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HER2 IHC score as a predictor of pathologic complete response in HER2-positive breast cancer after neoadjuvant therapy

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MAIN POINTS

- Patients with HER2 IHC 3+ tumors had substantially higher pCR rates than patients with HER2 IHC 2+/ISH+ disease, underscoring the prognostic significance of HER2 IHC scoring for neoadjuvant treatment response.
- Progesterone receptor (PR) negativity and HER2 IHC 3+ status emerged as independent predictors of pCR, highlighting the clinical utility of routine pre-treatment biopsy markers to identify patients most likely to benefit from neoadjuvant therapy.
- The higher prevalence of estrogen receptor (ER)/progesterone receptor (PR) positivity and the lower pCR rates observed in the HER2 IHC 2+/ISH+ subgroup suggest that this subgroup has a biologically less-responsive phenotype, reinforcing the need for careful therapeutic stratification within HER2-positive breast cancer.

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ABSTRACT

Aim: To evaluate factors associated with pathologic complete response (pCR) in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer receiving neoadjuvant therapy, with a specific focus on the prognostic relevance of HER2 immunohistochemistry (IHC) scores.

Materials and Methods: This retrospective study included 147 patients with HER2-positive breast cancer who underwent neoadjuvant chemotherapy (NAC) followed by surgery at a tertiary care center from late 2022 to early 2025. Patients were categorized into two groups based on their HER2 IHC status: IHC 2+/in situ hybridization-positive (ISH+) and IHC 3+. We compared patients' clinicopathological features and pCR rates. pCR was defined as the absence of residual invasive carcinoma in the breast and axillary lymph nodes (ypT0/is ypN0).

Results: The overall pCR rate was 54% (n=79). Among patients with HER2 IHC 3+ tumors, pCR was achieved in 73 of 121 cases (60%), compared with 6 of 26 cases (23%) in the IHC 2+/ISH+ group (p<0.001). In univariate analyses, HER2 IHC score (IHC 2+/ISH+ vs IHC 3, p<0.001), estrogen receptor negativity (p<0.001), and progesterone receptor negativity (p<0.001) were significantly associated with pCR. Multivariate analysis identified HER2 IHC 3+ status (p=0.035) and progesterone receptor-negative status (p=0.037) as independent predictors of achieving pCR.

Conclusion: Positivity for estrogen and progesterone receptors was more prevalent in the IHC 2+/ISH+ group than in the IHC 3+ group. HER2 IHC 3+ status and progesterone receptor negativity were identified as independent predictors of pCR.

Keywords: Breast cancer, Human epidermal growth factor receptor 2, Immunohistochemistry, Neoadjuvant, Pathological complete response

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) overexpression is observed in approximately 15–20% of all breast cancer patients [1]. HER2 overexpression identifies a subgroup of breast cancer patients who are highly responsive to neoadjuvant therapy, with anti-HER2 treatment protocols yielding pathologic complete response (pCR) rates nearing 50% [2-7]. This is of particular clinical significance, as achieving pCR after neoadjuvant treatment was previously associated with improved disease-free survival (DFS) and overall survival (OS) [8,9]. Accurately determining which individuals are likely to respond with a complete pathological remission to preoperative chemotherapy is crucial for optimizing treatment outcomes.

Assessment of HER2 receptor status is typically performed using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) techniques. As outlined in the ASCO/CAP recommendations, a tumor is considered HER2-positive if it receives an IHC score of 3+ or if a 2+ score is accompanied by evidence of gene amplification via FISH.

Interestingly, individuals whose tumors are scored as HER2 IHC 3+ have higher rates of pCR than those classified as IHC 2+in situ hybridization-positive (ISH+) [7,10-12].

In this context, identifying clinicopathological differences between HER2 IHC 2+ and IHC 3+ subgroups, as well as determining the patient profiles most likely to achieve pCR to NAC, holds significant clinical relevance. In this study, we aimed to identify factors influencing pCR by examining the clinical and pathological profiles of patients with HER2 IHC 2+ or 3+ expression. We anticipate that these insights could aid in predicting therapeutic outcomes and refining candidate selection for neoadjuvant treatment planning.

MATERIALS AND METHODS

A total of 147 patients diagnosed with HER2-positive breast cancer who underwent neoadjuvant chemotherapy (NAC) followed by surgical intervention at a tertiary medical institution between late 2022 and early 2025 were included in a retrospective analysis. Individuals lacking complete clinical records, those who failed to complete NAC, or those presenting with metastatic disease at the time of diagnosis were excluded from the study. Ethical approval for this research was granted by the institutional review board (Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee No. 2, Decision no: AEŞH-BADEK2-2025-41, Date: 29.04.2025).

pCR was defined as the complete absence of invasive carcinoma in breast tissue and axillary lymph nodes, as determined by examination of surgical specimens. The pCR was defined as the absence of residual invasive carcinoma in both the breast and axillary lymph nodes (ypT0/is ypN0). The presence of residual ductal carcinoma in situ (DCIS) was permitted.

Accordingly, cases classified as Miller–Payne grade 5, indicating no residual invasive tumor cells in the breast, regardless of residual DCIS, were considered to have achieved pCR.

The dataset comprised variables such as patient age, HER2 IHC classification, clinical nodal status prior to NAC, tumor histology, initial T stage, histologic grade, expression status of ER and PR, Ki-67 proliferation index, tumor focality, and the specific neoadjuvant chemotherapy regimen administered. Neoadjuvant chemotherapy regimens were categorized as AC-TH and TCHP. AC-TH consisted of doxorubicin and cyclophosphamide, followed by a taxane combined with dual HER2-targeted therapy (trastuzumab and pertuzumab). TCHP consisted of docetaxel, carboplatin, trastuzumab, and pertuzumab.

Tumor staging was performed in accordance with the 8th edition of the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) classification system [13]. Positivity for ER and PR was defined as ≥1% nuclear staining, in accordance with the 2010 ASCO/CAP recommendations [14]. The Ki-67 proliferation index was assessed via immunostaining using the MIB-1 monoclonal antibody (1:1000 dilution) with the Dako EnVision+ Labeled Polymer detection kit.

HER2 positivity was defined as an IHC score of 3+ or an IHC score of 2+ validated by FISH. A 3+ IHC score indicated intense, uniform membranous staining in more than 10% of tumor cells. Conversely, a 2+ score reflected either weak-to-moderate complete membrane staining in more than 10% of the tumor cells or strong staining in 10% or fewer of the tumor cells.

All individuals completed the entire course of neoadjuvant chemotherapy. Every patient received combined HER2-targeted therapy with trastuzumab and pertuzumab. The neoadjuvant protocol began with four treatment cycles con-

Table 1. Patients' clinicopathological characteristics (IHC 3+ vs. IHC 2+).

Clinicopathological Variables	IHC 2+/ISH+ (%) n=26	IHC 3+ (%) n=121	p-value
Age (years)			0.672
<50	16 (61.5)	69 (57)	
≥50	10 (38.5)	52 (43)	
pCR			<0.001*
Yes	6 (23.1)	73 (60.3)	
No	20 (76.9)	48 (39.7)	
Pre-NAC Nodal Status			0.467
Negative	10 (38.5)	56 (46.3)	
Positive	16 (61.5)	65 (53.7)	
Histopathology			0.642
NST	26	120 (99.2)	
Others	0	1 (0.8)	
Pre-NAC T stage			0.023*
T1	11 (42.3)	33 (27.3)	
T2	8 (30.8)	75 (62)	
T3	5 (19.2)	10 (8.3)	
T4	2 (7.7)	3 (2.5)	
Grade			0.758
Grade 1	1 (3.8)	8 (6.6)	
Grade 2	9 (34.6)	47 (38.8)	
Grade 3	16 (61.6)	66 (54.6)	
Estrogen Receptor			0.023*
Negative	4 (15.4)	47 (38.8)	
Positive	22 (84.6)	74 (61.2)	
Progesterone Receptor			<0.001*
Negative	4 (15.4)	73 (60.3)	
Positive	22 (84.6)	48 (39.7)	
Ki-67			0.137
≤15	2 (7.7)	24 (20)	
>15	24 (92.3)	96 (80)	
Disease Focality			0.178
Unifocal	21 (80.8)	109 (90.1)	
Multifocal	5 (19.2)	12 (9.9)	
CT Regimen			0.338
TCHP	16 (61.5)	86 (71.1)	
AC-TH	10 (38.5)	35 (28.9)	

• NAC: Neoadjuvant Chemotherapy; • pCR: Pathologic Complete Response; • TCHP = Docetaxel/Carboplatin/Trastuzumab/Pertuzumab; • AC-TH = Doxorubicin/Cyclophosphamide Followed by Taxane+HER2 Blockade.

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sisting of doxorubicin and cyclophosphamide, administered every three weeks. Subsequently, 102 patients underwent four cycles of docetaxel, also on a 21-day schedule, while the remaining 45 patients were treated with weekly paclitaxel over 12 sessions. Prior to each treatment cycle, complete blood counts and standard biochemical panels were reviewed. To prevent hypersensitivity reactions, patients routinely received premedication with 10 mg of intravenous hydrocortisone.

Statistical analysis

For cases with an IHC score of 2+, HER2 gene status and CEP17 (chromosome 17 enumeration probe) chromosomal changes were evaluated by FISH. Amplification of HER2 was defined as either a HER2/CEP17 ratio ≥2.0 or a mean HER2 gene copy number ≥6.0. To analyze the data, categorical variables were assessed using the Chi-square test, while continuous variables were evaluated using the independent samples t-test. Variables with p<0.05 in univariate analyses were subsequently included in a multivariable logistic regression model to identify independent predictors of pCR. Statistical significance was set at p<0.05, and all statistical analyses were performed using Jamovi (version 2.3.28).

RESULTS

The proportion of patients who reached pCR was 54% (n=79). The results showed that 18% of patients (n=26) had HER2 IHC 2+/ISH-amplified tumors, while 82% (n=121) had HER2 IHC 3+ tumors. All patients received taxane-based chemotherapy regimens: 69% received docetaxel-based regimens, and 31% received paclitaxel-based regimens. Among patients with HER2 IHC 3+ tumors, pCR was achieved in 73 of 121 cases (60%), compared with 6 of 26 cases (23%) in the IHC 2+/ISH+ group (p<0.001). Prior to NAC, nodal involvement was identified in 61% (n=16) of patients with IHC 2+ tumors and in 54% (n=65) of those with IHC 3+ expression. Among the IHC 2+ subgroup, T1 lesions were observed in 42% (n=11), T2 in 30.8% (n=8), T3 in 19% (n=5), and T4 in 7.7% (n=2). In contrast, within the IHC 3+ group, 27% (n=33) had T1 tumors, 62% (n=75) had T2 tumors, 8% (n=10) had T3 tumors, and 2.5% (n=3) had T4 tumors. (p=0.023). ER positivity was more prevalent in the IHC 2+ group (84%, n=22) than in the IHC 3+ group (61%, n=74).

Similarly, the rate of PR positivity was markedly higher in the IHC 2+ subgroup (85%; n=22) than in the IHC 3+ subgroup (40%; n=48); this difference was statistically significant (p<0.001). The Ki-67 index exceeded 15% in 92.3% (n=25) of patients in the IHC 2+/ISH+ group and 80.0% (n=96) of patients in the IHC 3+ group. Although no significant difference was observed in the distribution of neoadjuvant chemotherapy regimens between the groups, TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab) was more frequently used than AC-TH in both cohorts (61% in the IHC 2+ group and 71% in the IHC 3+ group) Table 1 summarizes patients' clinicopathological characteristics.

Table 2. Patients' clinical and pathological characteristics (pCR vs. non-pCR).

Clinicopathological Variables	pCR (%) n=79	Non-pCR (%) n=68	p-value
Age (years)			0.574
<50	44 (55.7)	41 (60.3)	
≥50	35 (44.3)	27 (39.7)	
HER2			<0.001*
IHC 2+/ISH+	6 (7.6)	20 (29.4)	
IHC 3+	73 (92.4)	48 (70.6)	
Pre-NAC Nodal Status			0.132
Negative	40 (50.6)	26 (38.2)	
Positive	39 (49.4)	42 (61.8)	
Histopathology			0.279
NST	79 (100)	67 (98.5)	
Others	0	1 (1.5)	
Pre-NAC T stage			0.180
T1	28 (35.4)	16 (23.5)	
T2	41 (51.9)	42 (61.8)	
T3	6 (7.6)	9 (13.2)	
T4	4 (5.1)	1 (1.5)	
Grade			0.429
Grade 1	3 (3.8)	6 (8.8)	
Grade 2	30 (38)	26 (38.2)	
Grade 3	46 (58.2)	36 (53)	
Estrogen Receptor			<0.001*
Negative	38 (48.1)	14 (20.6)	
Positive	41 (51.9)	54 (79.4)	
Progesterone Receptor			<0.001*
Negative	56 (70.9)	23 (39.1)	
Positive	23 (39.1)	45 (66.2)	
Ki-67			0.777
≤15	14 (17.9)	11 (16.2)	
>15	64 (82.1)	57 (83.8)	
Disease Focality			0.944
Unifocal	70 (88.6)	60 (88.2)	
Multifocal	9 (11.4)	8 (11.8)	
CT Regimen			0.671
TCHP	56 (70.9)	46 (67.6)	
AC-TH	23 (29.1)	22 (32.4)	

• HER2: Human Epidermal Growth Factor Receptor 2; •NAC: Neoadjuvant Chemotherapy; • TCHP = Docetaxel/Carboplatin/Trastuzumab/Pertuzumab; • AC-TH = Doxorubicin/Cyclophosphamide Followed by Taxane+HER2 Blockade.

When classified by pCR status, 92% (n=73) of individuals who achieved pCR and 71% (n=48) of those who did not had IHC 3+ expression. The T-stage distribution in the pCR group was as follows: T1, 35% (n=28); T2, 52% (n=41); T3, 8% (n=6); and T4, 5% (n=4). In the non-pCR group, we detected T1 in 24% (n=16), T2 in 62% (n=42), T3 in 13% (n = 9), and T4 in 2% (n=1). A significantly higher rate of ER negativity was observed in the pCR group (48%, n=38), compared with 21% (n=14) in the non-pCR group (p<0.001). Similarly, PR negativity was more frequent among patients who achieved pCR (71%, n=56) than among those who did not (34%, n=23) (p<0.001). Although the distribution of NAC

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Table 3. Multivariate analysis of the factors associated with pCR.

Predictor	Odds Ratio	Lower (95% CI)	Upper (95% CI)	p-value
Pre-NAC Her2 IHC 2+/ISH+- IHC 3+	3.12	1.09	8.98	0.035*
Progesterone Receptor Positive-Negative	2.86	1.07	7.61	0.037*
Estrogen Receptor Negative-Positive	0.664	0.24	1.84	0.430

regimens did not differ notably between the two groups, docetaxel-based chemotherapy was used in 71% (n=56) and 68% (n=46) of the pCR and non-pCR groups, respectively. Table 2 summarizes the clinical and pathological characteristics by pCR status.

Univariate analysis revealed that HER2 IHC score, ER expression, and PR status were significantly associated with achieving a pCR (p<0.001). Multivariate analyses demonstrated that pre-NAC HER2 IHC score (p=0.035) and PR negativity (p=0.037) were independent factors significantly associated with the outcome achieving pCR. PR negativity was associated with a higher likelihood of attaining pCR. Further details are provided in Table 3.

DISCUSSION

The aim of this study was to evaluate the clinicopathological characteristics and pCR rates in NAC patients with HER2 IHC 3+ or HER2 IHC 2+/ISH+ breast cancer. To the best of our knowledge, this is the first comprehensive study conducted in Türkiye to address this specific clinical distinction.

From a biological standpoint, higher HER2 IHC expression may reflect greater HER2 protein overexpression and, consequently, a higher likelihood of HER2-driven tumor biology. This may increase tumor dependence on the HER2 pathway and enhance sensitivity to HER2-targeted neoadjuvant therapy [10,11]. In addition, PR negativity is often associated with reduced hormone receptor signaling and may indicate diminished functional interaction between hormone receptor pathways and HER2-driven oncogenic signaling. Collectively, these features may contribute to a more HER2-dependent phenotype, rendering HER2 IHC 3+ and PR-negative tumors more responsive to dual HER2 blockade and cytotoxic chemotherapy, thereby increasing the probability of achieving pCR [6,15].

The membrane tyrosine kinase receptor HER2 is associated with aggressive tumor biology and poor prognosis in breast cancer [16]. Accurate assessment of HER2 receptor status is therefore critical for initiating NAC. As is well known, achieving pCR in HER2-positive breast cancer is one of the strongest prognostic indicators. In their cohort, Krystel-Whittemore et al. reported a pCR rate of 59% [7], while the largest series in the literature by Winer et al. demonstrated a pCR rate of 44.3% [17]. In our study, we identified a pCR rate of 54% in HER2-positive patients.

In determining HER2 positivity, both HER2 IHC 3+ and IHC 2+/ISH+ cases are classified as HER2-positive. In clinical practice, these subgroups are often combined under the HER2-positive category, and potential clinicopathological differences between them may be overlooked. However, patients with HER2 IHC 3+ status tend to exhibit higher pCR rates compared with those with HER2 IHC 2+/ISH+ status, suggesting that the IHC 3+ subgroup is more responsive to NAC [7, 18-24]. Krystel-Whittemore et al. reported a pCR rate of 67% in IHC 3+ patients versus 17% in IHC 2+/ISH+ patients [7]. Similarly, Wang et al. reported rates of 55.1% versus 17.6% [19]; Sun et al. found rates of 58.1% versus 26.7% for IHC 3+ and IHC 2+/ISH+ patients, respectively [24]. In our study, we observed pCR rates of 60.3% in the IHC 3+ group and 23.1% in the IHC 2+/ISH+ group.

Hormone receptor status also differed between the two subgroups. Previous research has shown that patients with IHC 2+/ISH+ exhibit higher ER positivity than IHC 3+ patients, whereas PR negativity is more frequent in the IHC 3+ subgroup [18,24]. Jia et al. reported ER positivity rates of 75% and 53%, and PR positivity rates of 49% and 41%, in the IHC 2+/ISH+ and IHC 3+ groups, respectively [18]. Consistent with these findings, our study revealed ER positivity in 84.6% of patients with IHC 2+/ISH+ tumors and 61.2% of patients with IHC 3+ tumors. PR positivity was observed in 84.6% of the IHC 2+/ISH+ group, whereas it was 39.7% in the IHC 3+ group.

Jung et al. confirmed that PR negativity (p=0.01) and preoperative HER2 IHC 3+ status (p=0.04) were independent predictors of pCR rates [15]. In their study, Krystel-Whittemore et al. identified dual blockade (p=0.001), high grade (p=0.04), HER2 IHC 3+ (p<0.001), and PR negativity (p=0.01) as independent predictors of pCR [7]. Katayama et al. also demonstrated that HER2 IHC 3+ and Grade 3 were independent predictors of pCR following neoadjuvant anti-HER2 therapy [20]. In our study, univariate analyses identified hormone receptor negativity (p<0.001) and IHC status as significant predictors of pCR. In multivariate analysis showed that PR negativity and HER2 IHC 3+ status were independent predictors of pCR. Therefore, the rate of complete response to NAC is likely higher in patients who are HER2 IHC 3+ and PR-negative.

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Although the study's design and results are relatively straightforward, identifying, through routine pathological workups, patients likely to respond well or poorly to NAC is highly useful in clinical practice. It can guide the management of borderline cases, for example, by allowing upfront surgery for patients unlikely to benefit from NAC. Yet, novel predictive and prognostic markers are still needed.

Limitations

This study has several limitations that should be acknowledged. Its retrospective and single-center design may limit the generalizability of the findings. In addition, the relatively small size of the HER2 IHC 2+/ISH+ subgroup (n=26) may have reduced the statistical power of subgroup analyses and limited the precision of effect estimates. Therefore, the results, particularly those derived from subgroup comparisons, should be interpreted with caution. Furthermore, the limited follow-up period precluded the calculation of OS and DFS. Despite these constraints, we assert that evaluating the complete response using data readily available from routine pre-treatment biopsies holds substantial clinical value. Given that this represents the first comprehensive investigation of its kind in our country, it is expected to make a significant contribution to the existing literature. Additionally, our findings may provide a foundation for prospective studies with larger sample sizes that could offer further insights and enhance the generalizability of the results.

CONCLUSION

In summary, the present study compared clinicopathological characteristics and pCR rates between HER2 IHC 3+ and HER2 IHC 2+/ISH+ patients who received NAC. The IHC 2+/ISH+ group exhibited higher ER and PR positivity than the IHC 3+ group. HER2 IHC 3+ status and PR negativity was identified as an independent predictor of pCR. Considering the HER2 IHC score and PR status together may help guide clinical decision-making regarding neoadjuvant therapy.

Ethics Committee Approval: Ethical approval was obtained from the Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee No. 2 (Decision no: AEŞH-BADEK2-2025-41, Date: 29.04.2025).

Informed Consent: It was not deemed necessary due to the retrospective nature of the study.

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