Comprehensive Analysis of Neoadjuvant Anti-HER2 Therapy Insensitivity in HER2-Positive Breast Cancer Patients

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Purpose

HER2-targeted therapy has been incorporated into the standard neoadjuvant treatment regimen for HER2-positive early-stage breast cancer, yet a subset of patients show limited pathological response. Early identification of these treatment-insensitive individuals may improve therapeutic decision-making.

Methods

This retrospective study included 13,004 HER2-positive breast cancer patients from the National Cancer Database (2010-2022) who received neoadjuvant chemotherapy plus HER2-targeted therapy. Neoadjuvant treatment (NAT) insensitivity was defined as the absence of pathologic T-stage downstaging after treatment. Pathological complete response (pCR) was defined as no residual invasive carcinoma in the breast and axillary lymph nodes (ypT0/is, ypN0). Baseline characteristics and overall survival (OS) were compared between NAT-sensitive and NAT-insensitive groups. A multivariable logistic regression model was developed using significant clinicopathological variables. Categorical variables and interaction terms were also tested by the likelihood ratio test. Model performance was assessed using the area under the receiver operating characteristic curve (AUC), Hosmer-Lemeshow test, and calibration curves.

Table 1. Logistic regression with interaction identifying independent predictors of neoadjuvant treatment sensitivity.

Variable	Estimate (β)	OR (95%CI)	P-value
Intercept	1.163	3.199(1.232, 8.307)	0.017*
Age (year)	-0.019	0.981(0.977, 0.985)	<0.001**
Race (Ref: White)			0.094
Black	-0.139	0.877(0.747, 1.029)	0.106
Asian	0.211	1.235(0.954, 1.600)	0.110
Other	-0.148	0.862(0.597, 1.246)	0.429
Ethnicity:(Ref:Non-Hispanic)			
Hispanic/Other	0.088	1.092(0.900, 1.324)	0.372
Clinical T stage (Ref: T1c)			<0.001**
T2	1.873	6.505(5.773, 7.33)	<0.001**
T3	2.479	11.924(9.526,14.927)	<0.001**
T4	2.321	10.182(7.669,13.519)	<0.001**
Clinical N stage (Ref: N0)			0.386
N1	-0.099	0.906(0.8, 1.026)	0.120
N2	-0.160	0.852(0.63, 1.152)	0.298
N3	-0.038	0.963(0.657, 1.412)	0.847
Histology (Ref: IDC)			<0.001**
ILC	-0.364	0.695(0.518, 0.932)	0.015*
IPC	-0.343	0.709(0.514, 0.979)	0.037*
Others	-0.649	0.522(0.421, 0.649)	<0.001**
Grade (Ref: 1)			<0.001**
2	0.610	1.840(0.717, 4.722)	0.205
3	0.311	1.365(0.543, 3.434)	0.508
HR status: (Ref: Negative)			
Positive	-0.605	0.546(0.211, 1.416)	0.213
Grade* HR status			<0.001**
2*Positive	-0.517	0.596(0.223, 1.596)	0.303
3*Positive	0.149	1.160(0.442, 3.047)	0.763

Results

Among all patients, 22.5% (n = 2926) were classified as NAT-insensitive, 49.4% (n = 6418) were partial responders, and 28.1% (n = 3660) achieved pCR. NAT-insensitive patients were older and more likely to have HR-positive, low-grade, and non-ductal tumors. They experienced significantly worse OS compared to NAT-sensitive patients ($p < 0.0001$). Patients who achieved pCR were more likely to be younger, have poorly differentiated tumors, HR-negative status, and invasive ductal carcinoma, indicating a more responsive biological subtype. The predictive model showed good discrimination (AUC = 0.760 in training, 0.753 in validation) and calibration.

Conclusion

Younger age, HR negativity, high tumor grade, and ductal histology were associated with higher pCR rates, whereas the opposite traits characterized treatment-insensitive patients. The predictive model developed in this study demonstrated good performance and may assist in early identification of individuals unlikely to benefit from neoadjuvant HER2-targeted therapy.

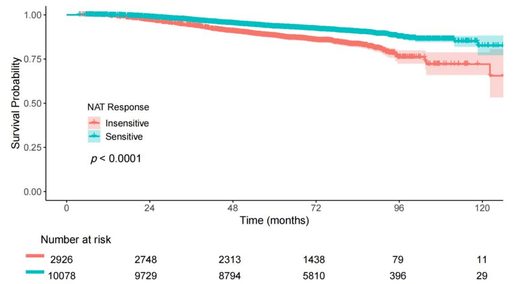


Figure 1. Kaplan-Meier overall survival curves by neoadjuvant treatment (NAT) response status.

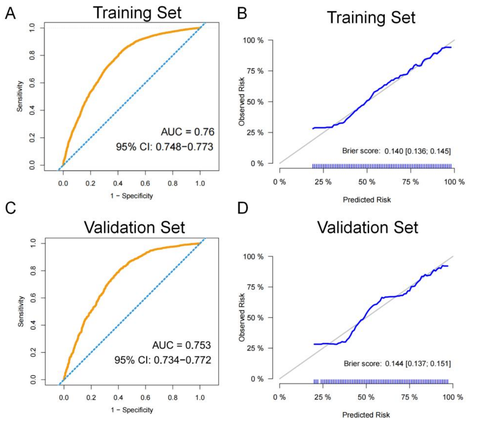


Figure 2. Discrimination and calibration performance of the predictive model. (A) Receiver operating characteristic (ROC) curve for the training cohort. (B) Calibration curve in the training cohort. (C) ROC curve for the internal validation cohort. (D) Calibration curve in the internal validation cohort.

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