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Clinicopathological Correlations of Hormone Receptors and HER2 Expression in Breast Cancer: A Retrospective Study from Iraq

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Abstract

Background: Breast cancer is a biologically heterogeneous disease with diverse clinical outcomes driven by molecular characteristics, particularly hormone receptors (HR), including estrogen receptor (ER) and progesterone receptor (PR), as well as human epidermal growth factor receptor 2 (HER2) expression. These biomarkers are essential for tumor classification, prognostic assessment, and therapeutic stratification. However, their relationship with clinicopathological features may vary across different populations, necessitating region-specific evaluation.

Methods: This retrospective study was conducted at the Oncology Teaching Hospital, Medical City, Baghdad, Iraq, and included 96 female patients diagnosed with breast cancer between February 2024 and January 2025. Data on HR and HER2 expression were obtained from pathology reports based on immunohistochemical analysis performed on formalin-fixed, paraffin-embedded tissue samples. Clinicopathological variables were collected from medical records. Statistical analysis was performed using the Chi-square test and logistic regression with SPSS, with a p-value of <0.05 considered significant.

Results: Hormone receptors (HR) positivity was observed in 79.2% of cases, while HER2 positivity was identified in 27.1%. No significant associations were found between HR expression and clinicopathological parameters, except for smoking status, which showed a significant inverse association (p=0.014). In contrast, HER2 expression was significantly associated with tumor stage (p=0.042), with higher expression observed in advanced stages. Multivariate analysis revealed that advanced lymph node involvement (N3) (OR=7.86, p=0.014) and higher tumor stages (III and IV) were independently associated with HER2 positivity.

Conclusion: Hormone receptors (HR) expression appears to be independent of most clinicopathological factors, whereas HER2 overexpression is significantly associated with advanced and aggressive disease features. These findings highlight the importance of HR and HER2 assessment in predicting tumor behavior and guiding clinical management in breast cancer patients.

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Introduction

Breast cancer is the most common female carcinoma in all national cancer registries (1,2). It ranks as the second cancer-leading cause of mortality among females (3,4). Early identification and screening, particularly when accompanied by effective therapy, provide the most immediate hope for a decrease in breast cancer mortality among the approaches advocated by the World Health Organization (5). According to the most recent Iraqi cancer registry, breast cancer is the most common cancer among females, accounting for almost one-third of all reported cancer cases, and it is regarded as the second largest cause of death after cardiovascular

disease (6). Studies conducted locally by Iraqi experts reported that over 40% of cases found in Iraq are still in advanced stages (7,8). It has been demonstrated that BC is not a single illness but encompasses certain biologic entities with diverse pathological traits and clinical consequences that differ according to their gene expression patterns, which contribute to their prognosis and prediction (9).

Despite advances in early detection and therapeutic strategies, its clinical behavior varies significantly due to its biological heterogeneity. This heterogeneity is largely driven by molecular characteristics, particularly the expression of hormone receptors (HR), including estrogen receptor (ER) and progesterone receptor (PR), as well as human epidermal growth factor receptor 2 (HER2) (10).

The assessment of HR and HER2 status plays a crucial role in the classification of breast cancer into distinct molecular subtypes, which directly influence prognosis and treatment decisions (11). HR-positive tumors are generally associated with a more favorable prognosis and responsiveness to endocrine therapy, whereas HER2-positive tumors are often linked to more aggressive behavior but may benefit from targeted anti-HER2 therapies. Therefore, accurate evaluation of these biomarkers is essential in guiding personalized treatment approaches (12).

In addition to their therapeutic implications, HR and HER2 expression have been widely studied in relation to various clinicopathological features, including tumor size, lymph node involvement, histological grade, and disease stage. However, the reported associations remain inconsistent across different populations, likely due to variations in genetic, environmental, and lifestyle factors (13). In particular, data from Middle Eastern populations are relatively limited, highlighting the need for region-specific studies to better understand the biological behavior of breast cancer in these settings.

the present study aimed to evaluate the association between HR (ER and PR) and HER2 expression and clinicopathological characteristics in breast cancer patients in Iraq. Additionally, this study sought to identify independent predictors of HR and HER2 expression, thereby contributing to a better understanding of tumor behavior in the studied population.

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Materials and Methods

This retrospective study was conducted at the Oncology Teaching Hospital, Medical City, Baghdad, Iraq. The study included 96 Iraqi female patients diagnosed with breast cancer between February 2024 and January 2025.Ethical approval for this study was obtained from the University of Baghdad College of Pharmacy. Patient confidentiality and data privacy were strictly maintained throughout the study.

The inclusion criteria comprised female patients with histologically confirmed breast cancer at the time of diagnosis, prior to receiving any form of treatment. Exclusion criteria included patients with other malignancies, non-invasive breast lesions, and patients with incomplete data.

Formalin-fixed, paraffin-embedded (FFPE) tissue blocks were retrieved from the archives of the pathology laboratory at the Oncology Teaching Hospital, Medical City. Immunohistochemical (IHC) staining for ER, PR, and HER2 had been previously performed as part of routine diagnostic workup in the hospital laboratory using standardized protocols and validated antibodies supplied by Dako (Denmark). The results of ER, PR, and HER2 expression were obtained from pathology reports and medical records. Evaluation and scoring of immunohistochemical markers were carried out by experienced pathologists in accordance with established guidelines.

ER and PR status were assessed based on the Allred scoring system, which incorporates both the proportion of positive tumor cells and staining intensity, with a total score ranging from 0 to 8. Scores of 0–2 were considered negative, while scores of 3–8 were considered positive (14). ER and PR staining is localized to the nuclei of tumor cells, as ER and PR are nuclear proteins. HR positivity was defined as positive expression of both ER and PR. HER2 expression was evaluated based on membranous staining patterns, according to established immunohistochemical scoring criteria: Score 0 and 1+ were considered negative, Score 2+ was considered equivocal and required further confirmatory testing (FISH test), Score 3+ was considered positive (15).

Clinical and pathological data were obtained from patient medical records, including age, family history, smoking status, tumor size, lymph node involvement, distant metastasis, tumor stage, and histological grade. Tumor staging was determined according to the TNM classification system (16), and grading was assessed by experienced pathologists based on standard histopathological criteria.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 28). Associations between categorical variables were evaluated using the Chi-square test. Logistic regression analysis was conducted to identify independent predictors of HR and HER2 expression. A p-value of <0.05 was considered statistically significant.

Results

Hormone receptors (HR) positivity was observed in 79.2% of patients. No significant association was found between HR expression and age groups or family history (p>0.05). However, a statistically significant association was identified between smoking status and HR expression, with lower HR positivity among smokers (p=0.014), as shown in (Table 1).

Table 1. Association between HR and demographic characteristics

Demographic characteristics		HR		Chi-square	p-value
		Positive (N=76)	Negative (N=20)		
Age	**30-40**	6 (75.0%)	2 (25.0%)	1.67	0.644

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Demographic characteristics		HR		Chi-square	p-value
		Positive (N=76)	Negative (N=20)		
	41-50	21 (72.4%)	8 (27.6%)		
	51-60	29 (85.3%)	5 (14.7%)		
	>60	20 (80.0%)	5 (20.0%)		
Family history	Positive	20 (76.9%)	6 (23.1%)	0.11	0.741
	Negative	56 (80.0%)	14 (20.0%)		
Smoking status	Yes	3 (42.9%)	4 (57.1%)	6.04	0.014
	No	73 (82.0%)	16 (18.0%)		

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No statistically significant associations were observed between HR expression and tumor size, lymph node involvement, distant metastasis, stage, histological grade, or HER2 status (p>0.05), as shown in (Table 2). HR positivity was relatively consistent across different tumor characteristics, suggesting limited correlation with disease severity indicators.

Table 2. Association of HR with clinical and pathological characteristics

Clinicopathological feature		HR expression		χ2	P value
		Positive (N=76)	Negative (N=20)		
Tumor size	T1	24 (85.7%)	4 (14.3%)	1.76	0.624
	T2	32 (74.4%)	11 (25.6%)		
	T3	15 (83.3%)	3 (16.7%)		
	T4	5 (71.4%)	2 (28.6%)		
Lymph node involvement	N0	32 (80.0%)	8 (20.0%)	3.28	0.351
	N1	23 (88.5%)	3 (11.5%)		
	N2	16 (72.7%)	6 (27.3%)		
	N3	5 (62.5%)	3 (37.5%)		
Distant metastases	Metastases	19 (79.2%)	5 (20.8%)	0.00	1.000
	Non	57 (79.2%)	15 (20.8%)		
Stage	I	19 (90.5%)	2 (9.5%)	2.49	0.478
	II	20 (76.9%)	6 (23.1%)		
	III	18 (72.0%)	7 (28.0%)		
	IV	19 (79.2%)	5 (20.8%)		
Histological grade	I	2 (25.0%)	6 (75.0%)	0.19	0.911
	II	19 (28.4%)	48 (71.6%)		
	III	5 (23.8%)	16 (76.2%)		
HER-2	Positive	19 (73.1%)	7 (26.9%)	0.80	0.371
	Negative	57 (81.4%)	13 (18.6%)		

Multivariate logistic regression analysis revealed that smoking was the only independent factor significantly associated with HR expression (OR=0.16, 95% CI: 0.03–0.81, p=0.026). Other variables, including age, tumor size, lymph node status, stage, grade, and HER2 status, were not significantly associated with HR expression, as shown in (Table 3).

Table 3. Logistic Regression Analysis of Factors Associated with HR Expression

HR ve+/ ve-			
Variable	**Category**	**OR (95% CI)**	**p-value**
Age groups	30–40 (Ref)	—	—
	41–50	0.88 (0.15–5.27)	0.884

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HR ve+/ ve-			
	51–60	1.93 (0.30–12.43)	0.487
	>60	1.33 (0.20–8.71)	0.764
Family history	-ve (Ref)	—	—
	+ve	0.83 (0.28–2.46)	0.742
Smoking	-ve (Ref)	—	—
	+ve	0.16 (0.03–0.81)	0.026
Tumor size	T1 (Ref)	—	—
	T2	0.49 (0.14–1.71)	0.260
	T3	0.83 (0.16–4.25)	0.826
	T4	0.42 (0.06–2.93)	0.379
Lymph node	N0 (Ref)	—	—
	N1	1.92 (0.46–8.02)	0.373
	N2	0.67 (0.20–2.25)	0.514
	N3	0.42 (0.08–2.12)	0.292
Distant metastasis	Non (Ref)	—	—
	Metastasis	1.00 (0.32–3.12)	1.000
Stage	I (Ref)	—	—
	II	0.35 (0.06–1.96)	0.232
	III	0.27 (0.05–1.48)	0.132
	IV	0.40 (0.07–2.32)	0.307
Grade	I (Ref)	—	—
	II	0.73 (0.08–6.52)	0.776
	III	0.23 (0.02–2.25)	0.208
HER2/neu	-ve (Ref)	—	—
	+ve	0.62 (0.22–1.78)	0.373

HER2 positivity was observed in 27.1% of patients. No statistically significant associations were found between HER2 expression and age, family history, or smoking status ($p>0.05$), indicating that demographic factors did not significantly influence HER2 status in this cohort, as shown in (Table 4)

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Table 4. Association between HER2 and demographic characteristics

Demographic characteristics		HER2		Chi-square	p-value
		Positive (N=26)	Negative (N=70)		
Age	30-40	2 (25.0%)	6 (75.0%)	1.46	0.691
	41-50	10 (34.5%)	19 (65.5%)		
	51-60	9 (26.5%)	25 (73.5%)		
	>60	5 (20.0%)	20 (80.0%)		
Family history	Positive	5 (19.2%)	21 (80.8%)	1.11	0.291
	Negative	21 (30.0%)	49 (70.0%)		
Smoking status	Yes	2 (28.6%)	5 (71.4%)	0.01	0.927
	No	24 (27.0%)	65 (73.0%)		

A statistically significant association was found between HER2 expression and tumor stage (p=0.042), with higher HER2 positivity observed in advanced stages. Although not statistically significant, higher HER2 expression was also noted in patients with lymph node involvement and distant metastasis, suggesting a trend toward more aggressive disease, as shown in (Table 5).

Table 5. Association of HER2 with Clinical and pathological characteristics

Clinicopathological feature		HER2 expression		χ2	P value
		Positive (N=26)	Negative (N=70)		
Tumor size	T1	4 (14.3%)	24 (85.7%)	3.78	0.287
	T2	13 (30.2%)	30 (69.8%)		
	T3	6 (33.3%)	12 (66.7%)		
	T4	3 (42.9%)	4 (57.1%)		
Lymph node involvement	N0	7 (17.5%)	33 (82.5%)	7.12	0.068
	N1	8 (30.8%)	18 (69.2%)		
	N2	6 (27.3%)	16 (72.7%)		
	N3	5 (62.5%)	3 (37.5%)		
Distant metastases	Metastases	10 (41.7%)	14 (58.3%)	3.45	0.063
	Non	16 (22.2%)	56 (77.8%)		
Stage	I	1 (4.8%)	20 (95.2%)	8.19	**0.042**
	II	7 (26.9%)	19 (73.1%)		
	III	8 (32.0%)	17 (68.0%)		
	IV	10 (41.7%)	14 (58.3%)		

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Clinicopathological feature		HER2 expression		χ2	P value
		Positive (N=26)	Negative (N=70)		
Histological grade	I	2 (25.0%)	6 (75.0%)	0.19	0.911
	II	19 (28.4%)	48 (71.6%)		
	III	5 (23.8%)	16 (76.2%)		
HR	Positive	19 (25.0%)	57 (75.0%)	0.80	0.371
	Negative	7 (35.0%)	13 (65.0%)		

Multivariate analysis demonstrated that advanced lymph node involvement (N3) was significantly associated with HER2 positivity (OR=7.86, p=0.014). Additionally, advanced stages (III and IV) were significantly associated with increased HER2 expression. Other variables, including age, family history, smoking, tumor size, and grade, were not significantly associated.

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Table.6 Logistic Regression Analysis of Factors Associated with HER2/neu Expression

	HER2 ve+/ ve-		
Variable	**Category**	**OR (95% CI)**	**p-value**
Age groups	30–40 (Ref)	—	—
	41–50	1.58 (0.27–9.31)	0.614
	51–60	1.08 (0.18–6.36)	0.932
	>60	0.75 (0.12–4.90)	0.764
Family history	-ve (Ref)	—	—
	+ve	0.56 (0.19–1.67)	0.295
Smoking	-ve (Ref)	—	—
	+ve	1.08 (0.20–5.96)	0.927
Tumor size	T1 (Ref)	—	—
	T2	2.60 (0.75–9.01)	0.132
	T3	3.00 (0.71–12.69)	0.136
	T4	4.50 (0.72–28.15)	0.108
Lymph node	N0 (Ref)	—	—
	N1	2.10 (0.65–6.72)	0.214
	N2	1.77 (0.51–6.13)	0.369
	N3	7.86 (1.51–40.81)	0.014
Distant metastasis	Non (Ref)	—	—
	Metastasis	2.50 (0.94–6.68)	0.068
Stage	I (Ref)	—	—
	II	7.37 (0.83–65.66)	0.074
	III	9.41 (1.07–83.02)	0.044
	IV	14.29 (1.64–124.63)	0.016
Grade	I (Ref)	—	—
	II	1.19 (0.22–6.41)	0.842
	III	0.94 (0.14–6.20)	0.947
HR	-ve (Ref)	—	—
	+ve	0.62 (0.22–1.78)	0.373

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Discussion

Breast cancer remains a heterogeneous disease with variable biological behavior influenced by hormone receptor (HR) and HER2 status (17). In the present study, HR positivity was observed in the majority of patients (79.2%), while HER2 positivity was identified in 27.1% of cases. These findings are consistent with previously reported data indicating that HR-positive tumors constitute the predominant subtype of breast cancer, particularly in Middle Eastern and developing populations (18,19).

In this study, no significant association was found between HR expression and most clinicopathological parameters, including tumor size, lymph node involvement, stage, and histological grade. This finding is in agreement with several studies suggesting that HR status reflects tumor biology rather than disease extent (20). However, a significant inverse association between smoking and HR expression was identified. This observation may be explained by the potential anti-estrogenic effects of tobacco exposure, which have been reported to influence hormonal pathways and receptor expression (21).

Regarding HER2 expression, a significant association was observed with tumor stage, with higher HER2 positivity in advanced stages. This finding supports the well-established role of HER2 as a marker of aggressive tumor behavior and disease progression (22). Furthermore, multivariate analysis demonstrated that advanced lymph node involvement (N3) and higher tumor stages (III and IV) were independent predictors of HER2 positivity. These results are consistent with previous studies reporting that HER2 overexpression is associated with increased tumor proliferation, metastatic potential, and poorer prognosis (22).

Although lymph node involvement and distant metastasis did not reach statistical significance in univariate analysis, a clear trend toward higher HER2 expression in advanced disease was observed. This may be attributed to the relatively limited sample size, which could reduce the statistical power to detect significant associations (23).

Interestingly, no significant association was found between HER2 expression and demographic factors such as age, family history, and smoking status. This suggests that HER2 overexpression is more strongly related to intrinsic tumor biology rather than patient-related factors, which is consistent with existing literature (24).

Overall, the findings of this study highlight the distinct biological roles of HR and HER2 in breast cancer. While HR expression appears to be relatively independent of tumor progression, HER2 overexpression is strongly associated with more advanced and aggressive disease. These results emphasize the importance of routine assessment of these biomarkers for prognostic evaluation and therapeutic decision-making (25).

Conclusion

This study demonstrates that hormone receptor (HR) expression in breast cancer appears to be largely independent of most clinicopathological characteristics, suggesting that HR status primarily reflects intrinsic tumor biology rather than disease progression. In contrast, HER2 overexpression was significantly associated with advanced tumor stage and lymph node involvement, indicating its role as a marker of aggressive disease behavior. This study provides valuable insight into the biological profile of breast cancer in the Iraqi population. Further large-scale, multicenter studies are recommended to validate these findings and explore their implications in personalized cancer management.

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