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ORIGINAL RESEARCH

The Impact of Androgen Receptor Expression on Neoadjuvant Therapy in HER2-Positive Breast Cancer

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Background: Androgen receptor (AR) is widely expressed in breast cancer, but its predictive value in HER2-positive disease remains uncertain. This study evaluated the association of AR expression with neoadjuvant therapy (NAT) response and survival in HER2-positive breast cancer.

Methods: We retrospectively reviewed 336 patients with primary HER2-positive breast cancer treated with NAT at the First Affiliated Hospital of Chongqing Medical University between December 2020 and July 2024. After screening, 210 patients were included. Clinicopathological characteristics, treatment response, and survival outcomes were analyzed. Factors associated with pathological complete response (pCR) and disease-free survival (DFS) were assessed using logistic regression and Cox proportional hazards models. The predictive value of AR expression, as well as AR/ER and AR/PR ratios, was also explored.

Results: The overall pCR rate was 51.9% (109/210). In the overall cohort, higher AR expression was associated with pCR, but not with DFS or overall survival (OS). Multivariate analysis identified T stage, HER2 status, and AR expression as independent predictors of pCR. In exploratory subgroup analyses, the association between higher AR expression and improved treatment response was mainly observed in hormone receptor-negative/HER2-positive patients, in whom higher AR expression was associated with both a higher pCR rate and better DFS. No significant differences in treatment response or survival according to AR expression were observed in the HR +/HER2+ subgroup. Higher AR/ER and AR/PR ratios were associated with better treatment response, whereas the direct associations between AR expression and ER/PR levels appeared limited.

Conclusion: Higher AR expression was associated with improved neoadjuvant treatment response in HER2-positive breast cancer, particularly in the hormone receptor-negative subgroup. However, given the retrospective single-center design and inconsistent findings in the overall population, the clinical value of AR assessment remains preliminary and requires validation in larger prospective studies.

Keywords: breast cancer, androgen receptor, human epidermal growth factor receptor-2, neoadjuvant treatment

Introduction

Breast cancer is the most common malignancy among women worldwide and remains a leading cause of cancer-related mortality.[1] Based on immunohistochemical markers, breast cancer is classified into four molecular subtypes: Luminal A, Luminal B, HER2-enriched, and basal-like.[2] HER2 is a transmembrane protein with tyrosine kinase activity that plays a critical role in promoting cancer cell proliferation and survival. The HER2 gene, located at chromosome 17q12, is amplified in approximately 15–20% of breast cancers.[3] In HER2-positive breast cancer, particularly cases with substantial tumor burden (T2+) or lymph node metastasis (N1+), the incorporation of anti-HER2 targeted agents with

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cytotoxic chemotherapy has been established as the NAT paradigm, demonstrating significant prognostic improvement in clinical outcomes.[4]

The androgen receptor (AR), along with estrogen receptor (ER) and progesterone receptor (PR), belongs to the hormone receptor (HR) family.[5] The role of AR in breast cancer has been increasingly recognized, particularly regarding its clinical implications. Previous studies have shown that in AR-positive triple-negative breast cancer (TNBC), the pCR is significantly lower than in AR-negative cases.[6] Moreover, reciprocal interactions between estrogen and androgen receptors could mediate partial inhibition of tumor progression.[7,8] However, high AR expression in ER-positive, HER2-negative breast cancers has been associated with reduced efficacy of NAT.[9]

Despite evidence implicating AR in multiple signaling pathways involved in tumor development, its biological and clinical significance in HER2-positive breast cancer remains uncertain. Some research suggests that activated AR can establish a positive feedback loop with the HER2 pathway to promote cell proliferation and may also activate transcriptional expression of HER3, a key component of HER2-driven tumorigenesis.[7,8] The introduction of HER2-directed therapies, including the monoclonal antibodies trastuzumab and pertuzumab, has substantially enhanced pCR, with contemporary clinical trials reporting pCR frequencies surpassing 50% in HER2-positive breast cancer populations. Nevertheless, not all patients experience substantial benefits from these regimens.[10–14]

Recent studies have suggested that, among hormone receptor-negative/HER2-positive patients receiving neoadjuvant chemotherapy, tumors with positive AR expression may be associated with a higher pCR rate than AR-negative tumors.[15,16] Conversely, other research—including work by Venema et al—suggests that elevated AR expression may be associated with poorer responses to NAT in HR/HER2 dual-positive populations.[17] These conflicting findings underscore the need for further investigation into how AR modulates treatment response among HER2-positive breast cancer patients.

However, the specific literature gap remains that the predictive value of AR in HER2-positive breast cancer treated with neoadjuvant therapy is still unclear, particularly after stratification by hormone receptor status, and its associations with survival outcomes and AR/ER or AR/PR ratios have not been sufficiently investigated. To bridge these knowledge gaps, we conducted a single-center retrospective study analyzing early-stage HER2-positive breast cancer cases treated with neoadjuvant therapy at the First Affiliated Hospital of Chongqing Medical University. Our objective was to elucidate the effect of androgen receptor expression on both therapeutic efficacy and long-term outcomes while exploring its correlation with other molecular biomarkers.

Materials and Methods

Patients

This retrospective study included 336 patients with primary HER2-positive breast cancer who underwent NAT (chemotherapy combined with targeted therapy) at the Department of Breast and Thyroid Surgery, First Affiliated Hospital of Chongqing Medical University between December 2020 and July 2024. The inclusion criteria were: (1) an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1; (2) histologically confirmed invasive breast cancer via core needle biopsy; (3) HER2 positivity defined as immunohistochemistry (IHC) 3+ or IHC 2+ with HER2 gene amplification confirmed by fluorescence in situ hybridization (FISH); and (4) clinical stage I–III based on the American Joint Committee on Cancer (AJCC) staging system assessed by radiological or clinical examination.

Exclusion criteria comprised: (1) presence of distant metastasis at initial diagnosis; (2) absence of AR expression data in pathology reports or inability to reassess specimens; (3) prior excisional biopsy or vacuum-assisted breast biopsy (VABB) before hospital admission; (4) lack of surgery or incomplete postoperative follow-up data; and (5) synchronous bilateral primary breast cancers.

Specimen Preparation and Staining

Breast tissue specimens were fixed in 10% neutral buffered formalin, dehydrated through a graded alcohol series, and embedded in paraffin according to standardized tissue-processing procedures. Hematoxylin and eosin (HE)-stained sections were reviewed independently by two associate chief pathologists, each with more than 10 years of experience

in breast pathology. Histopathological diagnosis was based on the latest World Health Organization (WHO) classification of breast tumors and the Nottingham histological grading system. Both pathologists were blinded to the patients' clinical and imaging information during evaluation.

Immunohistochemical staining for ER, PR, HER2, AR, and Ki-67 was performed on formalin-fixed, paraffin-embedded tissue sections. The primary antibodies were as follows: ER (clone SP1, Roche, ready-to-use), PR (clone 1E2, Roche, ready-to-use), HER2 (clone 4B5, Roche, ready-to-use), AR (clone EP120, Celnotive, ready-to-use), and Ki-67 (clone 30–9, Roche, ready-to-use). Antigen retrieval was performed using phosphate-buffered saline (PBS)-based buffer (pH 7.4–7.6) at room temperature, with marker-specific retrieval conditions according to routine laboratory protocols. ER, PR, and HER2 staining were performed on the UltraView platform, whereas AR and Ki-67 staining were performed manually.

According to the 2020 ASCO/CAP guidelines,[18] ER and PR positivity were defined as positive nuclear staining in ≥1% of tumor cell nuclei, whereas staining in <1% of tumor cell nuclei was considered negative. HER2 immunohistochemical expression was scored according to the 2018 ASCO/CAP guidelines as 0, 1+, 2+, or 3+; a score of 3+ was considered positive, 0–1+ negative, and 2+ equivocal, requiring further evaluation by fluorescence in situ hybridization (FISH). AR positivity was defined as nuclear staining in ≥1% of tumor cells. Ki-67 was evaluated as the percentage of tumor cells showing positive nuclear staining.

FISH testing was performed for all HER2 IHC 2+ cases and for selected IHC 1+ or 3+ cases with clinical suspicion of HER2 positivity, using a HER2 dual-probe kit (Guangzhou ABP Biotech Co., Ltd., Guangzhou, China). HER2 gene amplification was interpreted according to the kit instructions and contemporary ASCO/CAP criteria. HER2 positivity was defined as a HER2/CEP17 ratio ≥2.0 with an average HER2 copy number ≥4.0 signals/cell, or a HER2/CEP17 ratio <2.0 with an average HER2 copy number ≥6.0 signals/cell.

Neoadjuvant Treatment Regimens and Outcomes

Neoadjuvant therapy (NAT) refers to systemic anti-tumor treatment administered prior to definitive surgery. However, for patients with distant metastases (M1), even if comprehensive treatment is implemented before surgery, it is fundamentally categorized as salvage therapy rather than NAT. Therefore, in the present study, we excluded these cases from our data collection. NAT regimens were designed according to the Breast Cancer Diagnosis and Treatment Guidelines issued by the Chinese Society of Clinical Oncology (CSCO). The study included two main chemotherapy protocols: (1) an anthracycline-based regimen combined with cyclophosphamide for a minimum of six cycles, and (2) a taxane-based regimen administered either as monotherapy or in combination with carboplatin. Targeted therapy consisted of either trastuzumab alone or combined dual-targeted therapy with trastuzumab plus pertuzumab.

The effectiveness of the treatment was assessed after every two cycles through breast ultrasonography, which was employed to monitor the dynamic alterations in tumor dimensions. Following the conclusion of neoadjuvant therapy, surgical procedures were performed on all participants. The postoperative pathological response was evaluated according to the Miller-Payne classification system. Pathological complete response (pCR) was characterized by the complete absence of invasive cancer remnants within both the breast tissue and axillary lymph nodes; nonetheless, instances of remaining ductal carcinoma in situ (DCIS) were still categorized as achieving pCR.[19]

Statistical Analysis

Clinicopathological characteristics across different groups were compared using independent-sample t-tests for continuous variables, Pearson's chi-square test or Fisher's exact test for categorical variables, and Mann–Whitney *U*-test for ordinal data. To identify factors associated with pathological response, binary logistic regression models were used to calculate odds ratios (ORs). Long-term survival outcomes—including disease-free survival (DFS) and overall survival (OS)—were analyzed using Cox proportional hazards regression models to estimate hazard ratios (HRs). For interpretability, continuous variables were categorized according to clinical standards and expert consensus during regression analyses.

For descriptive analyses, patients were classified into the high-AR and low-AR groups using the median AR expression level of the study cohort as the cutoff value. For analyses evaluating pCR, the optimal cutoff for dichotomizing AR expression was determined by receiver operating characteristic (ROC) curve analysis. This ROC-derived cutoff

was subsequently used in subgroup analyses and Kaplan-Meier survival analyses. Subgroup analyses according to HR status and HER2 category were further performed because hormone receptor–related variables and HER2 status showed significant associations with treatment response in the overall analysis, suggesting potential heterogeneity in the effect of AR across clinically relevant strata. AR/ER and AR/PR ratios were calculated from the percentages of positively stained tumor cell nuclei in the same biopsy specimen (AR/ER = AR%/ER%; AR/PR = AR%/PR%). Cases with ER = 0% or PR = 0% were not assigned numerical ratio values. For categorical analyses, ratios were classified as >1 or ≤1, with ER- or PR-negative cases assigned to the >1 group.

Disease-free survival (DFS) is characterized as the interval extending from the initial diagnosis of breast cancer to the occurrence of the first recurrence, metastasis, mortality from any cause, or the final follow-up. Overall survival (OS) is defined as the duration from the time of diagnosis until death or the last recorded contact. The survival distributions were represented using Kaplan-Meier curves, and comparisons between different groups were conducted through the Log rank test. All statistical evaluations were two-tailed, with p values below 0.05 deemed to indicate statistical significance. The analyses were executed utilizing R software.

Results

Patients

A total of 210 patients with HER2-positive breast cancer were included in the final analysis after eligibility screening (Figure 1). Only 23 patients (10.9%) were aged 40 years or younger, while the vast majority (N=187, 89.1%) were older than 40. Using a BMI cutoff of 24, the cohort was nearly evenly split: 107 patients (50.1%) had a BMI ≤24, while 103 (49.9%) had a BMI >24. Additionally, 124 patients (59.1%) were menopausal, whereas 86 (40.9%) were premenopausal.

Most tumors were histological grade II (N=167, 79.5%), with grade I and III representing 1.4% (N=3) and 19.0% (N=40), respectively. The majority of patients presented with T2 stage tumors (N=148, 70.5%). Axillary metastases were present in more than half of the cohort (N=119, 56.7%). All patients underwent neoadjuvant therapy consisting of between two and eight cycles—most commonly six cycles (N=153, 72.9%). Regarding targeted treatment, the majority (N=183, 87.2%) received trastuzumab combined with pertuzumab. A smaller group received trastuzumab alone (N=7, 3.3%), while a minority did not receive any targeted therapy (N=20, 9.5%) (Table 1).

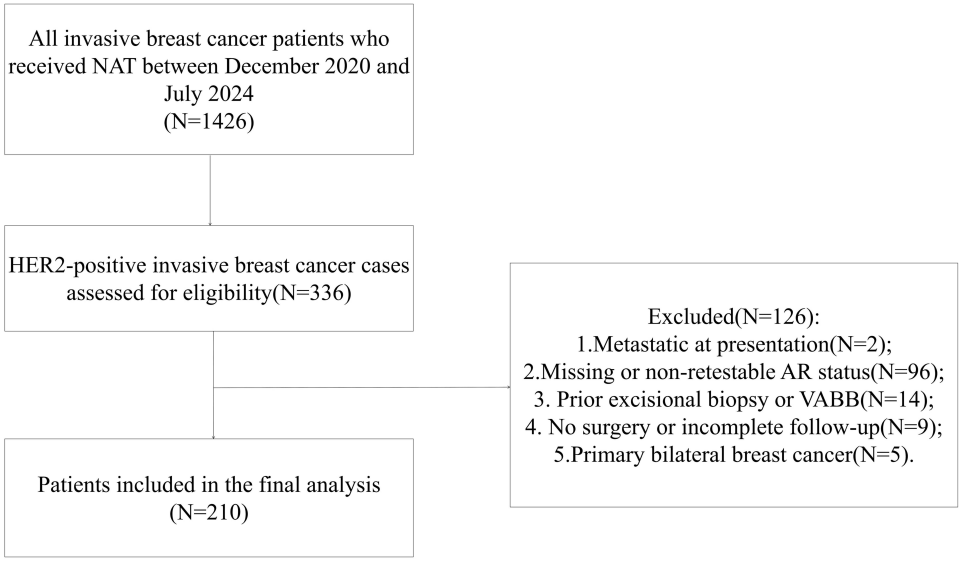

Figure 1 Flow chart of patient selection. Among 1,426 patients with invasive breast cancer who received neoadjuvant therapy (NAT) between December 2020 and July 2024, 336 patients with HER2-positive disease were assessed for eligibility. After exclusion of patients with metastatic disease at presentation, missing or non-retestable AR status, prior excisional biopsy or vacuum-assisted breast biopsy (VABB), no surgery or incomplete follow-up, and primary bilateral breast cancer, 210 patients were included in the final analysis.

Abbreviations: NAT, neoadjuvant therapy; AR, androgen receptor; VABB, vacuum-assisted breast biopsy.

Table 1 Baseline Characteristics of Patients with HER2-Positive Breast Cancer Stratified by AR Expression

		Grouping According to AR Expression Level			*P*
		Total (N=210)	AR-High (N=117)	AR-Low (N=93)	
Age					
	<= 40	23(10.9%)	14 (12.0%)	9(9.7%)	0.760
	>40	187(89.1%)	103(88.0%)	84(90.3%)	
BMI					
	<= 24	107(50.1%)	57(48.7%)	50 (53.8%)	0.557
	>24	103(49.9%)	60(51.3%)	43 (46.2%)	
Menstruation					
	Premenopause	86(40.9%)	48 (41.0%)	38 (40.9%)	1.000
	Menopause	124(59.1%)	69 (59.0%)	55 (59.1%)	
Multifocal					
	No	145(69.0%)	78(66.7%)	67 (72.0%)	0.492
	Yes	65(31.0%)	39 (33.3%)	26 (28.0%)	
T					
	T1	22(10.5%)	15 (12.8%)	7 (7.5%)	0.647
	T2	148(70.5%)	81 (69.2%)	67 (72.0%)	
	T3	28(13.3%)	15 (12.8%)	13 (14.0%)	
	T4	12(5.7%)	6 (5.1%)	6 (6.5%)	
N					
	N0	42(20.0%)	24 (20.5%)	18 (19.4%)	0.929
	N1	83(39.5%)	48 (41.0%)	35 (37.6%)	
	N2	49(23.3%)	26 (22.2%)	23 (24.7%)	
	N3	36(17.1%)	19 (16.2%)	17 (18.3%)	
Grade					
	G1	3(1.4%)	3 (2.6%)	0 (0.0%)	0.230
	G2	167(79.5%)	94 (80.3%)	73 (78.5%)	
	G3	40(19.0%)	20 (17.1%)	20 (21.5%)	
ER (%)					
	<10	140 (66.7%)	71 (60.7%)	69 (74.2%)	0.019
	10-30	14(6.7%)	6 (5.1%)	8 (8.6%)	
	>30	56(26.7%)	40 (34.2%)	16 (17.2%)	
PR (%)					
	<10	171(81.4%)	87 (74.4%)	84 (90.3%)	0.011
	10-30	14(6.7%)	10 (8.5%)	4 (4.3%)	
	>30	25(11.9%)	20 (17.1%)	5 (5.4%)	
HER2					
	2+FISH+	42(20.0%)	24 (20.5%)	18 (19.4%)	0.972
	3+	168(80.0%)	93 (79.5%)	75 (80.6%)	
Ki-67					
	<= 30	120(57.1%)	64 (54.7%)	56 (60.2%)	0.508
	>30	90(43.9%)	53 (45.3%)	37 (39.8%)	
Axillary metastases					
	No	91(43.3%)	51 (43.6%)	40 (43.0%)	1.000
	Yes	119(56.7%)	66 (56.4%)	53 (57.0%)	
Number of NAT cycles					
	2	2(0.9%)	2 (1.7%)	0 (0.0%)	0.104
	3	2(0.9%)	1 (0.9%)	1 (1.1%)	
	4	37(17.6%)	21 (17.9%)	16 (17.2%)	
	5	8(3.8%)	1 (0.9%)	7 (7.5%)	
	6	153(72.9%)	89 (76.1%)	64 (68.8%)	
	8	8(3.8%)	3 (2.6%)	5 (5.4%)	

(*Continued*)

Table 1 (Continued).

		Grouping According to AR Expression Level			*P*
		Total (N=210)	**AR-High (N=117)**	**AR-Low (N=93)**	
AR/ER					
	<= 1.00	67(31.9%)	25 (21.4%)	42 (45.2%)	<0.001
	>1.00	143(68.1%)	92 (78.6%)	51 (54.8%)	
AR/PR					
	<= 1.00	39(18.6%)	5 (4.3%)	34 (36.6%)	<0.001
	>1.00	171(81.4%)	112 (95.7%)	59 (63.4%)	
Target.therapy					
	None	20(9.5%)	11 (9.4%)	9 (9.7%)	0.995
	Trastuzumab	7(3.3%)	4 (3.4%)	3 (3.2%)	
	Trastuzumab + Pertuzumab	183(87.2%)	102 (87.2%)	81 (87.1%)	

Abbreviations: AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; BMI, body mass index; NAT, neoadjuvant therapy; AR/ER, ratio of AR expression to ER expression; AR/PR, ratio of AR expression to PR expression. Data are presented as n (%) unless otherwise indicated. P values were calculated using the independent-sample *t*-test, Pearson's chi-square test, Fisher's exact test, or Mann–Whitney *U*-test, as appropriate.

Comparison Between High and Low AR Expression Groups

Based on AR expression levels, patients were divided into a high AR group (N=117) and a low AR group (N=93). Significant differences between these groups were observed for ER expression level (P=0.019), PR expression level (P=0.011), AR/ER ratio (P=0.001), and AR/PR ratio (P<0.001) (Table 1).

There were no significant differences between the two groups regarding age, BMI, menstrual status, multifocality, T stage, N stage, histological grade, HER2 status, Ki-67 levels, axillary metastases, number of neoadjuvant chemotherapy cycles, or targeted therapy type.

To further stratify hormone receptor relationships with AR expression levels, AR/ER and AR/PR ratios were evaluated. In total, an AR/ER ratio >1.00 occurred in 68.1% of patients (N=143) and an AR/PR ratio >1.00 in 81.4% (N=171). Both ratios showed highly significant differences between the high and low AR expression groups (AR/ER p<0.001, AR/PR p<0.001, Table 1).

Risk Factors Associated with Neoadjuvant Treatment Response

To identify factors influencing pCRs in this HER2-positive cohort overall, both univariate and multivariate logistic regression analyses were performed (Table 2). Univariate analysis indicated that T stage, ER expression level, PR expression level, HER2 status, AR expression level, as well as AR/ER and AR/PR ratios were significantly associated with achieving pCR (p<0.05, Table 2).

All seven variables identified as significant in univariate analysis were subsequently entered into multivariate models. Results demonstrated that T stage, HER2 status, and AR expression level remained independent predictors of neoadjuvant therapy efficacy in this population (Table 2).

ROC Analysis for AR Cutoff Determination

To further define an outcome-oriented threshold for AR expression in predicting pCR, ROC curve analysis was performed. The optimal cutoff value for AR was 45%, with an area under the curve (AUC) of 0.586 (95% CI,0.510–0.662), indicating modest discriminatory ability (Supplementary Figure S1). Notably, because AR expression in routine pathology reports was recorded in 5% increments, dichotomization at 45% yielded the same effective patient classification as dichotomization at 50%, which was the cohort median used for descriptive analyses. Therefore, the subgroup analyses and Kaplan-Meier survival analyses remained unchanged after applying the ROC-derived cutoff.

Table 2 Analysis of Factors Associated with Neoadjuvant Treatment Efficacy in the Overall HER2-Positive Breast Cancer Population

		Grouping According to pCR			
		Non-pCR (N=101)	pCR (N=109)	OR (univariable)	OR (multivariable)
Age					
	Mean ± SD	52.4 ± 9.3	51.2 ± 8.8	0.99(0.96–1.02,p=0.337)	
Height					
	Mean ± SD	156.6 ± 5.1	157.5 ± 5.2	1.04(0.98–1.09,p=0.192)	
Weight					
	Mean ± SD	58.6 ± 7.6	59.7 ± 8.6	1.02(0.98–1.05,p=0.290)	
Menstruation					
	Premenopause	44(43.6%)	42(38.5%)		
	Menopause	57(56.4%)	67(61.5%)	1.23(0.71–2.14,p=0.459)	
Multifocal					
	No	70(69.3%)	75(68.8%)		
	Yes	31(30.7%)	34(31.2%)	1.02(0.57–1.84,p=0.938)	
T					
	T1	3(3.0%)	19 (17.4%)		
	T2	81(80.2%)	67 (61.5%)	0.13(0.03–0.40,p=0.002)	0.20(0.04–0.65,p=0.015)
	T3	12(11.9%)	16 (14.7%)	0.21(0.04–0.80,p=0.033)	0.232(0.06–1.29,p=0.130)
	T4	5(5.0%)	7 (6.4%)	0.22(0.04–1.13,p=0.077)	0.35(0.05–2.01,p=0.247)
N					
	N0	17(16.8%)	25 (22.9%)		
	N1	41(40.6%)	42 (38.5%)	0.70(0.32–1.47,p=0.346)	
	N2	25(24.8%)	24 (22.0%)	0.65(0.28–1.50,p=0.315)	
	N3	18(17.8%)	18 (16.5%)	0.68(0.27–1.67,p=0.400)	
Grade					
	G1	1(1.0%)	2 (1.8%)		
	G2	81(80.2%)	86 (78.9%)	0.53(0.02–5.64,p=0.608)	
	G3	19(18.8%)	21 (19.3%)	0.55(0.02–6.22,p=0.639)	
ER					
	Mean ± SD	30.1 ± 37.1	13.3 ± 27.1	0.98(0.98–0.99,p<0.001)	0.99(0.98–1.00,p=0.095)
PR					
	Mean ± SD	14.2 ± 27.4	4.6 ± 14.7	0.98(0.96–0.99,p=0.004)	0.99(0.97–1.01,p=0.344)
HER2					
	2+FISH+	31(30.7%)	11 (10.1%)		
	3+	70(69.3%)	98 (89.9%)	3.95(1.91–8.71,p<0.001)	2.84(1.12–5.78,p=0.029)
Ki-67					
	Mean ± SD	32.4 ± 16.8	36.0 ± 17.9	1.01(1.00–1.03,p=0.138)	
AR					
	Mean ± SD	48.5 ± 32.5	57.9 ± 30.7	1.01(1.00–1.02,p=0.034)	1.01(1.00–1.02,p=0.015)
Axillary metastases					
	No	44(43.6%)	47 (43.1%)		
	Yes	57(56.4%)	62 (56.9%)	1.02 (0.59–1.76, p =0.948)	
Number of NAT cycles					
	2	1(1.0%)	1 (0.9%)		
	3	2(2.0%)	0 (0.0%)	0.00(0.00-Inf,p=0.988)	
	4	22(21.8%)	15(13.8%)	0.68 (0.03–18.15, p =0.792)	
	5	5(5.0%)	3 (2.8%)	0.60(0.02–19.22,p=0.748)	
	6	67(66.3%)	86 (78.9%)	1.28(0.05–32.86,p=0.861)	
	8	4(4.0%)	4 (3.7%)	1.00(0.03–31.84,p=1.000)	
Treatment regimen					
	Taxane-based chemotherapy	12(11.9%)	8 (7.3%)		
	Chemotherapy plus single anti-HER2 blockade	5(5.0%)	2 (1.8%)	0.60 (0.07–3.59, p =0.592)	
	Chemotherapy plus dual anti-HER2 blockade	84(83.2%)	99 (90.8%)	1.77 (0.70–4.70, p =0.235)	

(*Continued*)

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Table 2 (Continued).

		Grouping According to pCR			
		Non-pCR (N=101)	**pCR (N=109)**	**OR (univariable)**	**OR (multivariable)**
AR/ER	Mean ± SD	22.5 ± 30.8	42.6 ± 35.6	1.02(1.01–1.03,p<0.001)	1.01(1.00–1.03,p=0.129)
AR/PR	Mean ± SD	32.4 ± 32.6	48.6 ± 34.4	1.01(1.01–1.02,p<0.001)	0.98(0.95–1.00,p=0.039)

Abbreviations: pCR, pathological complete response; OR, odds ratio; CI, confidence interval; AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; AR/ER, ratio of AR expression to ER expression; AR/PR, ratio of AR expression to PR expression. Data are presented as n (%) unless otherwise indicated.

Association Between AR Expression and Clinicopathological Features

Univariate linear regression analysis revealed that AR expression was significantly associated with ER expression (P<0.05) and marginally associated with PR expression (P=0.05). However, these associations did not remain statistically significant in the multivariate analysis (Table 3). Scatter plots with Spearman correlation analysis further showed no significant correlation between AR and ER expression, but a weak positive correlation between AR and PR expression (Supplementary Figures S2 and S3).

Table 3 Univariable and Multivariable Linear Regression Analyses of Factors Associated with AR Expression in the Overall HER2-Positive Breast Cancer Cohort

		Coefficient (Univariable)	**Coefficient (Multivariable)**
Age	[26,83]	0.39(−0.09–0.86, p=0.113)	
BMI	[15,33.3]	0.53(−0.81–1.86, p=0.439)	
Menstruation	Premenopause(N=86)		
	Menopause(N=124)	1.39(−7.44–10.23, p=0.756)	
Multifocal	No(N=145)		
	Yes(N=65)	0.01(−9.39–9.40, p=0.999)	
T	T1(N=22)		
	T2(N=148)	−8.32(−22.71–6.06, p=0.225)	
	T3(N=28)	−12.44(−30.37–5.50, p=0.173)	
	T4(N=12)	−8.03(−30.63–14.57, p=0.484)	
N	N0(N=42)		
	N1(N=83)	−1.62(−13.58–10.34, p=0.790)	
	N2(N=49)	−2.41(−15.70–10.87, p=0.720)	
	N3(N=36)	−5.20(−19.55–9.15, p=0.476)	
Grade	G1(N=3)		
	G2(N=167)	−19.14(−55.71–17.42, p=0.303)	
	G3(N=40)	−24.83(−62.41–12.74, p=0.194)	
ER	[0,100]	0.14(0.01–0.27, p=0.038)	0.09(−0.08–0.26, p=0.293)

(*Continued*)

Table 3 (Continued).

		Coefficient (Univariable)	Coefficient (Multivariable)
PR	[0,95]	0.19(0.00–0.39, p=0.050)	0.11(−0.15–0.36, p=0.411)
HER2	2+FISH+(N=42)		
	3+(N=168)	2.44(−8.41–13.30, p=0.658)	
Ki-67	[5,90]	−0.11(−0.36–0.14, p=0.395)	
Axillary metastases	No(N=91)		
	Yes(N=119)	−3.92(−12.67–4.83, p=0.378)	

Abbreviations: AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor; CI, confidence interval.

Subgroup Analysis

For subgroup and survival analyses, patients were dichotomized according to the ROC-derived optimal cutoff for AR expression (45%), yielding 128 patients in the high-AR group and 82 in the low-AR group. In HER2-stratified analyses, the pCR rate was numerically higher in the high-AR group than in the low-AR group in both HER2 2+ and HER2 3+ subgroups, but the differences were not statistically significant (HER2 2+: 33.3% vs. 16.7%, P = 0.299; HER2 3+: 62.5% vs. 51.6%, P=0.198; Figure 2).

In HR-stratified analyses, among HR-negative patients (N=129), high AR expression was significantly associated with a higher pCR rate than low AR expression (68.9% vs. 50.9%, P=0.045; Figure 3A). By contrast, among HR-positive patients (N=81), no significant difference in pCR rate was observed between the high- and low-AR groups (40.7% vs. 29.6%, P=0.465; Figure 3B). Overall, these results indicate that the association between elevated AR expression and improved pathological response was mainly confined to the HR-negative subgroup.

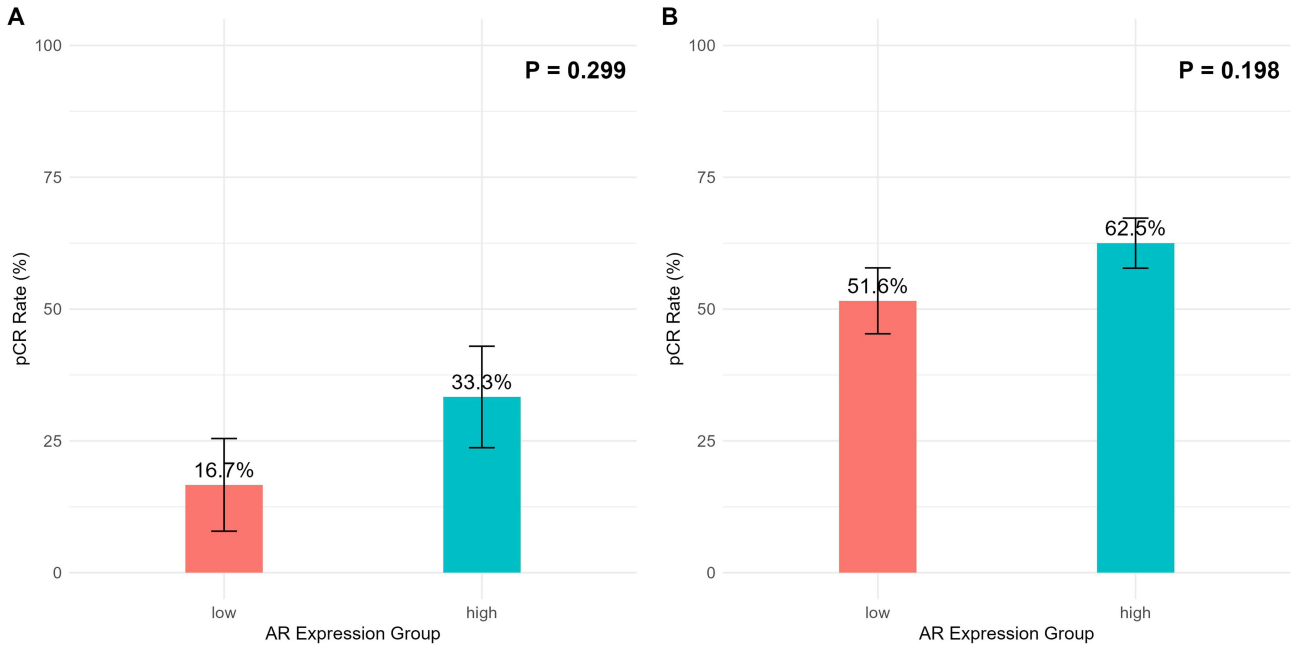

Figure 2 Comparison of pathological complete response rates according to AR expression in HER2-stratified subgroups. (**A**) Comparison of pCR rates between high- and low-AR expression groups in patients with HER2 2+ disease with FISH-confirmed amplification. (**B**) Comparison of pCR rates between high- and low-AR expression groups in patients with HER2 3+ disease.
Abbreviations: AR, androgen receptor; pCR, pathological complete response; FISH, fluorescence in situ hybridization.

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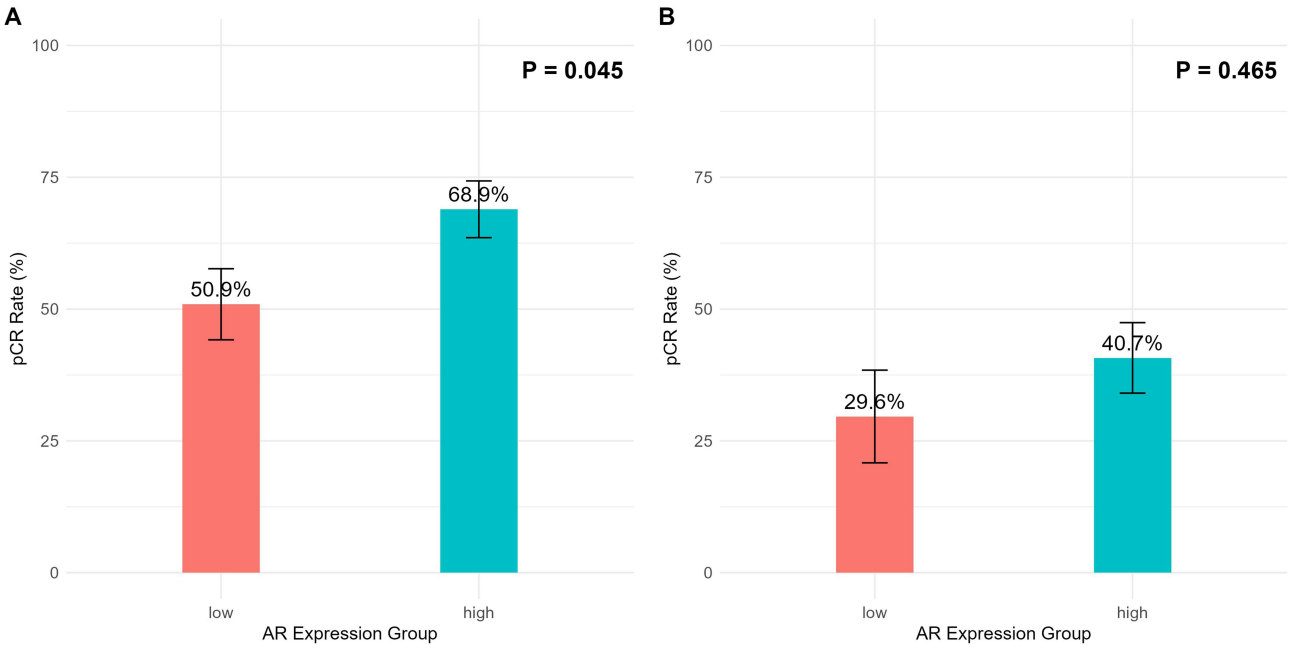

Figure 3 Comparison of pathological complete response rates according to AR expression in hormone receptor–stratified HER2-positive subgroups. (**A**) Comparison of pCR rates between high- and low-AR expression groups in HR−/HER2+ patients. (**B**) Comparison of pCR rates between high- and low-AR expression groups in HR+/HER2 + patients.

Abbreviations: AR, androgen receptor; HR, hormone receptor; pCR, pathological complete response.

Survival Analysis

As of February 2025, the median follow-up duration was 686 days (interquartile range [IQR], 433–955 days). Kaplan–Meier analysis showed that, in the overall HER2-positive cohort, there were no statistically significant differences in disease-free survival (DFS) or overall survival (OS) between the high- and low-AR expression groups. In the overall population, the estimated DFS probability was 97.0% in the high-AR group and 88.8% in the low-AR group (P=0.0838; Figure 4A), while the estimated OS probability was 93.4% and 86.6%, respectively (P=0.3119; Figure 4B).

In the HR-negative subgroup, patients with high AR expression had significantly better DFS than those with low AR expression (97.6% vs. 85.5%, P=0.0323; Figure 4C). However, no significant difference in OS was observed between the two groups (98.6% vs. 80.1%, P=0.2182; Figure 4D). In contrast, among HR-positive patients, neither DFS nor OS differed significantly according to AR expression level. The estimated DFS probabilities were 96.3% in the high-AR group and 94.4% in the low-AR group (P=0.9516; Figure 4E), and the estimated OS probabilities were 83.3% and 94.1%, respectively (P=0.9609; Figure 4F).

Discussion

HER2-targeted therapies, particularly anti-HER2 agents, have become integral across all stages of treatment for HER2-positive breast cancer. Numerous clinical trials have demonstrated that dual-targeted neoadjuvant therapy with trastuzumab and pertuzumab significantly increases pCRs and improves long-term prognosis in this patient population.[10–13,20] However, despite these advances, a substantial proportion of patients (approximately 35–60%) do not experience optimal benefit from current therapeutic strategies.[21] Increasing evidence suggests that the efficacy of neoadjuvant therapy is closely linked to long-term survival outcomes among HER2-positive breast cancer patients.[22,23] This study investigated AR—a commonly expressed and readily assessable biomarker—as a potential predictor of neoadjuvant treatment response in the HER2-positive subtype.

Recent research has highlighted AR's close association with breast cancer initiation, progression, and prognosis. Several studies have described molecular crosstalk between the AR signaling pathway and HER2 signaling.[24,25] In HER2-positive breast cancer models, preclinical data suggest a bidirectional positive feedback mechanism: AR regulates

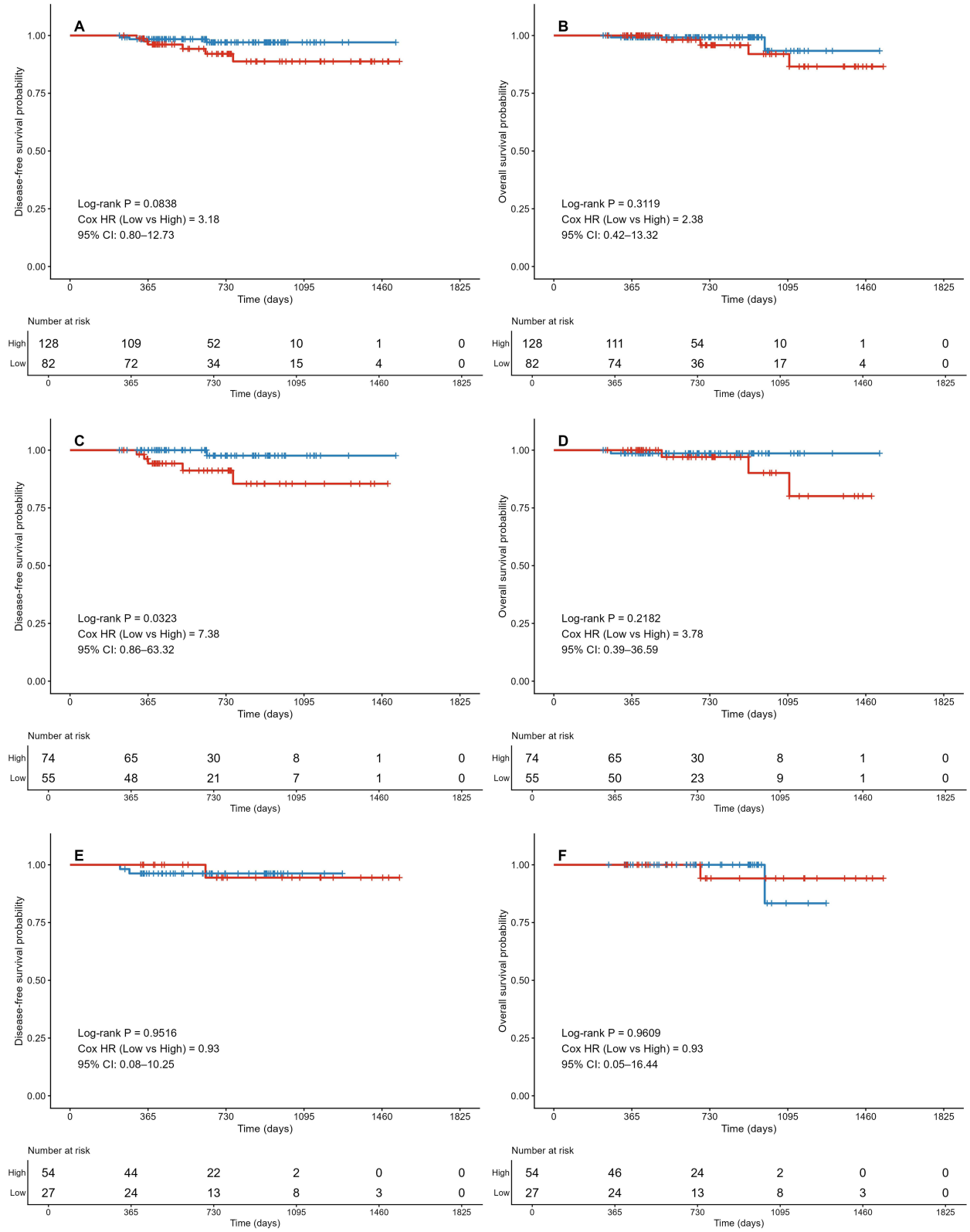

Figure 4 Kaplan–Meier analyses of disease-free survival and overall survival according to AR expression in HER2-positive breast cancer. (**A and B**) Disease-free survival (DFS) and overall survival (OS) in the overall HER2-positive cohort stratified by AR expression. (**C and D**) DFS and OS in the HR−/HER2+ subgroup. (**E and F**) DFS and OS in the HR+/HER2+ subgroup. Patients were dichotomized into high- and low-AR expression groups according to the ROC-derived cutoff.

Abbreviations: AR, androgen receptor; DFS, disease-free survival; OS, overall survival; HR, hormone receptor; ROC, receiver operating characteristic.

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WNT7B expression to promote nuclear translocation of β-catenin, where an AR/β-catenin complex interacts with FOXA1 to upregulate HER3 transcription.[26] The increased HER3 dimerizes with HER2, strongly activating the PI3K/AKT pathway and oncogenes such as MYC—thus promoting tumor proliferation.[26] Concurrently, activated HER2 signaling may enhance AR transcriptional activity via the ERK pathway—creating a loop that continually amplifies both signals. This interplay suggests tumors with high AR expression may exhibit greater dependency on HER2-driven signaling; consequently, they could be more sensitive to anti-HER2 therapies. When these critical pathways are blocked by targeted treatments, such tumors may be more likely to achieve pCR.[26,27]

Consistent with this hypothesis and findings from previous studies, we observed higher pCR following neoadjuvant therapy among patients with strong HER2 3+ expression compared to those classified as HER2 2+(FISH+).[27] Our data also revealed that AR expression levels were significantly higher in patients achieving pCR than those who did not (OR: 1.01[1.00–1.02], P=0.034). This aligns with multiple clinical reports showing a positive correlation between elevated AR expression and better treatment response or prognosis in HER2+ breast cancer.[15,28] For instance, Akashi et al identified that significantly more patients in the AR-positive group achieved pCR compared to their AR-negative counterparts (P<0.001), and multivariate analysis confirmed that AR-positive remained an independent predictor for higher pCRs (P<0.001).[15] Similarly, a multicenter study involving 258 cases found significantly higher pCRs among those with high versus low AR expression (P=0.031).[16] Although our subgroup analysis did not detect statistically significant differences in pCRs between high- and low-AR subgroups within either the HER2 3+ or the FISH-confirmed HER2 2+ populations specifically (Figure 2), our overall results support prior observations: AR expression does not correlate directly with categories of HER2 status itself (P=0.685).[16] Such discrepancies across studies may reflect variations in criteria used for classifying AR status or differences in included histological subtypes within study cohorts; inconsistencies in assay methodology or patient demographics likewise may contribute to conflicting outcomes.

In our cohort, the relationship between AR expression and ER/PR expression appeared to be limited rather than strong. Univariable linear regression showed a positive association between ER and AR expression and a borderline association for PR, but neither remained significant after multivariable adjustment. Likewise, scatter plot analysis showed no significant correlation between AR and ER expression and only a weak positive correlation between AR and PR expression. This suggests that the clinical impact of AR may depend less on its simple quantitative correlation with ER or PR than on the relative balance among these receptors, which may partly explain the predictive value of the AR/ER and AR/PR ratios observed in our analysis. In this study, ER expression (OR: 0.98–0.99) and PR expression (OR: 0.96–1.00) were also identified as factors influencing the efficacy of neoadjuvant therapy. However, previous reports on the predictive value of AR in HER2-positive breast cancer have yielded inconsistent results when stratified by hormone receptor status. For example, Akashi et al found that the proportion of patients achieving pCR was significantly higher in the AR-positive group than in the AR-negative group, regardless of hormone receptor status (p<0.001). In contrast, Shi et al reported no significant difference in pCRs between AR-positive and AR-negative groups among either HR−/HER2+ or HR+/HER2+ breast cancer patients.[29] In our subgroup analyses, we observed that within HR−/HER2+ breast cancers, high AR expression was associated with a higher pCR rate and better DFS. By contrast, in patients with HR+/HER2+ tumors, no significant differences in treatment response or survival were observed according to AR expression level. This suggests that high AR expression may be associated with improved neoadjuvant treatment response and longer DFS in this subset. These findings highlight the importance of considering ER and PR influence on AR levels and their subsequent impact on treatment outcomes. Prior studies have reported an AR positivity rate of approximately 74.8% in ER-positive breast cancers, compared with about 31.8% in ER-negative cases.[7,8] A similar trend was evident in our cohort: 66.67% of patients in the hormone receptor–positive subgroup exhibited high AR expression, compared to 57.36% among the hormone receptor–negative subgroup. Mechanistically, in ER-positive breast cancer, AR has been shown to interfere with ER-dependent transcription by competing for estrogen response element (ERE) binding sites or shared transcriptional co-regulators.[30] Experimental studies suggest that AR and ER signaling may interact in breast cancer, and AR has been shown to inhibit ERα transactivation and estrogen-stimulated growth in cell models, partly through binding to a subset of estrogen-responsive elements. In addition, higher AR/ER ratios have been associated with proliferation-related features in some ER-positive cohorts.[24,30,31] PR status can further influence this dynamic.[32] In our study, univariate analysis revealed that both the AR/ER and AR/PR ratios were significant predictors of neoadjuvant

therapy efficacy (OR:1.01–1.03,P<0.01), with higher ratios correlating with increased pCR. However, it is important to note that in Luminal B or ER-positive breast cancers, a high AR/ER ratio has also been associated with poorer prognosis. For example, Rangel et al reported that patients with an AR/ER ratio ≥2 were more likely to present with the Luminal B subtype characterized by higher proliferative activity and adverse outcomes.[31] This apparent paradox suggests that the biological role of AR may vary depending on whether tumor growth is driven primarily by HER2 or ER signaling pathways. Specifically, in HER2-driven disease, high AR expression may enhance sensitivity to anti-HER2 therapies; whereas in ER-driven tumors, elevated AR could potentially promote resistance to endocrine therapy or contribute to tumor progression. Future research should further elucidate the complex interplay among AR, ER, and HER2—especially regarding how these receptors interact within overlapping contexts of endocrine and anti-HER2 treatment. From a clinical perspective, our findings suggest that AR expression may be associated with differential response to neoadjuvant therapy in HER2-positive breast cancer, particularly within the HR-negative subgroup. However, this association was not consistently observed in the overall cohort or in the HR-positive subgroup, and therefore should be interpreted with caution. Given the retrospective design, single-center setting, relatively small sample size, and short follow-up duration, our results should be regarded as exploratory rather than practice-changing. At present, AR assessment may provide additional biological and prognostic information, but it is not sufficient to support routine clinical decision-making on its own. Further prospective studies with larger cohorts and standardized AR evaluation are needed to determine whether AR can be incorporated into treatment stratification for HER2-positive breast cancer.

Although high Ki-67 and high histological grade are traditionally associated with biologically aggressive disease and are often linked to an unfavorable baseline prognosis, their relationship with response to neoadjuvant therapy in HER2-positive breast cancer is more complex.[33,34] Highly proliferative tumors may also be more sensitive to chemotherapy and anti-HER2 treatment, which partly explains why higher Ki-67 has frequently been associated with increased pCR rates in this setting. In line with this, Karatli identified high Ki-67 as a significant predictor of pCR in HER2-positive breast cancer receiving neoadjuvant therapy. However, clinicopathological markers such as Ki-67 and histological grade do not fully capture the biological heterogeneity of HER2-positive disease. As highlighted by Schettini et al, molecular features such as the HER2-enriched subtype are associated with a substantially higher likelihood of achieving pCR beyond hormone receptor status and chemotherapy use.[35] Therefore, the lack of statistical significance for Ki-67 and histological grade in our cohort should not be interpreted as evidence against their biological relevance, but rather as an indication that response to neoadjuvant therapy in HER2-positive breast cancer is multifactorial and may not be consistently predicted by conventional proliferation-related markers alone.

This study has several limitations. First, the sample size was relatively small and drawn from a single center, which may introduce selection bias. Additionally, due to economic and policy constraints, not all patients received dual-targeted therapy. This variability in treatment limits the generalizability of the findings and warrants caution when applying these results to broader populations. Although we observed a significant association between AR expression and treatment response, it remains unclear whether these findings can be replicated in larger, more diverse cohorts.

Second, AR expression was evaluated using immunohistochemistry; however, there is currently no universally accepted definition of high AR expression. Variations in antibody selection, staining protocols, and interpretation criteria can influence AR testing outcomes. Therefore, technical standardization of AR assessment is essential to improve reproducibility and clinical applicability.[36,37] The lack of consensus regarding cutoff values—for example, using 1% versus 10% as the threshold—can significantly alter the reported rate of AR positivity.

Third, as a retrospective study, our analysis reveals only an association between AR expression and treatment response; causality cannot be established. While we propose mechanistic insights based on existing literature, these remain hypothetical without direct experimental validation. Thus, further prospective studies and mechanistic laboratory investigations are required to clarify causal relationships. Fourth, the relatively short follow-up duration meant that neither DFS nor OS reached median survival in this cohort. Extended longitudinal follow-up will be necessary to assess the true impact of steroid hormone receptors on endocrine therapy outcomes and long-term survival among HER2-positive breast cancer patients.

Conclusion

This study evaluated the association of AR expression with neoadjuvant treatment response and survival outcomes in HER2-positive breast cancer. Higher AR expression was associated with an increased likelihood of achieving pCR in the overall analysis, and exploratory subgroup analyses suggested that this association was mainly concentrated in the HR −/HER2+ subgroup, in which higher AR expression was also associated with better DFS. In contrast, no significant survival differences according to AR expression were observed in the overall cohort, and no clear benefit was identified in the HR+/HER2+ subgroup.

Taken together, these findings suggest that AR expression may be worthy of further evaluation as an exploratory predictive factor in HER2-positive breast cancer, particularly in HR-negative disease. However, given the retrospective nature of the study and the subgroup-specific nature of the findings, the clinical value of AR assessment remains preliminary and should be validated in larger prospective studies before being applied in routine practice.

Abbreviations

AJCC, American Joint Committee on Cancer; AR, androgen receptor; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BMI, body mass index; CSCO, Chinese Society of Clinical Oncology; DCIS, ductal carcinoma in situ; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ERE, estrogen response element; ERK, extracellular signal-regulated kinase; FISH, fluorescence in situ hybridization; FOXA1, forkhead box A1; HE, hematoxylin and eosin; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; HR, hormone receptor; IHC, immunohistochemistry; Ki-67, Ki-67 proliferation index; MYC, MYC proto-oncogene; NAT, neoadjuvant therapy; OR, odds ratio; OS, overall survival; PBS, phosphate-buffered saline; pCR, pathological complete response; PI3K, phosphatidylinositol 3-kinase; PR, progesterone receptor; TNBC, triple-negative breast cancer; VABB, vacuum-assisted breast biopsy; WHO, World Health Organization.

Data Sharing Statement

This study is based on confidential patient records collected retrospectively at our institution. Due to strict privacy protections, ethical restrictions, and institutional policies, the raw individual-level data cannot be shared publicly. Summary data relevant to the results are provided within the manuscript. Further data may be available upon reasonable request from the corresponding author, Dr. Haochen Yu, subject to approval by the relevant ethics committee and compliance with institutional data protection regulations.

Ethics Approval and Consent to Participate

This retrospective study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Approval No.: 2025-912-01). The requirement for informed consent was waived because the study involved the analysis of existing medical records and posed minimal risk to participants. All procedures were conducted in accordance with the Declaration of Helsinki. Patient data were anonymized and handled with strict confidentiality throughout the research process.

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Author Contributions

Cheng Tian and Jihan Qiu share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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