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ORIGINAL RESEARCH

Predictive and Prognostic Value of Androgen Receptor Expression Across All Molecular Subtypes in Patients with Breast Cancer Who Received Neoadjuvant-Treatment: Single-Center Retrospective Analysis

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Purpose: Androgen receptor (AR) expression is detectable in the majority of breast cancers across all molecular subtypes; however, its predictive value for pathological complete response (pCR) and its prognostic contribution to long-term survival in an all-comer neoadjuvant chemotherapy (NACT) cohort remain incompletely defined.

Patients and Methods: In this retrospective, single-center cohort study, 196 patients with early-stage breast cancer across all molecular subtypes received NACT at Istanbul Medipol University Hospital between 2013 and 2025. Pre-NACT AR expression was assessed by immunohistochemistry (SP107 clone) with a pre-specified threshold of 50% applied. The primary endpoint was event-free survival (EFS); 35 EFS events occurred. Multivariable Cox proportional hazards regression (three pre-specified covariates), Kaplan–Meier analyses, and competing risk modeling were performed.

Results: AR ≥50% was detected in 139 patients (70.9%). The overall pCR rate was 30.1% (59/196). AR ≥50% was independently associated with superior EFS in the multivariable model (hazard ratio [HR]=0.396, 95% CI: 0.199–0.786; p=0.008). The estimated 5-year EFS was 82.2% vs 69.8% for AR ≥50% versus AR <50% patients (log-rank p=0.031). A statistically significant AR × pCR status interaction was identified (p=0.032), with the prognostic gradient of AR most pronounced among patients with residual disease (5-year EFS 77.9% vs 52.9% for AR-high vs AR-low). In HR+/HER2− disease, AR-low status paradoxically predicted higher pCR rates (median AR 40% vs 90%; p=0.027) but inferior long-term EFS, consistent with a "luminal paradox". Subgroup analyses are exploratory and hypothesis-generating.

Conclusion: In this retrospective single-center cohort, pre-NACT AR ≥50% was independently associated with superior EFS in the multivariable model, complementary to pCR status. A formally significant AR × pCR interaction supports that AR provides differential prognostic information in the residual-disease population. These hypothesis-generating findings support prospective evaluation of AR-stratified risk assessment after NACT.

Keywords: androgen receptor, breast cancer, neoadjuvant chemotherapy, pathological complete response, event-free survival, luminal paradox

Introduction

Breast cancer is the most frequently diagnosed malignancy and a leading cause of cancer-related mortality in women worldwide.[1,2] Neoadjuvant chemotherapy (NACT) is now integral to the management of early stage breast cancer, enabling

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breast-conserving surgery and providing an in vivo assessment of chemosensitivity.[3] Pathological complete response (pCR) is a well-established surrogate endpoint associated with a 69% reduction in event-free survival (EFS) hazard in pooled analyzes.[4,5] However, most patients, particularly those with hormone receptor-positive (HR+) disease, do not achieve pCR, underscoring the need for biomarkers that can stratify outcomes within this residual-disease population.[6]

The androgen receptor (AR) is expressed in 70–90% of breast cancers across all molecular subtypes, with the highest prevalence in luminal disease and lowest in triple-negative breast cancer (TNBC).[7,8] The relationship between AR and pCR follows a subtype-specific, biologically intriguing pattern: in HR+/HER2- disease, AR positivity is associated with lower pCR rates, yet AR-positive patients with residual disease show superior long-term survival compared with AR-low counterparts - a phenomenon termed the "luminal paradox".[9–12] This dual, ostensibly contradictory role - AR as a marker of reduced chemosensitivity, yet favorable prognosis - has been corroborated across several retrospective and prospective cohorts.[9–12] In TNBC, AR expression defines the luminal androgen receptor (LAR) subtype, which is characterized by lower proliferative indices and lower pCR rates relative to AR-negative TNBC.[13–17]

A further underexplored dimension is the dynamic change in receptor expression between pretreatment biopsy and posttreatment surgical specimens. Receptor conversion after NACT, particularly loss of hormone receptor positivity, has been associated with an independent adverse prognostic impact in several cohorts,[18–20] prompting calls for routine post-NACT receptor reassessment.[21]

Despite this accumulating evidence, few studies have simultaneously evaluated the predictive (pCR) and prognostic (EFS) values of AR across all four molecular subtypes in a single all-comer cohort. Prior series have generally focused on individual subtypes, single endpoints, or have lacked paired pre/post-NACT biomarker data in the same patients. The independent prognostic contribution of AR specifically among patients who do not achieve pCR—the majority of HR+ patients—remains undercharacterized, and most existing series have been limited by short follow-up and the absence of residual-disease-specific analyses.

Therefore, we present a retrospective cohort of 196 patients with breast cancer across all molecular subtypes who received NACT at a single institution with a maximum follow-up of 136.8 months (median 36.7 months). Our objectives were (1) to evaluate the predictive value of pre-NACT AR expression for pCR, overall and by subtype; (2) to determine whether AR is an independent EFS prognostic factor after adjustment for pCR, nodal status, and molecular subtype; (3) to characterize the combined prognostic value of pCR and AR status; and (4) to assess post-NACT receptor dynamics in residual disease.

Materials and Methods

Study Design and Ethical Approval

This retrospective, single-center cohort study was conducted at Istanbul Medipol University Hospital, Turkey. Data were collected from the clinical records of patients who underwent NACT for early stage breast cancer between January 2013 and December 2025. This study was approved by the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (Decision No: 930; 31.07.2025). Given the retrospective design, individual informed consent was waived per the institutional policy. This study complied with the principles of the Declaration of Helsinki. All patient data were accessed and handled in accordance with applicable data protection regulations and institutional data governance policies. Patient data were de-identified prior to analysis, and patient privacy and confidentiality were maintained throughout the study.

Patient Selection

Eligible patients had histologically confirmed invasive breast carcinoma, completed a full course of NACT followed by curative-intent surgery, and had adequate pre-NACT core biopsy and postoperative specimens for immunohistochemical (IHC) analysis. Patients with metastatic disease at the time of diagnosis or those with incomplete NACT were excluded.

Immunohistochemical Assessment

All IHC analyses were performed at our institutional pathology laboratory. Estrogen receptor (ER) and progesterone receptor (PR) were scored as the percentage of positive nuclei (positivity ≥1%).[22] AR was evaluated using the SP107 clone (Ventana) and scored identically, and a prespecified 50% threshold was applied for primary analyses, consistent

with prior neoadjuvant literature, given the modest discriminatory performance of AR as a continuous biomarker in exploratory ROC analysis (Supplementary Figure S3). HER2 was scored 0–3+;[23] 2+ patients underwent silver in situ hybridization. Ki67 was scored as the percentage of positive nuclei (hot-spot method).[24]

Molecular Subtype Classification

Subtypes were assigned according to the St. Gallen 2021 criteria:[25] HR+/HER2-, HR+/HER2+, HR-/HER2+, and triple-negative breast cancer (TNBC).

Treatment

The NACT regimens followed contemporary guidelines (AC-T, dose-dense AC-T, AC-THP, TCHP, and KEYNOTE-522-based regimens for eligible TNBC).[26] Adjuvant decisions followed standard-of-care guidelines; capecitabine was administered per the CREATE-X criteria in residual HER2-negative disease.[27]

Outcome Definitions

Pathological complete response (pCR) was defined as ypT0/is ypN0.[28] The primary endpoint was event-free survival (EFS), the time from diagnosis to progression/recurrence (clinical or radiological), or death from any cause. Overall survival (OS) was defined as the secondary endpoint.

Statistical Analysis

Continuous variables were compared using the Mann–Whitney *U*-test or Wilcoxon signed-rank test (paired pre/post-NACT data); categorical variables were compared using the chi-square test or Fisher's exact test (for sparse categories with expected cell count <5). Spearman's rank correlation was used to assess pairwise associations between delta biomarker values. Survival analyses were performed using the Kaplan–Meier method with Log rank testing, and the multivariate Log rank test was applied for ≥3 group comparisons. To account for death as a competing event for disease progression, cumulative incidence functions (CIF) were estimated using the Aalen–Johansen estimator,[29,30] and cause-specific Cox proportional hazards models were used for regression analysis.[31,32] The incremental discriminatory contribution of AR was quantified using Harrell's concordance index (C-index)[33] across three nested Cox models. Bootstrap internal validation (200 iterations, Harrell's optimism-correction method) was performed to estimate the optimism-corrected C-index. In the multivariable Cox model, axillary nodal involvement was entered as an ordinal continuous variable representing the number of clinically involved axillary lymph nodes at baseline, assigned as 0 (cN0), 2 (cN1: 1–3 nodes), and 6 (cN2: 4–9 nodes), and 9 (cN3: ≥10 nodes; n=22) per AJCC staging categories; this ordinal nodal-burden score reflects the approximate mid-range node count per AJCC category, and the resulting HR=1.092 therefore represents the hazard ratio per unit increase in this score. The final model included three pre-specified covariates (AR status, pCR, axillary nodal score; EPV≈11.7),[34] selected a priori based on established biological and clinical relevance. A multiplicative AR × pCR interaction term was added to a separate model to formally test effect modification. The discriminatory performance of AR as a continuous biomarker was assessed using time-dependent AUC estimation (Heagerty–Sternberg IPCW estimator) across 12–84 months, comparing nested Cox models (Model A vs Model B; Supplementary Figure S5); Uno τ-concordance for Model B was 0.614 at 3 years and 0.634 at 5 years; a standard static ROC analysis is not appropriate for censored time-to-event data and was not used. Sensitivity analyses included: (i) EFS measured from date of surgery rather than diagnosis (guarantee-time correction; Supplementary Table S1); (ii) landmark analyses at 12 and 24 months[35] (Supplementary Table S2); (iii) Cox model adjusted for treatment era (2013–2017 vs 2018–2025; Supplementary Table S3); (iv) LASSO-penalized Cox regression (10-fold cross-validation; Supplementary Figure S6); (v) alternative AR thresholds (≥30%, ≥70%; Supplementary Table S5). An ordinal logistic regression model was used to assess the association between AR, tumor grade, and pre-NACT Ki67 with the four-category pathological response scale (Supplementary Table S4). For landmark analysis, follow-up time was reset at 12 and 24 months (Supplementary Table S2), excluding patients with events prior to the landmark. Reverse Kaplan–Meier estimation (Schemper–Smith method) was used to estimate the median potential follow-up time. No patients had missing AR IHC data; 2 patients had missing Ki67 (excluded from Ki67-specific analyses only). No imputation was performed. All

exploratory subgroup analyses (capecitabine interaction, receptor conversion) were interpreted as hypothesis-generating; no correction for multiple comparisons was applied. Analyses were performed using Python 3.12 (lifelines 0.30.3, scipy, statsmodels, scikit-learn; Python Software Foundation). A two-sided $p<0.05$ was considered statistically significant.

Results

Patient Characteristics

A total of 196 patients were included (median age, 46 years, IQR 38–54). The molecular subtypes were HR+/HER2− (41.3%), HR+/HER2+ (26.5%), HR−/HER2+ (14.3%), and TNBC (17.9%). The median potential follow-up by the reverse Kaplan–Meier method was 41.3 months (95% CI: 35.2–47.4). Of 196 patients, 68 (34.7%) were followed for ≥60 months; 5-year EFS estimates should be interpreted in the context of this limited proportion at risk beyond 5 years. Baseline characteristics stratified by AR expression are presented in Table 1; post-NACT biomarker dynamics, pathological response, and clinical outcomes are presented in Table 2.

Table 1 Baseline Characteristics of the Study Population According to AR Expression Level

Variable	Total (N=196)	AR ≥50% (n=139)	AR <50% (n=57)	p-value
Demographics				
Age, years—median (IQR)	46.0 (38.0–54.0)	47.0 (41.0–56.5)	43.0 (36.0–52.0)	*0.016*
Tumor size, cm—median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.1–4.0)	0.083
Histological Type				
IDC	154 (78.6%)	112 (80.6%)	42 (73.7%)	0.865
ILC	10 (5.1%)	6 (4.3%)	4 (7.0%)	
IC/Other	14 (7.1%)	9 (6.5%)	5 (8.8%)	
Mucinous	12 (6.1%)	8 (5.8%)	4 (7.0%)	
Mixed	6 (3.1%)	4 (2.9%)	2 (3.5%)	
Tumor Grade				
Grade 1	8 (4.1%)	7 (5.0%)	1 (1.8%)	*0.042*
Grade 2	86 (43.9%)	69 (49.6%)	17 (29.8%)	
Grade 3	97 (49.5%)	61 (43.9%)	36 (63.2%)	
Axillary Nodal Status				
cN0	73 (37.2%)	47 (33.8%)	26 (45.6%)	
cN1	62 (31.6%)	52 (37.4%)	10 (17.5%)	0.185
cN2	39 (19.9%)	24 (17.3%)	15 (26.3%)	
cN3	22 (11.2%)	16 (11.5%)	6 (10.5%)	
Molecular Subtype				
HR+/HER2-	81 (41.3%)	63 (45.3%)	18 (31.6%)	*<0.001*
HR+/HER2+	52 (26.5%)	45 (32.4%)	7 (12.3%)	
HR-/HER2+	28 (14.3%)	21 (15.1%)	7 (12.3%)	
TNBC	35 (17.9%)	10 (7.2%)	25 (43.9%)	

(*Continued*)

Table 1 (Continued).

Variable	Total (N=196)	AR ≥50% (n=139)	AR <50% (n=57)	p-value
Pre-nact IHC Markers				
ER (%)—median (IQR)	80.0 (0.0–95.0)	90.0 (7.5–95.0)	0.0 (0.0–80.0)	*<0.001*
PR (%)—median (IQR)	10.0 (0.0–80.0)	30.0 (0.0–82.5)	0.0 (0.0–10.0)	*<0.001*
AR (%)—median (IQR)	90.0 (25.0–100.0)	100.0 (90.0–100.0)	0.0 (0.0–5.0)	
Ki67 (%)—median (IQR)	40.0 (25.0–60.0)	40.0 (25.0–60.0)	40.0 (25.0–80.0)	0.061
AR positive (≥1%)	160 (81.6%)	139 (100.0%)	21 (36.8%)	
Neoadjuvant Regimen				
AC-T	40 (20.4%)	25 (18.0%)	15 (26.3%)	*0.003*
ddAC-T	56 (28.6%)	41 (29.5%)	15 (26.3%)	
AC-THP	68 (34.7%)	55 (39.6%)	13 (22.8%)	
TCHP	1 (0.5%)	1 (0.7%)	0 (0.0%)	
KN-522	18 (9.2%)	6 (4.3%)	12 (21.1%)	
AC-TH	11 (5.6%)	9 (6.5%)	2 (3.5%)	

Note: Italicized p-values indicate statistical significance ($p < 0.05$).

Table 2 Post-NACT Biomarker Dynamics, Pathological Response, and Clinical Outcomes (N=196)

Post-NACT IHC Markers (Residual Disease)				
AR (%)—median (IQR)	40.0 (0.0–92.5)	80.0 (0.0–98.8)	0.0 (0.0–40.0)	*<0.001*
ER (%)—median (IQR)	65.0 (0.0–95.0)	90.0 (0.0–100.0)	0.0 (0.0–73.8)	*<0.001*
PR (%)—median (IQR)	0.0 (0.0–30.0)	0.0 (0.0–40.0)	0.0 (0.0–5.0)	0.059
Ki67 (%)—median (IQR)	5.0 (0.0–25.0)	5.0 (1.0–15.0)	5.0 (0.0–50.0)	0.598
AR conversion: Stable Positive	95 (69.3%)	85 (83.3%)	10 (28.6%)	
AR conversion: AR Loss	21 (15.3%)	17 (16.7%)	4 (11.4%)	
AR conversion: AR Gain	10 (7.3%)	0 (0.0%)	10 (28.6%)	
AR conversion: Stable Negative	11 (8.0%)	0 (0.0%)	11 (31.4%)	
Pathological Response				
pCR (ypT0/is ypN0)	59 (30.1%)	37 (26.6%)	22 (38.6%)	0.137
No response	12 (6.1%)	10 (7.2%)	2 (3.5%)	0.143
Partial response	74 (37.8%)	58 (41.7%)	16 (28.1%)	
Near-complete	52 (26.5%)	35 (25.2%)	17 (29.8%)	
Adjuvant Treatment				
Endocrine therapy	98 (50.0%)	81 (58.3%)	17 (29.8%)	*<0.001*
Anti-HER2 maintenance	83 (42.3%)	69 (49.6%)	14 (24.6%)	*0.002*

(*Continued*)

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Table 2 (Continued).

Capecitabine	18 (9.2%)	5 (3.6%)	13 (22.8%)	*<0.001*
Immunotherapy	17 (8.7%)	5 (3.6%)	12 (21.1%)	*<0.001*
Outcomes				
Follow-up, months—median (IQR)	36.7 (15.7–73.5)	37.0 (16.9–74.6)	35.7 (14.1–66.5)	0.406
EFS event (progression or death)	35 (17.9%)	20 (14.4%)	15 (26.3%)	0.076
Disease progression/recurrence	29 (14.8%)	16 (11.5%)	13 (22.8%)	0.072
Death	21 (10.7%)	12 (8.6%)	9 (15.8%)	0.224

Notes: Pathological response categories: pCR (ypT0/is ypN0), absence of residual invasive cancer in breast and axillary nodes; near-complete response, minimal residual disease (ypT1mi or isolated nodal micrometastasis); partial response, residual invasive tumour without meeting pCR criteria; no response, no or minimal histological change. Italicized p-values indicate statistical significance ($p < 0.05$).
Abbreviations: AR, androgen receptor; ER, estrogen receptor; PR, progesterone receptor; IQR, interquartile range; pCR, pathological complete response; T-DM1, trastuzumab emtansine.

AR Expression and Distribution

Pre-NACT AR positivity (≥1%) was present in 160 patients (81.6%), and the median AR was 90% (IQR 25–100%). Applying the prespecified 50% threshold, 139 patients (70.9%) were AR-high. The AR-high prevalence varied markedly by subtype: 78% (HR+/HER2-), 87% (HR+/HER2+), 75% (HR-/HER2+), and 29% (TNBC) (Figure 1).

AR Expression and Pathological Complete Response

The overall pCR rate was 30.1% (59/196). AR was not a significant predictor of the pCR overall (p=0.137). However, in the HR+/HER2- subtype, AR was significantly lower in patients achieving pCR than in those with residual disease (median 40% vs 90%; p=0.027), consistent with the luminal paradox. No association was observed between HR+/HER2+, HR-/HER2+, or TNBC (all p>0.37) (Figure 2).

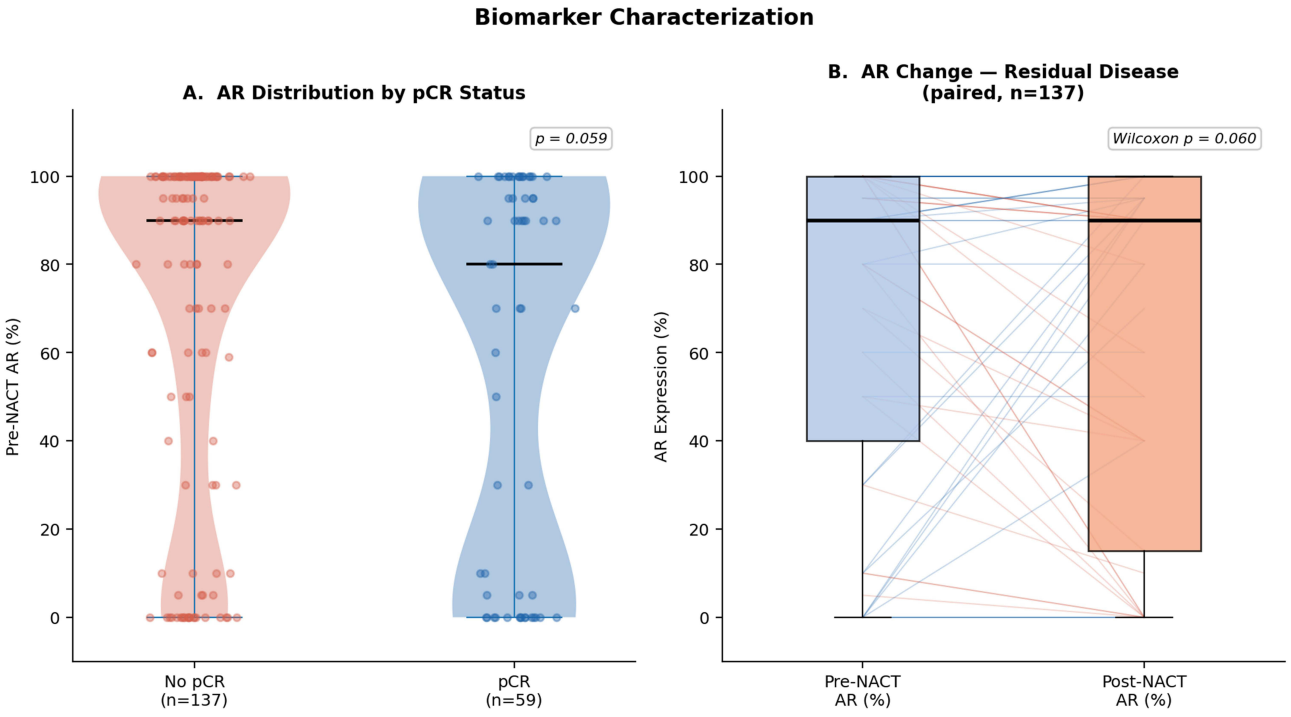
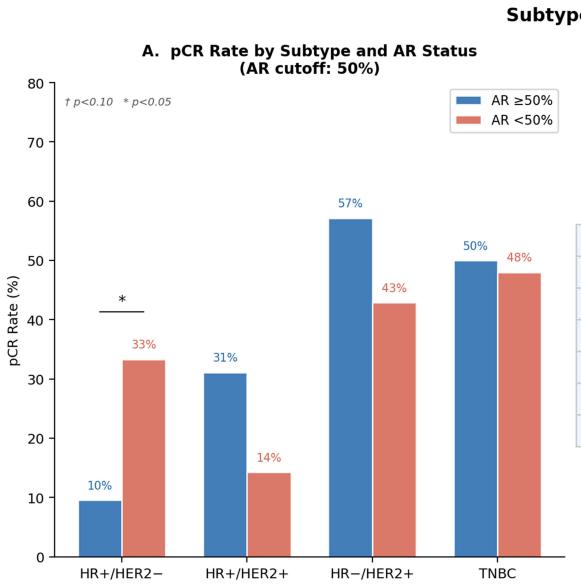


Figure 1 Androgen receptor expression patterns in relation to treatment response. (**A**) Pre-NACT AR expression by pCR status (p=0.059, Mann–Whitney U). (**B**) Paired pre- to post-NACT AR expression in residual disease (n=137; Wilcoxon p=0.060).
Abbreviations: AR, androgen receptor; NACT, neoadjuvant chemotherapy; pCR, pathological complete response.

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B. Summary Table by Molecular Subtype

	HR+/HER2− (n=81)	HR+/HER2+ (n=52)	HR−/HER2+ (n=28)	TNBC (n=35)
pCR rate	15%	29%	54%	49%
EFS events	15/81	8/52	8/28	4/35
5y-EFS (AR≥50%)	81.0%	85.6%	76.0%	90.0%
5y-EFS (AR<50%)	62.3%	40.0%	71.4%	84.2%
Log-rank p (EFS by AR)	0.185	0.101	0.142	0.999
AR positivity (≥50%)	78%	87%	75%	29%
Median AR pre-NACT (%)	90%	90%	60%	10%

Figure 2 Subtype-stratified pCR and survival outcomes by AR status. (**A**) pCR rates by molecular subtype and AR expression status (AR ≥50% vs <50%); *p<0.05. (**B**) Summary of pCR rates, EFS events, AR-stratified 5-year EFS, and AR prevalence across all molecular subtypes.
Abbreviations: EFS, event-free survival; pCR, pathological complete response.

AR Expression and Event-Free Survival

Over a median follow-up of 36.7 months (maximum 136.8 months), 35 EFS events occurred. AR ≥50% was associated with superior overall EFS (5-year EFS, 82.2% vs 69.8%; log-rank p=0.031) and in the HER2-positive subtype (83.1% vs 60.0%; p=0.005). In HR+/HER2− disease, the difference was numerically consistent (81.0% vs 62.3%) but not significant (p=0.185), reflecting the contrasting predictive and prognostic roles of AR in this subset (Figure 3A–C). In the univariate Cox model, AR ≥50% yielded HR=0.619 (95% CI: 0.281–1.365; p=0.235). This apparent discrepancy with the log-rank result reflects the different statistical sensitivities of the two tests: the Log rank test accumulates differences in survival probability across the entire follow-up and is particularly sensitive to the late progressive separation observed in our KM curves, whereas the Cox univariate HR represents a time-averaged estimate; with only ~14 events in the AR-low group, the Cox estimate carries wide CIs and limited power. Both statistics are correctly reported from the source analysis. The Schoenfeld residual test was not significant for AR (r=−0.114, p=0.514; Supplementary Figure S7), consistent with proportional hazards; however, this test also has limited power with 35 total events. The multivariable Cox result (HR=0.396, p=0.008) is not affected by this discrepancy.

Combined Impact of pCR and AR on EFS

Patients achieving pCR had excellent outcomes regardless of AR status (5-year EFS ≈100%). Among patients with residual disease, AR-high status was associated with markedly better EFS than AR-low status (77.9% vs 52.9%; Figure 3D). To formally test whether AR provides differential prognostic information by pCR status, a multiplicative AR × pCR interaction term was added to the Cox model. The interaction was statistically significant (p=0.032), supporting that AR's prognostic value differs between pCR achievers and patients with residual disease. This finding supports the clinical relevance of AR stratification in the residual-disease subgroup.

Multivariable Cox Regression and Sensitivity Analyses

In the final model, an AR ≥50% (HR=0.396, 95% CI 0.199–0.786; p=0.008), pCR (HR=0.238; p=0.020), and axillary nodal level (HR=1.092; p=0.035) were independently associated with EFS (model C-index=0.728; Figure 4 and Supplementary Table S6). The proportional hazards assumption was confirmed for AR (Schoenfeld r=−0.114, p=0.514) and axillary nodal score (r=0.278, p=0.106); pCR showed mild non-proportionality (r=0.629, p<0.001), consistent with attenuation of its protective effect at extended follow-up (Supplementary Figure S7). Bootstrap internal

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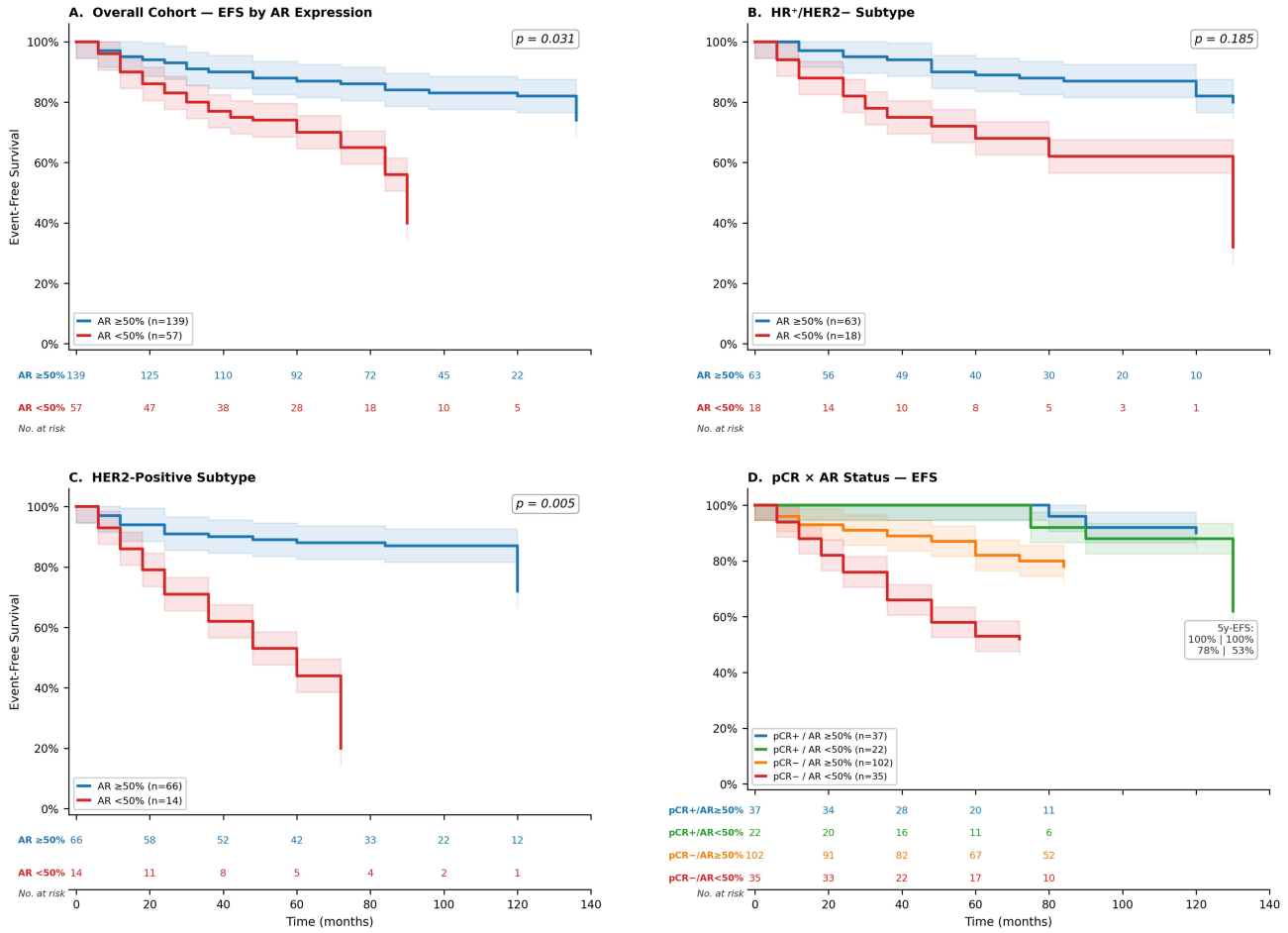


Figure 3 Event-free survival by androgen receptor expression after neoadjuvant chemotherapy. Kaplan-Meier EFS curves stratified by AR status (AR ≥50% [AR-high] vs AR <50% [AR-low]) in (**A**) the overall cohort (log-rank p=0.031; univariate Cox HR=0.619, 95% CI: 0.281–1.365, p=0.235), (**B**) HR+/HER2− subtype (p=0.185), (**C**) HER2-positive subtype (p=0.005), and (**D**) by pCR × AR composite groups (AR × pCR interaction p=0.032). Numbers at risk are shown below each panel. Tick marks indicate censored observations.

Abbreviations: AR, androgen receptor; EFS, event-free survival; pCR, pathological complete response.

validation confirmed minimal optimism (corrected C-index, 0.72). A pre-planned sensitivity analysis adjusted for molecular subtype confirmed that AR remained independently significant (HR=0.375, 95% CI 0.180–0.778; p=0.0085; model C-index=0.743), supporting that its prognostic value is not attributable to subtype confounding. Guarantee-time sensitivity analysis (EFS from surgery date) confirmed the AR association (HR=0.421, 95% CI 0.208–0.852, p=0.014; Supplementary Table S1). Landmark analyses at 12 and 24 months yielded consistent AR effect estimates (HR≈0.43, p<0.031 at both landmarks; Supplementary Table S2). Treatment-era sensitivity showed no significant era × AR interaction (p=0.61; Supplementary Table S3). Time-dependent AUC (Heagerty–Sternberg IPCW) demonstrated consistent discriminatory improvement with AR across all time horizons (ΔiAUC ≈ 0.038; Supplementary Figure S5). LASSO-penalized Cox regression (10-fold CV) retained exclusively AR expression, pCR, and axillary LN—concordant with the primary model (Supplementary Figure S6).

Competing risk analysis confirmed that AR's protective effect was specific to disease progression rather than competing mortality (5-year cumulative incidence of progression, 14.9% vs 28.3%; cause-specific HR=0.362, p=0.008; Supplementary Figure S2A). Overall survival showed a concordant but non-significant trend favoring AR-high patients (92.3% vs 82.1% at 5 years; p=0.099; Supplementary Figure S1C), reflecting still-maturing survival data. A formal multiplicative interaction test confirmed significant AR × pCR effect modification (interaction p=0.032; Supplementary Table S7): among pCR achievers, 5-year EFS was 100% regardless of AR status, whereas in patients with residual disease, AR expression remained a prognostic discriminator (AR-high: 78% vs AR-low: 53%).

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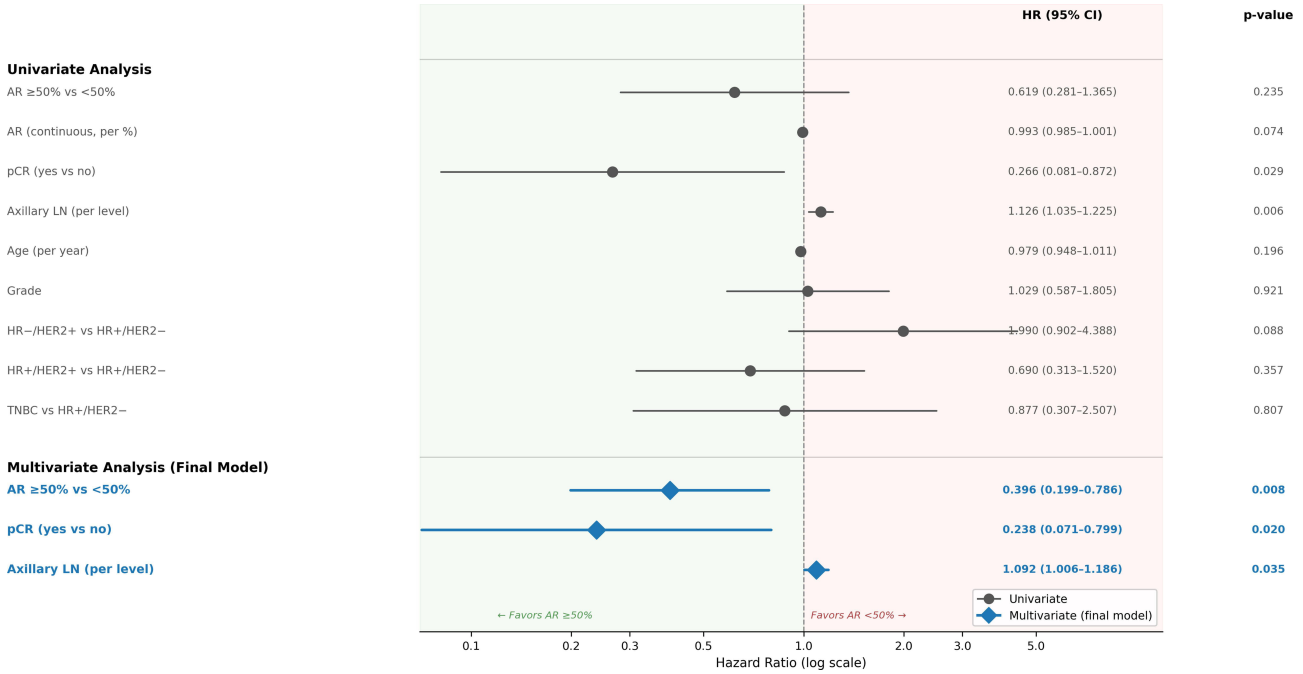


Figure 4 Forest plot of Cox proportional hazards regression for event-free survival. Upper panel: univariate analysis (AR ≥50% HR=0.619, 95% CI: 0.281–1.365, p=0.235; note: log-rank p=0.031 for the same comparison—see text for explanation of the discrepancy). Lower panel: final multivariable model (AR ≥50%, pCR status, axillary nodal score; model C-index=0.728, bootstrap-corrected 0.72).
Abbreviations: HR, hazard ratio; CI, confidence interval; LN, lymph node.

Post-NACT receptor dynamics in residual disease (n=137) showed significant reductions in PR (median 20%→1%; Wilcoxon p<0.001) and Ki67 (median 35%→10%; p<0.001), while AR (median 90%→40%; p=0.060) and ER (p=0.462) remained comparatively stable (Supplementary Figure S1A). Delta values across markers were essentially uncorrelated (Spearman rho<0.08 for all pairs). AR conversion categories among residual-disease patients were stable positive (n=95, 69.3%), AR loss (n=21, 15.3%), AR gain (n=10, 7.3%), and stable negative (n=11, 8.0%). However, the multivariate Log rank test across these groups was not significant (p=0.374; Supplementary Figure S1B). ER conversion occurred in 6/137 patients (4.4%) and was associated with a worse 5-year EFS (33.3% vs 74.3%; p=0.040), although this was based on a very small number of events. Competing risk analysis confirmed that AR's protective association of AR was specific to disease progression (5-year cumulative incidence of progression 14.9% vs 28.3%; cause-specific HR=0.362, p=0.008) rather than competing mortality (HR=0.635; p=0.610). Bootstrap-corrected C-index for the multivariable model was 0.72 (200 iterations), indicating minimal optimism. Twenty-one deaths were recorded; the estimated 5-year overall survival was 92.3% for AR ≥50% versus 82.1% for AR <50% patients (p=0.099). In an exploratory analysis of adjuvant capecitabine in residual disease, the Cox interaction term between capecitabine and AR status showed a trend that did not reach significance (p=0.071; Supplementary Figure S2B); given the small treated subgroups (n=5 and n=13, total n=18), this finding is hypothesis-generating only. Full methodological details for these analyses are provided below (Methods); the corresponding figures are provided in the Supplementary Information.

Discussion

Consistent with prior neoadjuvant studies,[9–12] our findings confirm that pre-NACT AR expression ≥50% is independently associated with superior EFS (HR=0.396; p=0.008) in a contemporaneous all-comer cohort spanning all four molecular subtypes. This confirmatory analysis extends the evidence base in several respects: the inclusion of paired pre-/post-NACT biomarker data in the same cohort; characterization of the prognostic gradient specifically within the residual-disease population; and formal demonstration that the AR × pCR interaction is statistically significant (p=0.032), establishing effect modification rather than relying on descriptive stratification alone. The prognostic benefit was most

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pronounced among patients with residual disease, where AR status defined a 25 percentage-point EFS gradient (77.9% vs 52.9%), consistent with a clinically meaningful prognostic gradient in the majority HR+ non-pCR population.

The inverse relationship between AR and pCR specifically in HR+/HER2- disease, alongside its favorable prognostic role, reproduces the "luminal paradox" described in the GeparTrio trial, where AR-positive tumors had lower pCR (12.8% vs 25.4%) yet better survival, particularly among non-pCR patients.[12] This may reflect AR's role in promoting luminal differentiation and suppressing the proliferative, chemosensitive phenotype;[7] AR-high luminal tumors are therefore less likely to achieve pCR but retain more indolent biology. Comparable findings have been reported in Chinese cohorts, where AR positivity independently predicted improved DFS in HR+/HER2- and HR+/HER2+ disease.[10,20] No significant AR-pCR association was observed in the HER2-positive or TNBC subgroups, plausibly reflecting the dominant effect of dual HER2 blockade and limited AR-high prevalence in TNBC (29%).

The receptor dynamics observed showed significant decreases in PR and Ki67, with comparatively stable AR and ER, and very weak correlations between marker changes (Spearman rho <0.08), supporting comprehensive post-NACT biomarker reassessment rather than reliance on any single marker 21. Competing risk analysis indicated that the AR–EFS association was specific to disease progression as a competing event (5-year cumulative incidence 14.9% vs 28.3%; cause-specific HR=0.362, p=0.008) rather than to competing mortality (HR=0.635; p=0.610), consistent with (rather than establishing) a role for AR in tumor biology. This observational finding does not permit causal inference.

Clinically, the pCR × AR stratification identifies AR-low residual disease as the highest-risk subgroup in which intensified adjuvant strategies (capecitabine, CDK4/6 inhibitors, or AR-targeted agents) merit prospective evaluation. AR-targeted agents, such as enzalutamide, have shown activity in AR-positive triple-negative and ER-positive disease,[36,37] though our highest-risk (AR-low) patients may not benefit from AR-directed approaches and could instead require alternative escalation strategies.

This study has several strengths: inclusion of all molecular subtypes within one cohort, maximum follow-up of 136.8 months (median 36.7 months), capturing both early and late recurrences in patients enrolled from 2013 onwards, paired pre/post-NACT biomarker data, and a sensitivity analysis supporting that AR's effect is not attributable to subtype confounding.

This study has several important limitations that must be considered when interpreting the findings. First, the retrospective, single-center design limits generalizability and introduces unmeasured confounding. Second, the eligibility criterion of completing NACT and undergoing curative-intent surgery may introduce guarantee-time selection bias, as patients who progressed on NACT, died before surgery, or became inoperable were excluded; a sensitivity analysis measuring EFS from date of surgery showed consistent results (AR≥50% HR=0.421; p=0.014; Supplementary Table S1). Third, with only 35 EFS events (EPV≈11.7), the study is at the lower margin of adequate power for three-covariate Cox regression; the wide confidence intervals throughout the analyses reflect this limitation, and subtype-specific findings are particularly underpowered. Fourth, the cohort spans 2013–2025, encompassing substantial treatment-era heterogeneity (introduction of dual HER2 blockade, KEYNOTE-522-based regimens, and evolving adjuvant standards); a treatment-era sensitivity analysis confirmed that AR remained significant (HR=0.411; p=0.014; Supplementary Table S3), though residual era-related confounding cannot be excluded. Fifth, the ≥50% AR threshold was pre-specified based on prior neoadjuvant literature rather than derived from formal cutoff validation; AR thresholds vary widely across published studies (≥1% to ≥90%), and sensitivity analyses at ≥30% and ≥70% showed consistent directional but attenuated associations. Sixth, multiple exploratory comparisons were conducted without correction for multiplicity; all subgroup analyses (capecitabine interaction, receptor conversion, subtype-specific pCR associations) must be considered hypothesis-generating. Seventh, the proportional hazards assumption was not fully met for pCR (mild non-proportionality beyond five years); sensitivity analyses yielded consistent results. Eighth, the median follow-up of 36.7 months (reverse KM median 41.3 months) limits the maturity of both EFS and OS data, with only 34.7% of patients followed for ≥60 months; the maximum follow-up of 136.8 months should not be interpreted as evidence of overall cohort maturity. Finally, this cohort predates routine adjuvant CDK4/6 inhibitor use (monarchE, NATALEE), which may modify the adjuvant risk-stratification landscape in future cohorts.

Conclusion

In this retrospective single-center cohort, pre-NACT AR expression ≥50% was independently associated with superior EFS in the multivariable model, complementary to pCR status. A statistically significant AR × pCR interaction (p=0.032) formally supports that AR provides differential prognostic information in the residual-disease population. These hypothesis-generating findings support prospective evaluation of AR-stratified risk assessment after NACT; however, prospective external validation is required before AR can be incorporated into routine post-NACT risk stratification.

Abbreviations

AR, androgen receptor; CI, confidence interval; EFS, event-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor-positive; IHC, immunohistochemistry; IQR, interquartile range; NACT, neoadjuvant chemotherapy; OS, overall survival; pCR, pathological complete response; PR, progesterone receptor; TNBC, triple-negative breast cancer.

Data Sharing Statement

The data underlying this study potentially contain identifying patient information and are, therefore, not publicly available. De-identified data may be made available by the corresponding author upon reasonable request and subject to institutional approval.

Ethics Approval and Informed Consent

This study was approved by the Non-Interventional Clinical Research Ethics Committee of the Istanbul Medipol University (Decision No: 930; date: July 31, 2025). Given the retrospective nature of the study, the requirement for individual informed consent was waived in accordance with institutional policy. This study was conducted in compliance with the principles of the Declaration of Helsinki. All patient data were accessed and handled in accordance with applicable data protection regulations and institutional data governance policies. Patient data were de-identified prior to analysis, and patient privacy and confidentiality were maintained throughout the study.

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During the preparation of this work, generative AI tools (including large language models) were used to assist with: (1) statistical analysis scripting in Python; (2) generation of data visualization code; and (3) language refinement (grammar, clarity, and phrasing) of the English-language manuscript. No AI tool was used to generate scientific content, interpret data, draw conclusions, or make editorial decisions. All AI-assisted outputs were reviewed, verified, and approved by the authors, who take full and sole responsibility for the accuracy, integrity, and content of the final manuscript.

Author Contributions

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 report no conflicts of interest in this work.

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