International Journal of Research and Review
[Indexed, Peer-Reviewed Journal]
Volume 13; Issue: 4; April 2026
Website: www.ijrrjournal.com
Research Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

HER2-Low Breast Cancer: A Clinicopathological Study

Hemangini Vora[1], Priti Trivedi[2], Nupur Patel[1], Kruti Rajvik[1], Bhumi Vaniya[1], Anisha Sharma[1], Nikul Gohel[1], Srushti Kardani[1]

[1]Immunohematology Lab, Cancer Biology Department, [2]Oncopathology Department,
The Gujarat Cancer & Research Institute, Medicity Civil Hospital Campus, Asarwa, Ahmedabad-380008

Corresponding Author: Dr Hemangini Vora

DOI: https://doi.org/10.52403/ijrr.20260406

ABSTRACT

Background: Breast cancer exhibits biological heterogeneity, and recent attention has focused on the subset of tumors classified as HER2-low. This study aimed to evaluate the clinicopathological characteristics and associations of HER2-low breast cancer.

Methods: A total of 100 female breast cancer cases with a median age of 52 years were analyzed. Clinicopathological parameters including age, menopausal status, tumor size, lymph node status, disease stage, histologic grade, Bloom–Richardson (BR) score, and hormone receptor status were assessed. HER2 status was categorized as HER2-low (1–2+ immunohistochemistry without FISH amplification) or HER2-negative.

Results: Of the 100 cases, 65 were classified as HER2-low and 35 as HER2-negative. HER2-low tumors were significantly more frequent in histologic grade III tumors compared to grade I–II tumors. A similar trend was observed in tumors with high BR scores compared to low or intermediate BR scores. No significant association was observed between HER2-low status and age, menopausal status, tumor size, lymph node involvement, or disease stage. Among hormone receptor subgroups, HER2-low incidence was significantly higher in hormone receptor–positive tumors with low or intermediate BR scores compared to hormone receptor–negative tumors with high BR scores (81% vs. 59%, $P = 0.019$). A similar association was noted with histologic grade.

Conclusion: HER2-low breast cancer is significantly associated with higher histologic grade and BR score, particularly within specific hormone receptor subgroups. These findings suggest that HER2-low tumors represent a biologically distinct subset of breast cancer, independent of traditional clinicopathological parameters.

Keywords: Breast cancer, HER2-low breast cancer, HER2-low tumor

INTRODUCTION

Breast cancer is a biologically heterogeneous disease with diverse molecular subtypes that influence prognosis and therapeutic decision-making. Traditionally, classification based on hormone receptor (estrogen receptor [ER] and progesterone receptor [PR]) status and human epidermal growth factor receptor 2 (HER2) expression has guided treatment strategies and risk stratification. HER2 status has historically been dichotomized as positive or negative; however, emerging evidence has identified a distinct subset of tumors characterized by low HER2 expression, termed HER2-low breast cancer**,** defined as immunohistochemistry (IHC) 1+ or 2+

staining without HER2 gene amplification by fluorescence in situ hybridization (FISH) [1]. HER2-low breast cancer represents a biologically and clinically relevant subgroup, accounting for approximately 45–55% of all breast cancers, with a higher prevalence reported among hormone receptor–positive tumors [2]. Although classified as HER2-negative under current guidelines, HER2-low tumors have recently gained attention due to their responsiveness to novel antibody–drug conjugates, such as trastuzumab deruxtecan, which have demonstrated significant survival benefits in this population [3]. These findings have highlighted the importance of better understanding the clinicopathologic characteristics and prognostic implications of HER2-low breast cancer.

Several studies have suggested that HER2-low expression may be associated with distinct tumor biology, including higher histologic grade, increased proliferative activity, and variable associations with hormone receptor status [4-5]. However, data regarding the relationship between HER2-low status and established prognostic parameters such as tumor grade, Bloom–Richardson (BR) score, disease stage, and lymph node involvement remain inconsistent, particularly across different populations. Furthermore, the interaction between HER2-low expression and hormone receptor status in relation to tumor differentiation and aggressiveness is not fully elucidated.

In this context, the present study aimed to evaluate the frequency of HER2-low breast cancer in a cohort of female breast cancer patients and to analyze its association with clinicopathologic features, including age, menopausal status, tumor size, lymph node status, disease stage, histologic grade, BR score, and hormone receptor status. By correlating HER2-low expression with tumor grade and differentiation, particularly within hormone receptor–defined subgroups, this study seeks to contribute to the growing body of evidence defining the biological and clinical significance of HER2-low breast cancer.

MATERIAL AND METHOD

Patients Characteristics

This retrospective study was approved by Institutional Scientific Review Board and Ethics Committee, included 100 triple negative breast cancer patients treated at Gujarat Cancer and Research Institute during the time period of 2015 to 2018. Detailed clinical history of patients such as age, menopausal status, disease stage, histopathological findings, treatment offered and disease status was recorded from the case files maintained at the Medical Record Department of the Institute. Disease staging was done according to AJCC classification. Patients subjected to neo-adjuvant treatment and HIV/HCV/HBsAg positive patients were excluded from this study.

Immunohistochemical localization

Formalin-fixed paraffin embedded tissue blocks were cut into 4µm thin sections using a microtome (Leica, Germany) and placed on slides coated with 3-aminopropyl triethoxysilane (APES). Immunohistochemical localization of ER, PR, and Her-2 was performed on histopathologically confirmed FFPE tumor tissue blocks using Ventana Benchmark XT autoimmunostainer and Ventana reagents (Ventana, USA). The protocol consists of the following steps: deparaffinization using EZ solution; antigen retrieval using cell conditioning (CC1); incubation with ultra-view DAB inhibitor for 4 minutes; 100µl of primary antibody for ER (clone SP1), PR (clone 1E2) for 16 minutes at 37ºC, and Her2 (clone 4B5) for 32 minutes at 37ºC from Roche Ventana; ultra view HRP multimer for 8 minutes; counterstain with hematoxylin for 8 minutes; bluing reagent for 4 minutes; and mounted with DPX.

Scoring

Two individual observers scored the sections under microscope. Nuclear staining pattern for ER and PR and membranous staining

pattern Her2 was noted. Based on the surrogate molecular categorization, all of the cases were classified as luminal A, luminal B, HER2 enriched, and triple-negative breast cancer. Patients were classified as HER2 low (1–2+ staining without amplification on FISH), HER2 3+ (full membranous staining), and HER2 negative (no staining or incomplete weak membrane staining in around 10% of tumor cells).

Statistical analysis

Statistical analysis was carried out using SPSS statistical software version 27 (SPSS Inc, USA). The chi-square and Fischer exact tests were performed for comparison of the clinicopathological parameters with HER2 status. P values ≤ 0.05 were considered statistically significant.

RESULTS

A total of 100 female patients with breast cancer were enrolled in this study. The age of the patients ranged from 27 to 83 years, with a median age of 52 years. Of these, 71 patients were postmenopausal and 29 were premenopausal. Histopathological examination revealed invasive ductal carcinoma (IDC) in 89 cases, while 11 cases showed IDC with an associated ductal carcinoma in situ component. Tumor size assessment showed that 85 patients had T1 or T2 tumors, whereas 15 patients had T3 or T4 tumors. Lymph node involvement was present in 65 cases, while 35 cases showed no nodal involvement. Based on tumor size and nodal status, 73 patients were classified as having early-stage disease (stage I–II), and 27 patients had advanced-stage disease (stage III–IV). Histologic grading demonstrated grade III tumors in 43 cases, while 57 cases had grade I or II tumors. Bloom–Richardson (BR) scores were available for 95 cases; among these, 37 tumors had high BR scores and 58 had low or intermediate BR scores.

Among the 100 cases, 65 were classified as HER2-low (1+ or 2+ immunohistochemical staining without amplification by FISH), while 35 cases were HER2-negative (Figures 1-3). Within the HER2-low group, 21 cases were ER+ PR+ and 14 cases were ER- PR-. The prevalence of HER2-low tumors was significantly higher in histologic grade III tumors (46%, 20/43) compared with grade I or II tumors (26%, 15/57; P = 0.036). A similar trend was observed in tumors with high BR scores (46%, 17/37) compared with those having low or intermediate BR scores (28%, 16/58). No significant associations were identified between HER2-low status and age, menopausal status, tumor size, lymph node involvement, or disease stage (Table 1).

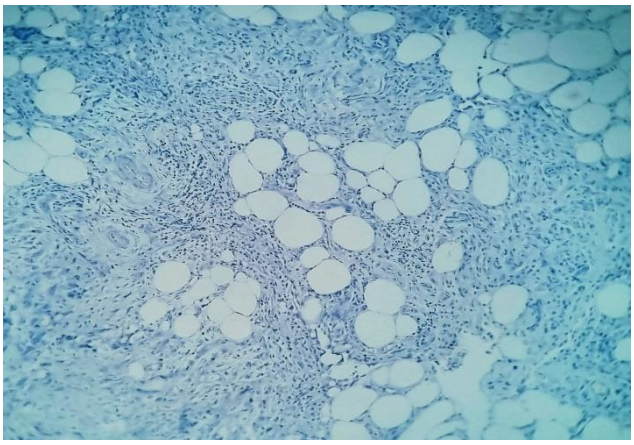

Figure 1: No expression of Her-2-neu in breast carcinoma.

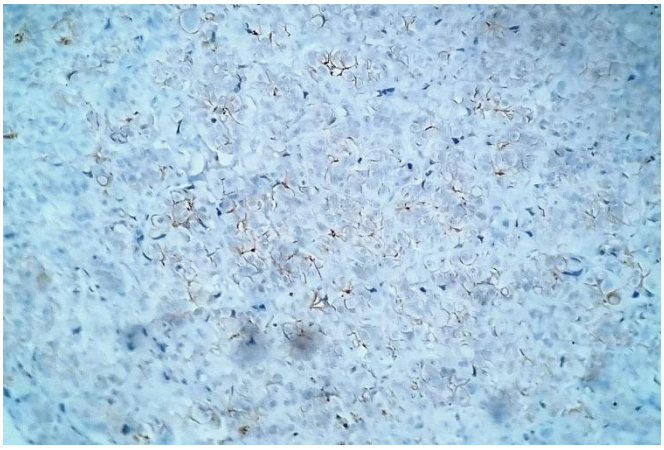

Figure 2: Her-2-neu 1+ expression in breast carcinoma.

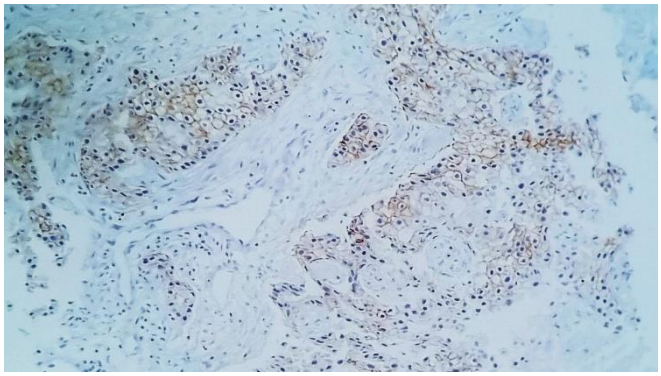

Figure 3: Her-2-neu 2+ expression in breast carcinoma.

Table 1: Correlation between Her-2-neu expression and Clinicopathological parameters

Parameters	**No. of patients N (%)**	**Her-2-neu expression**		**χ^2**	**r**	**P**
		Negative	**Low**			
Age						
< 52 years	49(49)	29(59)	20(41)	1.429	-0.120	0.232
≥ 52 years	51(51)	36(71)	15(29)			
Menopausal status						
Pre	29(29)	17(59)	12(41)	0.731	-0.085	0.393
Post	71(71)	48(68)	23(32)			
Histopathology						
IDC	89(89)	57(64)	32(36)	0.324	-0.057	0.569
IDC+DCIS	11(11)	08(73)	03(27)			
Tumor size						
T1-T2	85(85)	55(65)	30(35)	0.022	-0.015	0.883
T3-T4	15(15)	10(67)	05(33)			
Lymph node status						
N0	35(35)	22(63)	13(37)	0.109	-0.033	0.742
N1-N3	65(65)	43(66)	22(33)			
Stage						
Early	73(73)	46(74)	27(37)	0.469	-0.068	0.493
Advance	27(27)	19(70)	08(30)			
Histologic Grade						
I or II	57(57)	42(74)	15(26)	4.394	0.210	**0.036**
III	43(43)	23(54)	20(46)			
BR Score						
Low (3-5) or Intermediate (6-7)	58(61)	42(72)	16(28)	3.359	0.188	0.067
High (8-9)	37(39)	20(54)	17(46)			

Further analysis comparing hormone receptor positive (ER+ PR+) and hormone receptor negative (ER- PR-) tumors demonstrated a higher incidence of HER2 low expression in hormone receptor positive tumors with low or intermediate BR scores (81%, 13/16) compared with hormone receptor negative tumors with high BR scores (59%, 10/17; P = 0.019). A similar trend was observed with respect to histologic grade of the tumor. Further, significant associations were not found with age, menopausal status, tumor size, lymph node status, or disease stage (Table 2).

Table 2: Correlation of Her-2-neu expression with Hormone Receptor Status

Parameters	**No. of patients N (%)**	**Her-2-neu expression**		χ^2	**r**	**P**
		Hormone receptor Positive	**Hormone receptor Negative**			
Age						
< 52 years	20(57)	13(65)	07(35)	0.486	-0.118	0.486
≥ 52 years	15(43)	08(53)	07(47)			
Menopausal Status						
Pre	12(34)	07(58)	05(42)	0.021	0.025	0.864
Post	23(66)	14(61)	09(39)			
Histopathology						
IDC	32(91)	18(56)	14(44)	3.251	0.250	0.071
IDC+DCIS	03(09)	03(100)	00(00)			
Tumor size						
T1-T2	30(84)	19(63)	11(37)	0.243	-0.167	0.622
T3-T4	05(14)	02(40)	03(60)			
Lymph node status						
N0	13(37)	07(54)	06(46)	0.326	0.097	0.568
N1-N3	22(63)	14(64)	08(36)			
Stage				0.331	0.167	0.155
Early	27(77)	15(56)	12(44)			
Advance	08(23)	06(75)	02(25)			
Histologic Grade						
I or II	15(43)	11(73)	04(27)	1.944	-0.231	0.163
III	20(57)	10(50)	10(50)			
BR Score						
Low (3-5) or Intermediate (6-7)	16(48)	13(81)	03(19)	5.544	-0.410	**0.019**
High (8-9)	17(52)	07(41)	10(59)			

DISCUSSION

Breast cancer is a heterogeneous disease characterized by diverse clinicopathological and molecular features that influence prognosis and therapeutic response. In the present study, we evaluated the clinicopathological characteristics of breast cancer cases with particular emphasis on HER2-low expression and its association with tumor grade, Bloom–Richardson (BR) score, and hormone receptor status.

The median age of patients in this cohort was 52 years, with the majority being postmenopausal, which is consistent with the epidemiological pattern of breast cancer reported in Indian and other Asian populations, where the peak incidence occurs at a relatively younger age compared to Western populations [6,7]. A higher proportion of cases presented with early-stage disease, most tumors were invasive ductal carcinoma, reflecting its known

predominance among breast cancer histological subtypes [8].

In this study, 65% of cases were classified as HER2-low**,** a proportion comparable to previously reported studies where HER2-low tumors constitute approximately 45–65% of all breast cancers [2,4-5]. HER2-low breast cancer has recently emerged as a biologically distinct subgroup, particularly due to its therapeutic relevance with antibody–drug conjugates such as trastuzumab deruxtecan [3].

A significant association was observed between HER2-low expression and higher histologic grade**,** with grade III tumors showing a higher incidence of HER2-low status compared to grade I/II tumors. A similar trend was noted with high BR score tumors**,** suggesting that HER2-low expression may be linked to increased tumor aggressiveness. These findings are in agreement with prior studies that have reported a higher prevalence of HER2-low expression in poorly differentiated tumors and tumors with higher proliferative indices [6,9]. This association may reflect underlying biological heterogeneity within HER2-negative breast cancers.

Importantly, HER2-low expression was not associated with age, menopausal status, tumor size, lymph node involvement, or disease stage**,** indicating that HER2-low status may be independent of traditional clinicopathological parameters. Similar observations have been reported by Denkert et al. and Schettini et al., who found no consistent association between HER2-low status and tumor stage or nodal status [4,10].

When stratified by hormone receptor status, HER2-low expression was more frequent in hormone receptor–positive tumors**,** particularly those with low or intermediate BR scores. This finding aligns with existing literature demonstrating that HER2-low tumors are more commonly estrogen receptor–positive and luminal in phenotype [5,10]. The significantly higher incidence of HER2-low tumors in hormone receptor–positive cases with lower BR scores compared to hormone receptor–negative cases with high BR scores suggests potential biological interplay between hormone receptor signaling and HER2 expression at low levels.

The observed trend with histologic grade further supports the concept that HER2-low breast cancers are a heterogeneous group, spanning both less aggressive hormone receptor–positive tumors and more aggressive subtypes. This heterogeneity has important clinical implications, particularly in light of emerging targeted therapies that expand treatment options for patients previously classified as HER2-negative [7,11].

Despite its strengths, this study has certain limitations, including a relatively small sample size. Future studies with larger cohorts and survival analyses are warranted to further elucidate the clinical and therapeutic implications of HER2-low breast cancer.

CONCLUSION

This study demonstrates that HER2-low breast cancer constitutes a substantial proportion of cases and is significantly associated with higher histologic grade and BR score, particularly in hormone receptor–positive tumors. These findings add to the growing body of evidence supporting HER2-low breast cancer as a distinct biological entity with potential therapeutic relevance.

Declaration by Authors

Ethical Approval: Approved

Acknowledgement: None

Source of Funding: None

Conflict of Interest: No conflicts of interest declared.

REFERENCES

1. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update**.** J Clin Oncol. 2018;36(20):2105–2122. doi: 10.1200/JCO.2018.77.8738

2. Schettini F, Chic N, Braso-Maristany F, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer**.** NPJ Breast Cancer. 2021;7(1):1. doi: 10.1038/s41523-020-00208-2
3. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer**.** N Engl J Med. 2022;387(1):9–20. doi: 10.1056/NEJMoa2203690
4. Denkert C, Seither F, Schneeweiss A, et al. Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. Lancet Oncol. 2021;22(8):1151-1161. doi: 10.1016/S1470-2045(21)00301-6
5. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: Pathological and clinical landscape**.** J Clin Oncol. 2020;38(17):1951-1962. doi: 10.1200/JCO.19.02488
6. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. doi: 10.3322/caac.21492
7. Malvia S, Bagadi SA, Dubey US, Saxena S. Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2017;13(4):289–295. doi: 10.1111/ajco.12661
8. Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van de Vijver MJ. WHO Classification of Tumours of the Breast, WHO Classification of Tumours, 4th Edition, Volume 4, 2012, ISBN-13, 978-92-832-2433-4
9. Eggemann H, Ignatov T, Burger E et al. Moderate HER2 expression as a prognostic factor in hormone receptor positive breast cancer. Endocr Relat Cancer. 2015;22(5):725-33. doi: 10.1530/ERC-15-0335
10. Schettini F, Pascual T, Conte B et al. HER2-enriched subtype and pathological complete response in HER2-positive breast cancer: A systematic review and meta-analysis. Cancer Treat Rev. 2020; 84:101965. doi: 10.1016/j.ctrv.2020.101965
11. Tarantino P. Emerging Treatments and Evolving Paradigms in HER2-Low Breast Cancer. Cancer Network, Home of the Journal Oncology.2023;37:496-501

How to cite this article: Hemangini Vora, Priti Trivedi, Nupur Patel, Kruti Rajvik, Bhumi Vaniya, Anisha Sharma et al. HER2-Low breast cancer: a clinicopathological study. *International Journal of Research and Review*. 2026; 13(4): 67-73. DOI: *10.52403/ijrr.20260406*

******