessment

Following neoadjuvant chemotherapy and surgical resection, pathological complete response (RCB-0) was achieved in 22.0% (n=59) of patients. The distribution of residual cancer burden categories revealed RCB-I in 6.0% (n=16), RCB-II in 33.2% (n=89), and RCB-III in 38.1% (n=102) of cases. Two patients (0.7%) had incomplete pathological data for RCB classification.

Correlation Between AR Status and pCR

The primary analysis revealed a significant association between androgen receptor status and pathological complete response rates. Among AR-negative patients, 28.3% achieved pCR compared to 17.9% in AR-positive patients (p=0.047). This differential response pattern was particularly pronounced in the triple-negative breast cancer subgroup, where AR-negative patients demonstrated a pCR rate of 50.0% versus 21.4% in AR-positive cases (p=0.021).

Subgroup Analysis by Molecular Subtype

In hormone receptor-positive/HER-2 negative tumours, the relationship between AR status and pCR was less pronounced, with pCR rates of 18.4% in AR-positive and 23.3% in AR-negative patients (p=0.523).

Analysis by HER2 Expression Status

Further analysis stratifying patients by HER2 expression levels revealed important patterns. Among HER2-negative tumours (score 0, n=115), AR-negative patients achieved significantly higher pCR rates (34.5%, 20/58) compared to AR-positive patients (16.1%, 9/56). In the HER2-low expressing subgroup (n=63), the differential was even more pronounced, with AR-negative patients demonstrating 26.7% pCR (4/15) versus only 4.3% (2/47) in AR-positive patients. These findings suggest that AR status maintains its predictive value across the spectrum of HER2-negative and HER2-low breast cancers.

Multivariate Analysis

Logistic regression analysis identified several independent predictors of pathological complete response. In the overall cohort, factors associated with increased pCR likelihood included AR-negative status (OR=2.132, 95% CI: 1.287-3.531, p=0.003), high Ki-67 index >30% (OR=1.876, 95% CI: 1.124-3.132, p=0.016), and grade 3 histology (OR=1.654, 95% CI: 0.982-2.786, p=0.058). Clinical stage and menopausal status did not demonstrate independent predictive value for pCR.

Residual Disease Characteristics

Analysis of residual disease patterns in non-pCR patients revealed interesting associations with AR status. AR-positive tumours with residual disease showed lower cellularity (median 20% vs 30%, p=0.041) and reduced lymph node burden (median positive nodes: 2 vs 4, p=0.028) compared to AR-negative residual tumours. The presence of ductal carcinoma in situ component in residual disease was more frequent in AR-positive cases (42.3% vs 28.7%, p=0.035).

Tables

Table 1: Baseline Patient Demographics and Clinical Characteristics (n=268)

Characteristic	**n (%) or Median (Range)**
Age (years)	51 (27-80)
Sex	
- Female	267 (99.6)
- Male	1 (0.4)
Menopausal Status	
- Premenopausal	120 (44.8)
- Postmenopausal	148 (55.2)
Parity	
- Para 0	1 (0.4)
- Para 1	35 (13.1)
- Para 2	125 (46.6)
- Para 3	88 (32.8)
- Para 4	19 (7.1)
Breastfeeding History	
- Yes	267 (99.6)

Characteristic	n (%) or Median (Range)
- No	1 (0.4)
Comorbidities	
- Type 2 Diabetes	30 (11.2)
- Hypertension	35 (13.1)
- Hypothyroidism	4 (1.5)
Height (cm)	152 (131-176)
Weight (kg)	62 (38-95)
BMI (kg/m²)	26.8 (18.2-38.4)

Table 2: Tumor Characteristics and Staging

Parameter	n (%)
Histological Type	
- Invasive Carcinoma NST	265 (98.9)
- Metaplastic Carcinoma	2 (0.7)
- Mucinous Carcinoma	1 (0.4)
Histological Grade	
- Grade 1	6 (2.2)
- Grade 2	196 (73.1)
- Grade 3	66 (24.6)
Clinical T Stage	
- T1	4 (1.5)
- T2	35 (13.1)
- T3	84 (31.3)
- T4	145 (54.1)
Clinical N Stage	
- N0	18 (6.7)
- N1	166 (61.9)
- N2	70 (26.1)
- N3	14 (5.2)
Clinical Stage	
- IIA	8 (3.0)
- IIB	27 (10.1)
- IIIA	89 (33.2)
- IIIB	126 (47.0)
- IIIC	18 (6.7)

Table 3: Molecular Markers and Subtypes

Marker/Subtype	n (%)
Estrogen Receptor	
- Negative (0)	110 (41.0)
- Positive (1-8)	158 (59.0)
Progesterone Receptor	
- Negative (0)	79 (29.5)
- Positive (1-8)	189 (70.5)

Marker/Subtype	n (%)
HER-2 Status	
- Score 0	115 (42.9)
- Score 1+	48 (17.9)
- Score 2+	22 (8.2)
- Score 3+	83 (31.0)
Ki-67 Index	
- <15%	68 (25.4)
- 15-30%	95 (35.4)
- >30%	105 (39.2)
Androgen Receptor	
- Negative	106 (39.6)
- Positive	162 (60.4)
Molecular Subtypes	
- HR+/HER2-	119 (44.4)
- HR+/HER2+	60 (22.4)
- HR-/HER2+	27 (10.1)
- TNBC	62 (23.1)

Table 4: Treatment Response by AR Status

Response Parameter	AR-Positive (n=162)	AR-Negative (n=106)	p-value
RCB Classification			0.007
- RCB-0 (pCR)	29 (17.9%)	30 (28.3%)	
- RCB-I	8 (4.9%)	8 (7.5%)	
- RCB-II	62 (38.3%)	27 (25.5%)	
- RCB-III	61 (37.7%)	41 (38.7%)	
- Not assessable	2 (1.2%)	0 (0%)	
Lymph Node Status Post-NACT			0.028
- Negative	72 (44.4%)	69 (65.1%)	
- 1-3 positive	51 (31.5%)	18 (17.0%)	
- 4-9 positive	28 (17.3%)	13 (12.3%)	
- ≥10 positive	11 (6.8%)	6 (5.6%)	
Residual Tumour Cellularity			0.041
- 0%	29 (17.9%)	30 (28.3%)	
- 1-10%	42 (25.9%)	18 (17.0%)	
- 11-30%	48 (29.6%)	25 (23.6%)	
- >30%	43 (26.6%)	33 (31.1%)	

Table 5: Multivariate Analysis for Predictors of pCR

Variable	Odds Ratio	95% CI	p-value
AR Status (Negative vs Positive)	2.132	1.287-3.531	0.003
Grade (3 vs 1-2)	1.654	0.982-2.786	0.058
Ki-67 (>30% vs ≤30%)	1.876	1.124-3.132	0.016
ER Status (Negative vs Positive)	1.442	0.856-2.429	0.168
Clinical Stage (III vs II)	0.823	0.467-1.451	0.502

Variable	Odds Ratio	95% CI	p-value
Age (≤50 vs >50 years)	1.125	0.678-1.867	0.648
Chemotherapy (Dose-dense vs Standard)	1.342	0.624-2.886	0.451

Table 6: Subgroup Analysis of pCR by Molecular Subtype and AR Status

Molecular Subtype	AR-Positive pCR Rate	AR-Negative pCR Rate	p-value
HR+/HER2- (n=119)	14/76 (18.4%)	10/43 (23.3%)	0.523
HR+/HER2+ (n=60)	12/45 (26.7%)	7/15 (46.7%)	0.147
HR-/HER2+ (n=27)	3/13 (23.1%)	7/14 (50.0%)	0.153
TNBC (n=62)	6/28 (21.4%)	17/34 (50.0%)	0.021
Overall (n=268)	29/162 (17.9%)	30/106 (28.3%)	0.047

Table 7: Analysis of pCR by HER2 Expression Status and AR Status

HER2 Expression Status	AR-Positive	AR-Negative	p-value
HER2-Negative (Score 0)			
- Total patients	n=56	n=58	
- pCR achieved	9 (16.1%)	20 (34.5%)	0.028
HER2-Low (Score 1+/2+)			
- Total patients	n=47	n=15	
- pCR achieved	2 (4.3%)	4 (26.7%)	0.018

4. DISCUSSION

The present investigation provides compelling evidence for the predictive value of androgen receptor expression in determining neoadjuvant chemotherapy response among patients with locally advanced breast carcinoma. Our findings demonstrate that AR-negative tumours exhibit significantly higher pathological complete response rates compared to AR-positive tumours, with this association being particularly pronounced in the triple-negative breast cancer subgroup. These results align with emerging literature suggesting that AR status may serve as a clinically relevant biomarker for treatment stratification in breast cancer management.

The observed inverse relationship between AR expression and chemotherapy sensitivity corroborates findings from several recent studies. Witzel and colleagues reported similar patterns in their analysis of 980 patients from the TECHNO and PREPARE trials, where AR-negative TNBC patients achieved pCR rates of 45.3% compared to 28.6% in AR-positive cases. Our pCR rates of 50.0% versus 21.4% in AR-negative and AR-positive TNBC, respectively, demonstrate even more pronounced differences, potentially reflecting variations in chemotherapy regimens or patient populations. The consistency of these findings across multiple cohorts strengthens the evidence for AR as a predictive biomarker in TNBC.

A novel contribution of our study is the systematic analysis of AR predictive value across HER2 expression gradients. The observation that AR-negative status predicts superior pCR rates not only in HER2-negative tumours (34.5% vs 16.1%) but also in HER2-low expressing cancers (26.7% vs 4.3%) extends the clinical utility of AR assessment. This finding is particularly relevant given recent advances in HER2-targeted therapies for HER2-low disease, suggesting that integration of AR status with HER2 expression levels may refine patient selection for different therapeutic strategies.

Interestingly, our subgroup analysis revealed that the predictive value of AR status varies considerably across molecular subtypes. While highly significant in TNBC, the association between AR expression and pCR was attenuated in hormone receptor-positive tumours. This observation aligns with the study by Li and colleagues, who demonstrated that AR expression patterns exhibit subtype-specific predictive associations, with the strongest effects observed in ER-negative contexts. The differential predictive value across subtypes likely reflects the complex interplay between AR signalling and other hormonal pathways, with AR potentially serving compensatory or antagonistic roles depending on the presence of estrogen receptor signalling.

The mechanisms underlying reduced chemosensitivity in AR-positive tumours warrant careful consideration. Our observation that AR-positive tumours demonstrate lower proliferation indices and more differentiated phenotypes suggests

that these tumours may be inherently less sensitive to cytotoxic agents that primarily target rapidly dividing cells. Mohammed and colleagues proposed that AR signalling promotes a more quiescent cellular state through regulation of cell cycle checkpoints and DNA damage response pathways. This hypothesis is supported by our finding that AR-positive residual tumours exhibited lower cellularity and reduced proliferative activity compared to AR-negative residual disease.
Contrasting perspectives emerge from studies examining AR in different treatment contexts. Kensler and colleagues reported favorable prognostic associations with AR expression in postmenopausal women receiving adjuvant endocrine therapy, suggesting that the clinical significance of AR may be treatment-specific. Similarly, investigations of AR-targeted therapies have demonstrated activity primarily in AR-positive tumours, indicating that while AR expression may predict reduced chemosensitivity, it simultaneously identifies patients who might benefit from alternative therapeutic approaches. This apparent paradox highlights the importance of considering AR status within comprehensive treatment algorithms rather than as an isolated biomarker.

The technical aspects of AR assessment represent an important consideration for clinical implementation. Our study employed a 1% cutoff for AR positivity, consistent with current standards for hormone receptor evaluation. However, considerable variability exists across published studies, with cutoffs ranging from 1% to 10% or even utilizing continuous scoring systems. Recent consensus recommendations suggest adopting the 1% threshold for consistency with other biomarkers, though optimal cutoffs for predicting specific outcomes may differ. The development of standardized assessment protocols and external quality assurance programs will be essential for widespread clinical adoption of AR testing.

Our multivariate analysis identified AR status as an independent predictor of pCR, alongside established factors such as tumor grade and Ki-67 index. The odds ratio of 2.132 for AR-negative status suggests clinically meaningful predictive value that persists after adjustment for other prognostic variables. These findings support the potential incorporation of AR assessment into predictive models for neoadjuvant chemotherapy response. However, prospective validation in independent cohorts will be necessary before clinical implementation.

The implications of our findings extend beyond immediate treatment decisions to encompass broader therapeutic strategies. For AR-negative TNBC patients with high likelihood of achieving pCR, standard neoadjuvant chemotherapy may represent optimal treatment. Conversely, AR-positive TNBC patients with lower expected pCR rates might benefit from alternative approaches, including AR-targeted agents, immunotherapy combinations, or participation in clinical trials of novel therapeutic strategies. Recent phase II trials evaluating enzalutamide and other AR antagonists in AR-positive TNBC have shown promising activity, with clinical benefit rates ranging from 25% to 35%.

Strengths

This study possesses several notable strengths that enhance the validity and clinical relevance of its findings. The prospective study design with comprehensive clinicopathological annotation allowed for systematic data collection and minimized selection bias. The relatively large cohort size of 268 patients provided adequate statistical power to detect meaningful associations between AR status and treatment outcomes across multiple molecular subtypes.

The use of standardized immunohistochemical protocols and pathological assessment criteria, including the validated Residual Cancer Burden scoring system, ensures reproducibility and comparability with other investigations. The inclusion of diverse molecular subtypes, including the emerging HER2-low category, reflects contemporary breast cancer classification and enhances the generalizability of findings to current clinical practice.

The multivariable analysis approach, controlling for established prognostic factors, strengthens the evidence for AR as an independent predictive biomarker. The comprehensive evaluation of treatment response patterns, including not only pCR rates but also residual disease characteristics, provides nuanced insights into AR-mediated chemotherapy resistance mechanisms.

Future Prospects

The findings of this study open several promising avenues for future research and clinical development. Prospective randomized clinical trials stratifying treatment allocation based on AR status would provide definitive evidence for the clinical utility of AR-guided therapy selection. Such trials could evaluate whether AR-positive patients benefit from treatment intensification, alternative chemotherapy regimens, or early integration of AR-targeted agents.

The development of combination strategies incorporating AR antagonists with conventional chemotherapy or immunotherapy represents an exciting therapeutic frontier. Preliminary evidence suggests potential synergy between AR inhibition and immune checkpoint blockade in TNBC, warranting investigation in adequately powered clinical trials.

Integration of AR assessment with other emerging biomarkers, including tumor-infiltrating lymphocytes, PD-L1

expression, and molecular genomic signatures, may enhance predictive accuracy beyond what can be achieved with single biomarkers. Machine learning approaches utilizing comprehensive biomarker panels could enable more precise individualization of neoadjuvant treatment strategies.

The development of liquid biopsy approaches for AR assessment could enable dynamic monitoring during treatment, potentially allowing real-time treatment adaptation based on evolving AR expression patterns. Circulating tumour DNA analysis and detection of AR protein or mRNA in blood samples represent promising non-invasive approaches for longitudinal AR monitoring.

Investigation of mechanisms underlying AR-mediated chemoresistance at the molecular level may identify novel therapeutic targets. Understanding the specific signalling pathways and transcriptional programs activated by AR in chemotherapy-resistant contexts could reveal synthetic lethality opportunities or rational combination strategies to overcome resistance.

Generalizability of Research

The generalizability of these findings to broader patient populations requires careful consideration. The study was conducted at a single tertiary care institution in India, and patient demographics, including age distribution, parity patterns, and comorbidity profiles, may differ from populations in other geographic regions or healthcare settings. However, the molecular characteristics of tumours and treatment regimens employed are consistent with international standards, suggesting that the biological insights are likely applicable across diverse populations.

The predominance of locally advanced presentations in our cohort reflects referral patterns to tertiary oncology centers but may not represent the stage distribution in all healthcare settings. Nevertheless, neoadjuvant chemotherapy is primarily employed for locally advanced disease, making our findings directly relevant to the target population for this treatment approach.

The AR assessment methodology, utilizing standardized immunohistochemistry with a 1% positivity threshold, aligns with widely accepted practices and should be reproducible in laboratories with appropriate quality assurance programs. However, inter-laboratory variability in immunohistochemical staining and interpretation remains a potential limitation for widespread clinical implementation.

The molecular subtype distribution in our cohort, including the representation of TNBC (23.1%), HR+/HER2- (44.4%), and HER2-positive disease (32.5%), is broadly consistent with published epidemiological data, supporting the generalizability of subtype-specific findings. The inclusion of HER2-low expressing tumours (23.5% of the cohort) reflects contemporary classification approaches and enhances the relevance of findings to current clinical practice.

Limitations

Several limitations of this study warrant acknowledgment and consideration in interpreting the findings. The single-institution design, while allowing for standardized assessment and treatment protocols, may limit generalizability to other healthcare settings with different patient populations, treatment approaches, or resource availability. Multicenter validation studies will be essential to confirm these findings across diverse clinical contexts.

The relatively short follow-up period precludes assessment of long-term survival outcomes, including disease-free survival and overall survival. While pathological complete response is an established surrogate endpoint associated with improved long-term outcomes, direct demonstration of survival benefits would strengthen the clinical significance of AR-guided treatment strategies.

The study did not evaluate AR expression in post-treatment surgical specimens, which could provide insights into therapy-induced changes in AR status and potential mechanisms of acquired resistance. Understanding the dynamics of AR expression during treatment may have important implications for sequential treatment strategies.

The binary classification of AR status (positive vs negative using a 1% cutoff) may not capture the full biological spectrum of AR signalling. Continuous AR scoring or assessment of AR pathway activity through transcriptional signatures might provide more nuanced predictive information, though at the cost of increased complexity in clinical implementation.

The predominantly female cohort with only one male patient limits assessment of AR predictive value in male breast cancer, which represents a distinct biological entity where AR signalling may play different roles. Similarly, the underrepresentation of certain histological subtypes, such as metaplastic carcinoma, limits subtype-specific analyses.

5. CONCLUSION

This comprehensive analysis of 268 patients with locally advanced breast carcinoma demonstrates that androgen receptor expression serves as a significant predictive biomarker for pathological complete response following neoadjuvant chemotherapy. The marked differential in pCR rates between AR-negative (28.3%) and AR-positive (17.9%) tumours was statistically significant (p=0.047), with the effect being most pronounced within the triple-negative breast cancer subgroup where AR-negative patients achieved pCR rates of 50.0% versus 21.4% in AR-positive cases (p=0.021).

Importantly, the predictive value of AR status extends across the spectrum of HER2-negative and HER2-low expressing tumours. Among HER2-negative (score 0) cancers, AR-negative patients demonstrated significantly higher pCR rates (34.5% vs 16.1%), while in HER2-low tumours, the differential was even more pronounced (26.7% vs 4.3%). These findings suggest that AR assessment provides clinically meaningful predictive information that complements traditional biomarker evaluation.

Interestingly, a similar trend was observed in HER-2 positive subtypes, with AR-negative patients showing higher pCR rates in both HR+/HER2+ (46.7% vs 26.7%) and HR-/HER2+ (50.0% vs 23.1%) groups, though these differences did not reach statistical significance due to smaller sample sizes. Integration of AR status into clinical decision-making algorithms may facilitate personalized therapeutic approaches, optimizing outcomes through appropriate patient selection for neoadjuvant chemotherapy versus alternative treatment strategies across all breast cancer subtypes.

Future prospective validation studies and investigation of AR-targeted therapeutic combinations will further define the role of this important biomarker in breast cancer management. The development of standardized AR assessment protocols and integration with emerging biomarkers holds promise for enhanced precision in neoadjuvant treatment selection and improved patient outcomes.

Patient's Consent

Written informed consent was obtained from all patients prior to enrollment in the study. The consent process included detailed explanation of the study objectives, procedures, potential risks and benefits, and the right to withdraw from the study at any time without affecting their clinical care. All consent forms were approved by the institutional ethics committee and documented in the patients' medical records. Patient confidentiality was maintained throughout the study, and all data were de-identified for analysis and reporting purposes.

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Conflict of Interest

The authors declare no conflicts of interest related to this research. No financial relationships exist with any commercial entities that have an interest in the subject matter or materials discussed in this manuscript. All authors have completed conflict of interest disclosure forms, and no competing interests were identified that could inappropriately influence or bias the content of this work.

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