Comparative Evaluation of Clinical and Pathological Characteristics of Breast Cancers with Low HER2 Receptor and Negative HER2 Receptor

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Abstract:

Background and Objective: Breast cancers that overexpress the HER2 receptor tend to exhibit more aggressive behavior compared to other breast cancer subtypes. As a result, HER2 status plays a critical role in prognosis and treatment planning. Recently, increasing attention has been given to differences among HER2-Negative cases, which include three subgroups: 0, 1+, and 2+ (with Negative results on FISH or CISH tests), collectively referred to as "HER2-low." Emerging evidence suggests that these subgroups may differ biologically. This study aimed to investigate the clinical and pathological characteristics of these three HER2-Negative subgroups, with a particular focus on tumor features.

Materials & Methods: This retrospective, cross-sectional analytical study included data from 3,745 patients with HER2-Negative breast cancer. Categorical variables were analyzed using the Chi-Square test, while continuous variables were assessed based on normality with appropriate test.

Results: The mean age of the patients was 50.96 ± 11.37 years. Comparative analysis showed that patients in the HER2-intermediate ISH-Negative group were significantly younger than those in the other two groups (p = 0.03). Tumor size was smaller, and the mean Ki-67 index was higher in this group compared to the others (p < 0.001). Additionally, grade 3 tumors (22.1%), positive surgical margins (9%), and metastasis (11.1%) were more common in the HER2-intermediate ISH-Negative group. This group also had the highest recurrence (26.1%) and mortality rates (24.7%). Conversely, the HER2-zero group had the largest average tumor size (28.74 ± 19.59 mm), the highest lymph node involvement (53.2%), and the greatest incidence of lymphovascular invasion (58.6%). The HER2-low 1+ group appeared to be the least aggressive, showing the lowest rates of grade 3 tumors (13.7%), positive margins (4.3%), and recurrence (11.5%). Regarding treatment, the majority of HER2-zero and HER2-low 1+ patients received adjuvant chemotherapy (62.3% and 51.3%, respectively), while neoadjuvant chemotherapy was more commonly administered to patients in the HER2-intermediate ISH-Negative group (52%).

Conclusion: Based on the findings of this study, patients in the HER2-intermediate ISH-Negative group exhibited more aggressive tumor characteristics and poorer outcomes compared to the other HER2-Negative subgroups. In contrast, the HER2-low 1+ group demonstrated the most favorable prognosis. These results suggest that patients with HER2-intermediate ISH-Negative status may benefit from closer monitoring and more frequent follow-up to improve clinical outcomes.

***Keywords:** Breast Cancer; HER-2 receptor; HER2-low; HER2-borderline*

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Background and Objective

HER2 (Human Epidermal Growth Factor Tumor Receptor 2) is a tumor biomarker with significant prognostic and therapeutic implications in breast cancer. Its overexpression occur in approximately 20–25% of primary invasive breast cancers. This subtype is associated with an aggressive phenotype with a higher potential of metastasis, and a different response to both hormonal and chemotherapeutic treatments.[1]

Nearly half of patients with HER2-negative breast cancer reveal some level of HER2 expression on immunohistochemistry (IHC) who are referred to as HER2-low group. This group includes tumors with an IHC score of 1+ or 2+ with a negative gene amplification in ISH test including FISH (Fluorescence In Situ Hybridization) or CISH (Chromogenic In Situ Hybridization). Clinical and pathological characteristics of patients with HER2-low tumors appear different from those which are categorized as HER2-negative on initial IHC assessment.

Studies have shown that about 45–55% and 30–40% of all breast cancers are HER2-low and HER2-negative (zero), respectively. Among patients with luminal-type breast cancer, around 65% are classified as HER2-low, whereas in triple-negative breast cancer, about one-third fall into the HER2-low category. Recent studies have extensively examined the clinical, pathological, and molecular characteristics of HER2-low tumors, indicating potential biological differences between estrogen receptor (ER)-positive HER2-low and ER-positive HER2-zero diseases.[2,3]

The prognostic importance of HER2-low expression remains controversial. Several studies have reported worse outcomes in both early-stage and advanced disease.[4-6] In a study by Rossi et al.[4], patients with FISH-negative intermediate HER2 expression had worse disease-free survival (DFS) compared to patients with HER2-zero and HER2 1+. These patients also had poorer DFS compared to those with HER2-positive tumors. Furthermore, a higher frequency of larger tumor size, grade 3 tumors, elevated Ki-67 index, and lymph node involvement was observed in the FISH-negative intermediate HER2 group compared to the others.[4] Similarly, two additional studies reported more aggressive behavior and reduced survival in ISH-negative intermediate HER2 patients compared to HER2-zero patients.[5,6]

However, more recent studies have suggested a better prognosis for HER2-low patients compared to HER2-zero patients. In a retrospective study by Horisawa et al. involving 4,918 breast cancer patients, the clinical characteristics and prognosis of HER2-low and HER2-zero groups were compared. In the HER2-low group, 58% of patients were hormone receptor-positive, compared to only 13.9% in the HER2-zero group. Even without consideration of hormone receptor status, HER2-low patients had better prognoses.[7]

In a study by Denkert et al. in 2021, 1,098 HER2-low patients were compared with 1,212 HER2-zero patients. The HER2-low group showed a lower pathological complete response (PCR) rate to neoadjuvant chemotherapy (29% vs. 39%), yet exhibited a longer disease-free survival (DFS) at three years (83.4% vs. 76.1%).[3]

Similarly, in a study by Russo et al. involving 391 HER2-low breast cancer patients, overall survival was longer in the HER2-low group compared to HER2-zero over a 6-year follow-up period.[8] Another study by Almstedt et al., focusing on 351 node-negative breast cancer patients, also found better prognosis in HER2-low patients compared to HER2-zero.[9]

Given the findings in the studies, it appears that further investigation is needed to clarify the prognostic and clinical differences among HER2-negative subgroups. Therefore, the present study was designed to evaluate clinical and pathological differences between HER2-low and HER2-zero breast cancer patients.

Materials and Methods

All patients diagnosed with invasive breast cancer who were treated between 2014 and 2023 (1393 to 1402 in the Iranian

calendar) at the active breast surgery departments of Tehran University of Medical Sciences and the private clinic of the corresponding author were included in the study. Eligible patients had positive estrogen and progesterone hormone receptor status and HER2 scores of 0, 1+, or 2+ based on their immunohistochemistry (IHC) result.

Patients were excluded if their HER2 status was unknown, or if they were identified as HER2-intermediate (IHC 2+) without confirmatory FISH (Fluorescence In Situ Hybridization) or CISH (Chromogenic In Situ Hybridization) testing, or if the results of those tests were unavailable. Patients with metastatic disease and In-situ breast cancers at diagnosis were also excluded.

The variables extracted for analysis included date of diagnosis, demographic characteristics (age at diagnosis, age at menarche, pregnancy history, age at menopause, body mass index [BMI]), Pathologic features (tumor grade, disease stage, vascular invasion, Ki-67 proliferative index, number of positive lymph nodes), family history of breast or ovarian cancer in first-degree relatives, HER2 status based on IHC and FISH/CISH results for IHC 2+ cases, tumor location, type of breast surgery performed, surgical margin involvement, use of adjuvant and neoadjuvant chemotherapy, disease recurrence or metastasis, and site of metastasis.

This research project (Proposal Code: 1401-3-417-63080) was reviewed and approved by the Ethics Committee of Tehran University of Medical Sciences under the ethics code IR.TUMS.IKHC.REC.1401.353. All collected data were handled confidentially and anonymously in accordance with the principles of the Declaration of Helsinki.

All data were entered into SPSS software (version 23) for statistical analysis. Demographic, clinical, and pathological characteristics were compared among the three groups: HER2-zero, HER2 1+, and HER2 2+ (with ISH-negative). Continuous quantitative variables were presented as mean ± standard deviation (SD), and categorical variables were reported as frequency (percentage). The Kolmogorov-Smirnov test was used to assess the normal distribution for continuous variables. Based on the distribution, comparisons between two groups were performed using parametric or non-parametric tests. Comparisons of continuous variables among the three independent groups were conducted using the ANOVA or Kruskal-Wallis test, depending on data normality. Categorical variables were compared using the Chi-square test or Fisher's Exact test. A p-value < 0.05 was considered statistically significant for all analyses.

Findings

Out of the 3,745 patients included in the study, 47.8% were classified as HER2-zero and 52.2% as HER2-low. Table 1 presents a comparison of demographic and reproductive factors—age, body mass index (BMI), age at menarche, number of pregnancies, and duration of breastfeeding—among the three groups: HER2-zero, HER2 1+, and HER2 2+ (ISH-negative). Since the continuous data did not follow a normal distribution (as assessed by the Kolmogorov-Smirnov test), the Kruskal-Wallis test was used for comparison. Statistically significant differences were observed among the three groups for all evaluated variables except for age at menarche. Patients in the HER2-zero group had higher age, greater BMI, more pregnancies, and longer breastfeeding duration compared to the HER2-low groups. In oppose of that, patients in the HER2 2+ (ISH-negative) group had larger tumor sizes and a higher Ki-67 proliferative index on pathology reports. These differences were statistically significant ($p < 0.001$).

Table 1. Comparison of quantitative variables among three groups

Variable	Mean ± Standard Deviation			P-Value*
	HER2=0	HER2=1+	HER2=2+	
age	50.74 ± 11.37	51.58 ± 11.97	50.25 ± 12.05	0.04
BMI	27.91 ± 4.71	27.1 ± 4.75	26.98 ± 4.88	0.01
Age of menarche	13.19 ± 1.62	13.33 ± 1.46	13.44 ± 1.65	0.30
Number of pregnancies	3.18 ± 2.20	2.80 ± 1.93	2.61 ± 1.73	0.02
Duration of breastfeeding (months)	47.32 ± 41.96	41.05 ± 38.93	38.04 ± 39.11	0.02
Tumor size in ultrasonography	19.78 ± 20.22	21.31 ± 14.31	21.75 ± 14.63	<0.001
Tumor size in pathology	28.74 ± 19.95	23.35 ± 14.32	22.80 ± 14.96	<0.001
Ki-67	20.85 ± 16.55	20.13 ± 15.03	23.97 ± 17.16	<0.001

**P-value is determined by Kruskall-Wallis test.*

Table 2 presents the comparison of categorical variables across the three study groups. The proportion of patients with positive surgical margins was highest in the HER2 2+ (ISH-negative) group, and a greater number of patients in this group had higher tumor grades. However, axillary lymph node involvement was observed in only 13% of these patients, representing the lowest rate among the three groups. The highest rate of axillary lymph node involvement was seen in the HER2-zero group, accounting for 72.5% (715 out of 986 cases) of all lymph node-positive patients. The highest rate of lymphovascular invasion was also observed in the HER2-zero group, followed by the HER2 2+ (ISH-negative) group. In terms of family history of breast and ovarian cancer, the HER2 2+ (ISH-negative) group had the lowest frequency of positive family history. Interestingly, this same group also demonstrated the highest rate of distant metastasis. Adjuvant chemotherapy was more frequently administered in the HER2-zero group, whereas neoadjuvant chemotherapy was more commonly used in patients with HER2 2+ (ISH-negative) tumors.

According to Table 3, patients in the HER2 2+ (ISH-negative) group had the highest recurrence rate, at 26.1%, as well as the highest mortality rate, at 24.7%.

Table 2. Comparison of categorical variables among three groups

Variable		Frequency (percentage)			P-Value
		HER2=0	HER2=1+	HER2=2+	
Margin	Involved	113 (7.2%)	50 (4.3%)	50 (9%)	<0.001
	Free	1454 (92.8%)	1124 (95.7%)	504 (91%)	
Lymph node	Involved	715 (53.2%)	196 (16.8%)	75 (13.4%)	<0.001
	Free	629 (46.8%)	974 (83.2%)	486 (86.6%)	
LVI	Positive	850 (58.6%)	513 (49.2%)	279 (49.9%)	<0.001
	Negative	597 (41.2%)	518 (49.7%)	249 (42.9%)	
	Doubtful	3 (0.2%)	216 (17.5%)	59 (10.8%)	
Tumor Grade	I	316 (20.4%)	206 (17.5%)	59 (10.8%)	<0.001
	II	975 (62.9%)	811 (68.8%)	368 (67.2%)	
	III	260 (16.8%)	162 (13.7%)	121 (22.1%)	
Family History	Yes	350 (23.2%)	275 (22.7%)	89 (15.4%)	<0.001
	No	1156 (76.8%)	934 (77.3%)	488 (84.6%)	
Metastasis	Yes	75 (5.1%)	76 (7.7%)	31 (11.1%)	<0.001
	No	1401 (94.9%)	916 (92.3%)	249 (88.9%)	
Chemotherapy	Adjuvant	816 (62.3%)	457 (51.3%)	125 (41.1%)	<0.001
	Neo-adjuvant	299 (22.8%)	245 (27.5%)	158 (52.0%)	
	Not indicated	194 (14.8%)	189 (21.2%)	21 (6.9%)	

Table 3. Comparison of follow up data among three groups

Variable		Frequency (percentage)			P-Value
		HER2=0	HER2=1+	HER2=2+	
Recurrence	Yes	133 (19.1%)	37 (11.5%)	24 (26.1%)	<0.001
	No	562 (80.9%)	285 (88.5%)	68 (73.9%)	
Status at last follow up	Alive	529 (76.1%)	277 (87.1%)	64 (75.3%)	<0.001
	Deceased	166 (23.9%)	41 (12.9%)	21 (24.7%)	

Discussion and Conclusion

The present study evaluated the clinicopathological characteristics and survival outcomes of patients with HER2-low breast cancer in comparison with HER2-negative (HER2-zero) cases. In summary, patients in the HER2 2+ with ISH-negative group demonstrated more aggressive tumor biology, higher proliferative indices, higher recurrence rates, and poorer survival outcomes. In contrast, the HER2-zero group presented with larger tumors and more lymph node involvement, yet had better survival compared to the HER2 2+ with ISH-negative group. Among all, patients with HER2 1+ tumors had the best prognosis. Patients who have hormone receptor-positive HER2-low tumors do not benefit from anti-HER2 therapies such as trastuzumab (Herceptin). However, recent studies like the DESTINY-Breast04 trial have shown promising results with antibody-drug conjugates (ADCs), particularly trastuzumab deruxtecan, which has nearly doubled overall survival in this subset of patients.[10] Therefore, understanding the biological and prognostic significance of HER2-low expression has important clinical implications.

In the current study, 52.2% of patients with luminal subtype breast cancer were classified as HER2-low. Since only hormone receptor-positive patients were included, this study could not evaluate associations between HER2-low status and hormone receptor negativity, unlike other reports that have demonstrated a higher prevalence of HER2-low in hormone receptor-positive patients.

In the study by Schettini et al. (2), which analyzed clinicopathological features and PAM50 subtypes in 3,689 HER2-negative patients, HER2-low cases were associated with older age and more lymph node involvement, but no worse prognosis.[2] In contrast, our study found that lymph node involvement was highest in HER2-zero patients, followed by HER2 1+ and HER2 2+ with ISH-negative groups.

Similarly, Won et al. reported that HER2-low tumors in hormone receptor-positive patients were associated with larger size, higher grade,[11] and less lymphovascular invasion. In our study, tumor size was actually greater in the HER2-zero group

compared to HER2 1+ and 2+ groups (28.7 mm vs. 23.3 mm and 22.8 mm, respectively). However, despite the smaller tumor size, the HER2 2+ ISH-negative group had the highest proliferative index (mean Ki-67: 23.9%), possibly reflecting more aggressive tumor behavior and contributing to worse outcomes. Other studies like Ayana Sato show lower Ki-67 in HER2-low in comparison with HER-2 zero yet there is no improvement in their overall survival.[12]

Differences in tumor grade, size, lymph node status, and proliferative index between HER2-zero and HER2-low tumors have been widely reported[2,3,13,14], but findings have been inconsistent[1,14-17] and often dependent on hormone receptor status.[2,3,11,18]

Genomic differences (PAM50) between HER2-low and HER2-zero tumors have also been observed in various studies[2,3,18], particularly in hormone receptor-positive patients[2]. Agostinetto et al. analyzed PAM50 profiles in 410 HER2-low patients and found that intrinsic HER2-enriched subtypes were more common among HER2-low tumors, especially in hormone receptor-positive cases. Nonetheless, no significant differences in disease-free survival (DFS) or overall survival (OS) were detected between HER2-low and non-HER2-low groups.[19]

There are conflicting evidence regarding the prognosis of HER2-low patients among studies. A large meta-analysis involving 636,535 patients reported better OS in HER2-low compared to HER2-zero, regardless of estrogen receptor status.[20] Similarly, in the study by Almstedt et al., which included 351 HER2-negative patients, 15-year DFS and the OS were higher in the HER2-low group.[9]

In contrast, two other studies by Tarantino and Man Yung with 232 and 415 patients, respectively, found no difference in survival between two groups of HER2-low and HER2-zero.[21,22] Denkert et al. found better DFS in triple-negative HER2-low tumors but no significant difference in hormone receptor-positive HER2-low cases.[3]

In a systematic review and meta-analysis by Molinelli et al., which screened 1,916 studies and included 42, with over 1,797,175 patients, HER2-low was associated with improved OS and DFS in early-stage disease, particularly among hormone receptor-positive patients. However, HER2-low tumors were associated with lower pathologic complete response (PCR) rates to neoadjuvant chemotherapy across all groups, while OS improved even in metastatic cases, regardless of hormone receptor status.[23]

Another meta-analysis by Ergun et al.[20], covering 636,535 patients, showed that HER2-low tumors comprised 67.5% of hormone receptor-positive cases and 48.6% of hormone receptor-negative cases. Among hormone-positive patients, premenopausal status, high tumor grade, younger age (<50), and larger tumors (T3/T4) were more common in HER2-zero cases. In both hormone receptor-positive and negative groups, HER2-low status was associated with better OS and DFS.[20]

In our study, recurrence and metastasis rates were highest in the HER2 2+ with ISH-negative group (26.1% recurrence in HER2 2+ with ISH-negative, 19.1% in HER2-zero and 11.5% in HER2 1+). Similarly, mortality was highest in the HER2 2+ with ISH-negative group compared to HER2-zero and HER2 1+.

Although differences in prognosis between HER2-low and HER2-zero tumors have been suggested in several studies,[3,8,9,13,17,25] many fail to demonstrate significant differences after adjusting for hormone receptor status.[2,14,15,18,24-27] As a result, current evidence does not support HER2-low as a distinct biological subtype.

In general, for estrogen receptor-positive breast cancer, HER2-low status should not be considered an independent prognostic or predictive factor in determining response to neoadjuvant chemotherapy.[28] One meta-analysis on 38 studies including 70,104 patientseven showed that HER2-zero tumors had higher PCR rates compared to HER2-low, both in hormone receptor-positive and triple-negative subsets.[29]

In our study, adjuvant chemotherapy was more frequently used in HER2-zero patients, while neoadjuvant chemotherapy was more common in HER2 2+ with ISH-negative cases. This may be attributed to

larger tumor sizes and preference for upfront surgery in HER2-zero patients, while the more aggressive nature of HER2 2+ with ISH-negative tumors led surgical decisions to use neo-adjuvant treatment for downstaging. Despite the large sample size and multi-center design which are strengths of the current study, there are some limitations.

The most significant is the lack of complete follow-up and survival data for all patients. Since the distinction between HER2-zero and HER2-low has only recently gained clinical importance, some pathology reports did not differentiate between 0 and 1+, leading to patient exclusion and possible misclassification. Furthermore, HER2 status in patients who received neoadjuvant chemotherapy and responded completely, was based on core biopsy only. Therefore, re-evaluation of HER2 status on the surgical specimen was not possible which could affect accuracy.

This study demonstrates that HER2-low breast cancer is a heterogeneous group, with HER2 1+ tumors showing the most favorable prognosis, and HER2 2+ with ISH-negative tumors displayed more aggressive behavior. Further research with standardized pathology protocols, larger sample sizes and long-term follow-up is needed to better define the biological and clinical implications of HER2-low status in breast cancer.

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