International Journal of Clinical and Diagnostic Pathology

ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2025; 8(3): 26-35
Received: 09-06-2024
Accepted: 12-07-2024

All author's name and affiliations are given below, after references

Clinicopathological and prognostic comparative study of HER2-low versus HER2-zero breast cancer

Samiksha R Shindegalwekar, Yogesh M Mistry, Bhawana Chaudhari, Ajay Junnarkar, Bhumi Chhatbar, Dipayan Nandy, Ghanish Panjwani, Pramod Patil, Samarth Chhatbar, Himanshu Mekap, Amrendra Kumar, Santosh Vandanasetti, Ameya Koranne and Malik Jamadar

DOI: https://www.doi.org/10.33545/pathol.2025.v8.i3a.2090

Abstract

Background: Breast cancer is a biologically diverse disease and recent advancements further highlight the significance of the level of HER2 expression for determining prognosis and therapy. While HER2-positive tumors respond significantly to targeted anti-HER2 therapy, the novel emerging subgroup of HER2-low breast cancer, defined by immunohistochemistry expression 1+ or 2+ with negative for gene amplification on in-situ hybridization has shown good results following the treatment by antibody-drug conjugates (ADCs) like trastuzumab deruxtecan. However, there remains limited comparative data on HER2-low versus HER2-zero breast cancers.

Objective: To compare the clinicopathological features and disease-free survival outcomes between HER2-low and HER2-zero breast cancer patients and to assess their prognostic differences, especially in relation to hormone receptor (HR) status.

Methods: A retrospective, single-center study was done at Kailash Cancer Hospital and Research Centre, Gujarat, involving 783 HER2-negative breast cancer patients who were subjected to surgical and systemic interventions between January 2016 and December 2023. This cohort was further subdivided into tumors with low HER2 expression (N=329) and tumors with absent/ zero HER2 expression (N=454) groups analyzed over IHC and ISH results. Clinicopathological data, treatment details and disease-free survival outcomes were interpretated using chi-square tests, Kaplan-Meier survival curves, and Cox proportional hazards regression models.

Results: In this study, HER2-low tumors were found to be frequently positive for hormone receptor expression (ER &/ PR) (81.76% in HER2 low and 67.62% in HER2 zero, p<0.0001), they were more frequently associated with lymphovascular invasion (72.34% in HER2 low and 59.25% in HER2 zero, P=0.0001), nodal involvement (67.47% in HER2 low and 56.60% in HER2 zero, P=0.002) and presented at advanced stage (44.07% in HER2 low and 34.8% in HER2 zero, P=0.008. Other factors including age, tumor size or histological grade did not reveal any significant differences amongst the two groups. Among the patients with hormone receptor negative breast cancers, those with low HER2 expression revealed a worse disease-free survival (P=0.007) when followed up to a median follow-up period of 51 months. However, disease free survival was not significantly different in overall cohort or those with HR-positive subgroup. On performing multivariate analysis, HER2-low status, HR-negativity, and LVI were identified as independent predictors of worse DFS.

Conclusion: Breast cancers with low HER2 expression in hormone receptor negative cases show a trend towards poorer prognosis compared to HER2-zero tumors. These findings further emphasizes that HER2 low tumors are heterogenous and there is a need for refined classification, standardized HER2 testing, and prospective validation in larger, multicenter studies to improve patient stratification and treatment planning.

Keywords: HER2 low, Breast cancer, Hormone receptor, treatment planning, trastuzumab deruxtecan

Corresponding Author:
Dr. Samiksha R Shindegalwekar
(MBBS, MD Pathology), Fellow in Oncopathology, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Introduction

Breast cancer is the most common cancer affecting female globally [1] along with being the most common cause for cancer associated with mortality in female worldwide [1]. It is a heterogeneous disease and reveals varied molecular subtypes. Every subtype has a different clinical behavior and responds differently to therapy. Overexpression of human epidermal growth factor receptor 2 (HER2) is a well-established biomarker associated with poor prognosis in breast cancer and such cases often show increased risk of disease recurrence and a poor prognosis [2-4].

Along with this, the HER2 overexpression also act as therapeutic target for anti-HER2 agents [2] including trastuzumab, lapatinib, adotrastuzumab emtansine (T-DM1) etc., which have significantly improved survival rates and prognosis in HER2-positive breast cancer [5-7]. Breast cancers which on immunohistochemistry (IHC) show an expression of 3 + or 2 + with ERBB2 gene amplification detected by in situ hybridization (ISH) [2] are defined as HER2 positive. Tumors which on immunohistochemistry (IHC) show an expression of 0, 1 + or 2 + with no ERBB2 gene amplification detected by in situ hybridization are defined as HER2 negative [6, 8]. However, some HER2-negative tumors with an IHC expression of 1 + and 2+ with negative gene amplification on ISH do not entirely lack HER2 expression but express low levels of HER2 protein on the cell surface. These tumors are now defined as HER2-low tumors [2].

HER2-Positive vs HER2-Negative Breast Cancer

HER2 (also known as c-erbB-2), a human epidermal growth factor receptor and oncogene, encodes a transmembrane glycoprotein with intrinsic tyrosine kinase activity that plays a key role in cellular signaling pathways regulating proliferation and survival [9]. Amongst all cases of breast cancer, approximately 20-25% show HER2 overexpression and thus aggressive tumor behavior and poor prognosis [10]. It is important to identify these HER2-positive tumors as they benefit from targeted monoclonal antibody therapies like trastuzumab which inhibits HER2 receptor signaling, improving overall survival and reducing the risk of recurrence [11].

HER2-negative breast cancers, on the contrary, do not exhibit HER2 overexpression or gene amplification and thus not suitable candidates for traditional HER2 targeted therapies existing for HER2 overexpressing tumors. The emerging distinct category-HER2-low breast cancer has led to increasing interest in exploring its unique clinical and pathological characteristics, which may have important implications for personalized patient management.

Emerging Concept of HER2-Low Breast Cancer

HER2-low breast cancer is defined as tumors when subjected to immunohistochemistry investigation reveal an expression of score 1+ or 2+ and lack ERBB2 gene amplification when determined by in-situ hybridization [10]. Neither these tumors qualify as HER2-positive according to traditional criteria which require HER2 overexpression or amplification, nor do they entirely lack HER2 expression. These tumors display some level HER2 expression not sufficient to be categorized as overexpression. This suggests there may be biological and therapeutic differences when compared to HER2-negative cancers [12].

Researches reveals that tumors with low HER2 expression may exhibit different prognostic outcomes compared to their HER2-negative counterparts, potentially due to their differential receptor expression profiles or other underlying molecular characteristics [2]. Given their lack of response to traditional HER2-targeted therapies, HER2-low breast cancers are being investigated as a potential distinct molecular subtype with unique features such as tumor grade, histology, and treatment response patterns.

The clinical significance of HER2-low status is receiving increasing attention, particularly following the development of an antibody-drug conjugate (ADC) trastuzumab deruxtecan which shows promising results HER2-low metastatic breast cancer [13].

Although increasing research is focused on distinguishing HER2-low from HER2-negative breast cancers in terms of molecular and clinical characteristics, a unified approach regarding their management has yet to be established. Till date, few comparative studies have systematically examined the clinical and pathological features of HER2-low and HER2-negative breast tumors, particularly with respect to histological grade, receptor status, molecular subtype, and clinical outcomes.

Aims and objectives

The main aim of this study is to compare the clinical, pathological characteristics and survival outcomes between breast cancers with low HER2 expression versus those with absent/ zero HER2 expression. By studying these differences between two subgroups, this study aims to increase understanding of HER2-low breast tumors and provide insights to guide therapeutic strategies for this distinct subset of breast tumors.

Methodology

This is a single-center, retrospective, comparative study conducted on patients diagnosed to have carcinoma breast and have undergone surgery between January 2016 and December 2023 at Kailash cancer hospital and research centre, Goraj, Gujarat. The institutional pathology archives and hospital information system were used for data retrieval. Strict criteria were defined to include and exclude the patients to ensure the reliability of data and consistency in interpretation throughout the study.

Inclusion Criteria

Patients with newly diagnosed invasive breast carcinoma with definite surgical and systemic treatment records and confirmed pathological assessments, including IHC and FISH results for equivocal HER2 are included in this study.

Exclusion Criteria

Patients with HER2-over-expression tumors i.e., IHC expression score of 3+ or 2+ with ERBB2 gene amplification by in-situ hybridization, unknown HER2 status, those with incomplete surgical or pathological records and those with metastatic disease at presentation are excluded from this study.

The patients were followed up till last visit for survival information, deadline being October 2024.

The clinicopathological and treatment data were extracted retrospectively from archived pathology records and electronic hospital databases. Each case was assessed for the following parameters:

- Age
- Gender
- Hormone receptor (HR) status (Estrogen, progesterone)
- HER2 status (Immunohistochemistry and in-situ hybridisation)
- Tumor laterality (right/left)
- Histological type and morphology
- Tumor grade (based on modified Bloom-Richardson grading)
- Lymphovascular invasion (LVI)
- Maximum tumor size (in centimeters)
- Tumor (T), Node (N), and Stage grouping (AJCC staging)

- Pathological stage
- Presence of local recurrence or distant metastasis (Mets)
- Type of surgery performed
- Type of systemic therapy received (Neoadjuvant chemotherapy (NACT), Adjuvant chemotherapy (CT), Radiotherapy (RT), Hormonal therapy (HRT))
- Disease-Free Survival (DFS)
- Overall Survival (OS)

The study protocol was approved by the Ethics Committee of Kailash cancer hospital and research centre, Goraj, Gujarat.

When subjected to immunohistochemistry investigation, those tumors which showed nuclear positivity in > 1% of nuclei of invasive neoplastic cells for hormone receptors-estrogen or progesterone were reported as Hormone receptor positive (ER&/PR). The clone used for ER IHC is monoclonal rabbit anti-human estrogen receptor alpha clone EP1 and that for PR IHC is monoclonal mouse anti-human progesterone receptor clone PgR636.

For assessing levels of HER2 expression, both immunohistochemistry and in-situ hybridization results were interpretated according to the most recent version of the American Society of Clinical Oncology/College of American Pathologists Clinical Practice (ASCO/CAP) guidelines that was prevalent at the time of surgery. The clone used for HER2 IHC is polyclonal rabbit anti-human c-erbB-2 oncoprotein. FISH was performed for equivocal HER2 using a dual probe (Zytovision SPEC ERBB2/CEN17-HER2/Neu (17q12), (Green) & CEP17 (Orange) dual color probe). Those breast tumors with immunohistochemistry expression of score 1+ and those with expression score of 2+ but lacking ERBB2 gene amplification by in-situ hybridization were categorized as HER2-low tumors. Those tumors which revealed an immunohistochemistry expression of score 0 were categorized as HER2 zero tumors.

The disease-free survival (DFS) was defined as the time from surgery to evidence of local-regional recurrence or presence of distant metastasis [14].

The collected data was entered into an Excel sheet and all statistical analyses were interpretated using R studio software version 2024.04.1. The clinical and pathological features were interpretated using chi-square. The disease-free survival curve was generated using Kaplan–Meier method, to study survival outcomes between HER2 low and HER2 zero groups in our cohort. Further, our cohort was sub-divided according to hormone receptor status (Hormone receptor positive vs. Hormone receptor negative) and compared for survival outcome differences between these sub-groups. To evaluate prognostic factors, univariate Cox regression was used to analyze each variable separately, followed by multivariate analysis to determine which factors independently influenced outcomes. P value less than 0.05 was considered significant.

Results and data analysis

Between January 2016 and December 2023, 1468 patients who were diagnosed with breast cancer received surgical intervention at Kailash cancer hospital and research centre, Goraj. Of these, 486 patients were HER2 +3 on IHC, 104 were HER2 positive on FISH, 26 patients with no FISH records for equivocal HER2 and 44 patients with incomplete surgical records. 25 patients presented with metastasis at presentation. Hence, after excluding these patients, our cohort included 783 patients for this study.

The mean age of patients was 51.82 years (range: 22-90 years). Most patients (N=686; 87.61%) were ≤ 65 years of age, while 97 (12.38%) were > 65 years. The largest age group was 51-60 years (N=231; 29.50%), followed closely by the 41-50 years group (N=229; 29.24%).

Table 1: Age distribution of cohort

	N	Minimum	Maximum	Mean	Standard deviation
Age (in years)	783	22	90	51.82	11.850

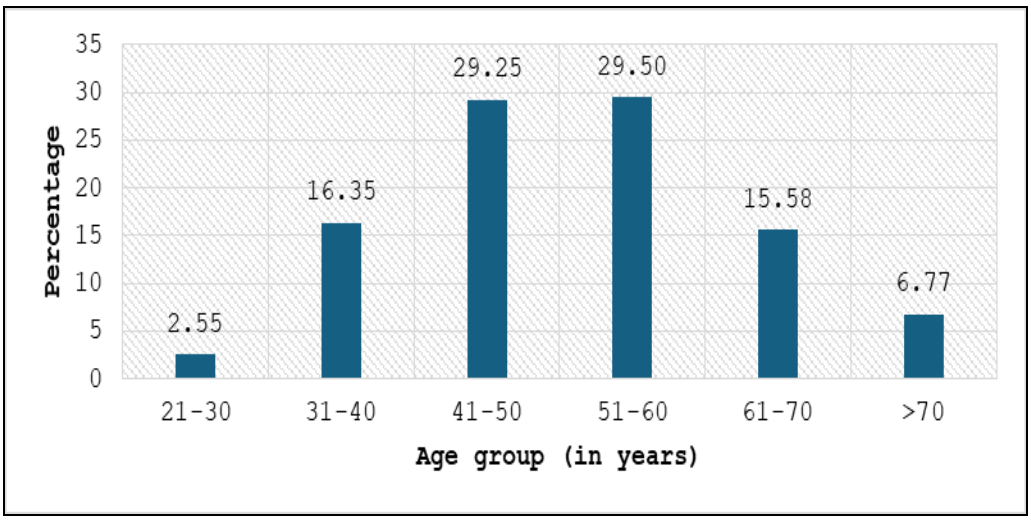

Fig 1: Age distribution of cohort

Among the study cohort, 329 patients (42.01%) had tumors with low HER2 expression (107 with HER2 1+ and 222 with HER2 2+/ISH−), while 454 patients (57.98%) had tumors with zero HER2 expression. In terms of hormone receptor status, 207 patients (26.43%) were negative for hormone receptors and 576 (73.56%) were positive for hormone receptors.

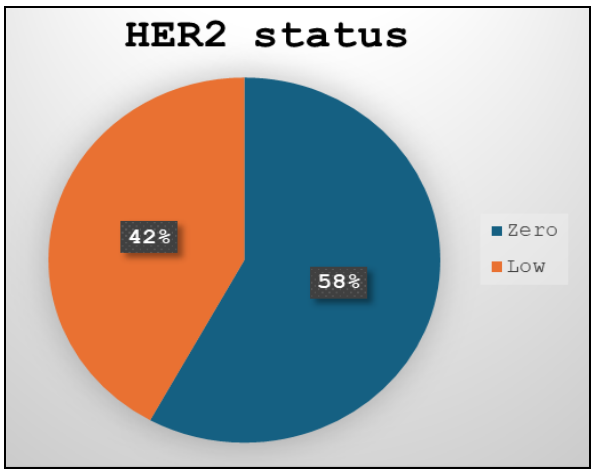

Fig 2: HER2 distribution of cohort

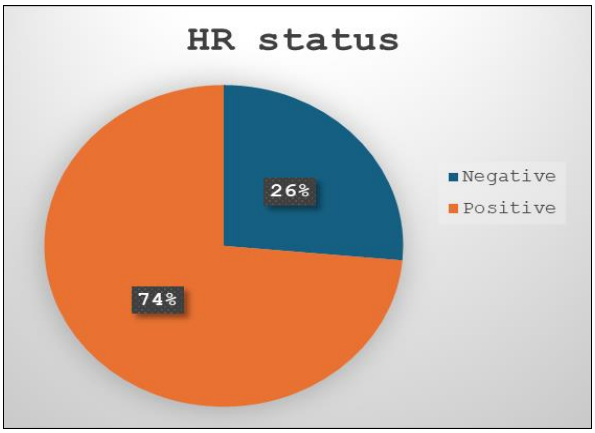

Fig 3: HR distribution of cohort

The average tumor size was 4.09cms ranging from 0.1cm to 20.0cm. Laterality was fairly balanced (right breast=49.04% and left breast=50.95%).

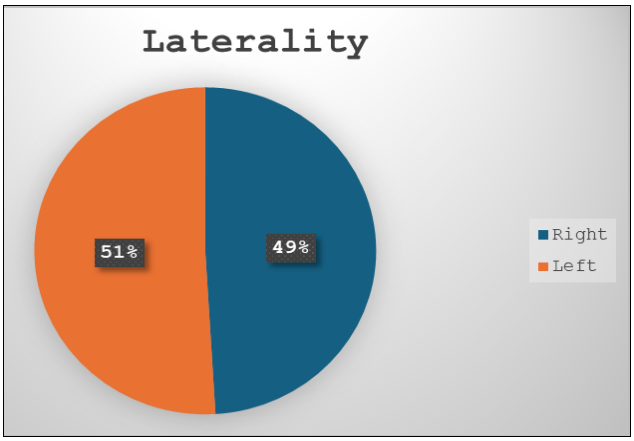

Fig 4: Laterality distribution of cohort

Table 2: Maximum tumor size distribution of cohort

	N	Minimum	Maximum	Mean	Standard deviation
Maximum tumor size (in cms)	783	0.1	20.0	4.090	2.1600

Invasive ductal carcinoma was the most prevalent histological subtype (N=669; 85.44%) followed by invasive lobular carcinoma (N=40; 5.1%). Ductal carcinoma in situ (DCIS) was identified in 44.69% of cases, with high-grade DCIS exhibiting comedonecrosis being the most frequent subtype (N=233; 29.75%).

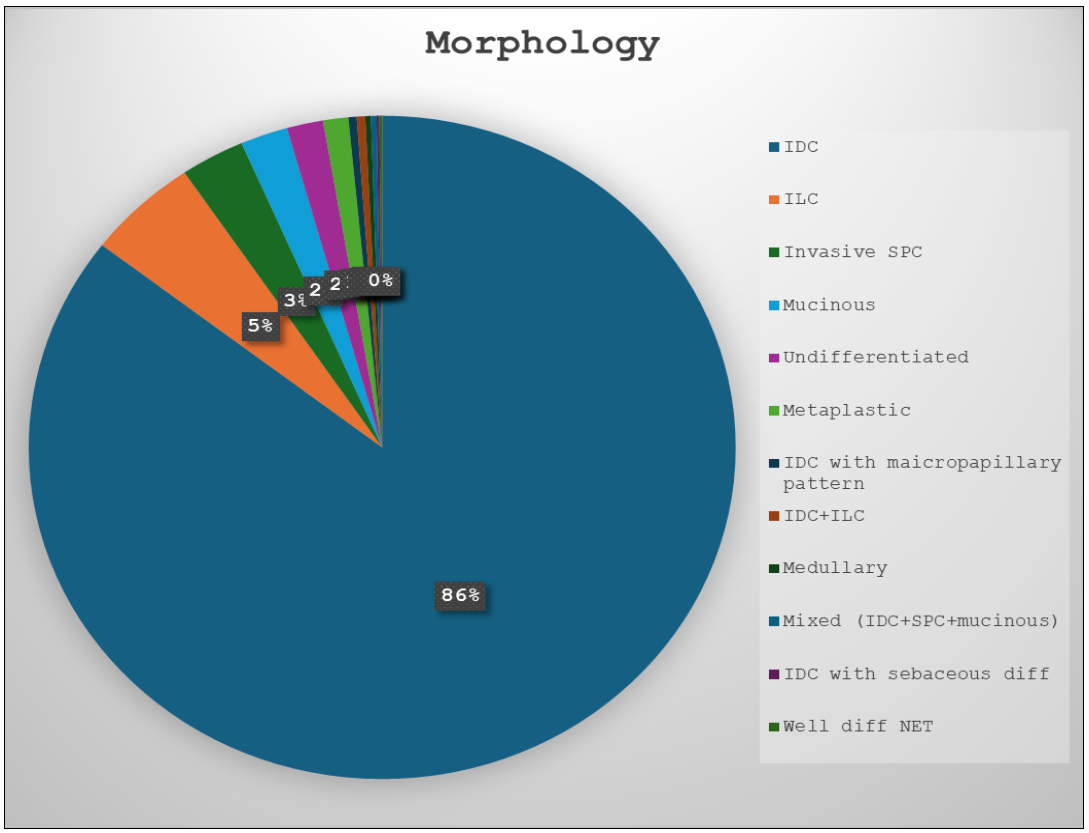

Fig 5: Morphology frequency of cohort

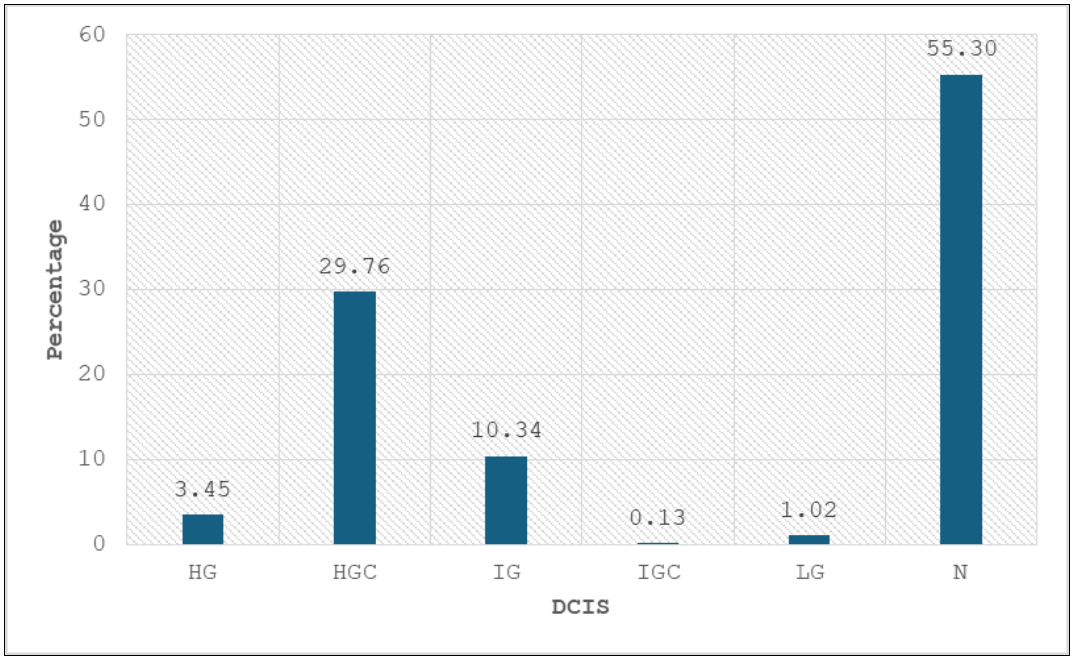

Fig 6: DCIS distribution of cohort

The total study population, 186 patients received neoadjuvant (pre-operative) chemotherapy while 609 received adjuvant (post-operative) chemotherapy. Radiotherapy was administered to 428 patients and 576 received hormone therapy. The most frequently performed surgical procedure was modified radical mastectomy (N=629; 79.2%).

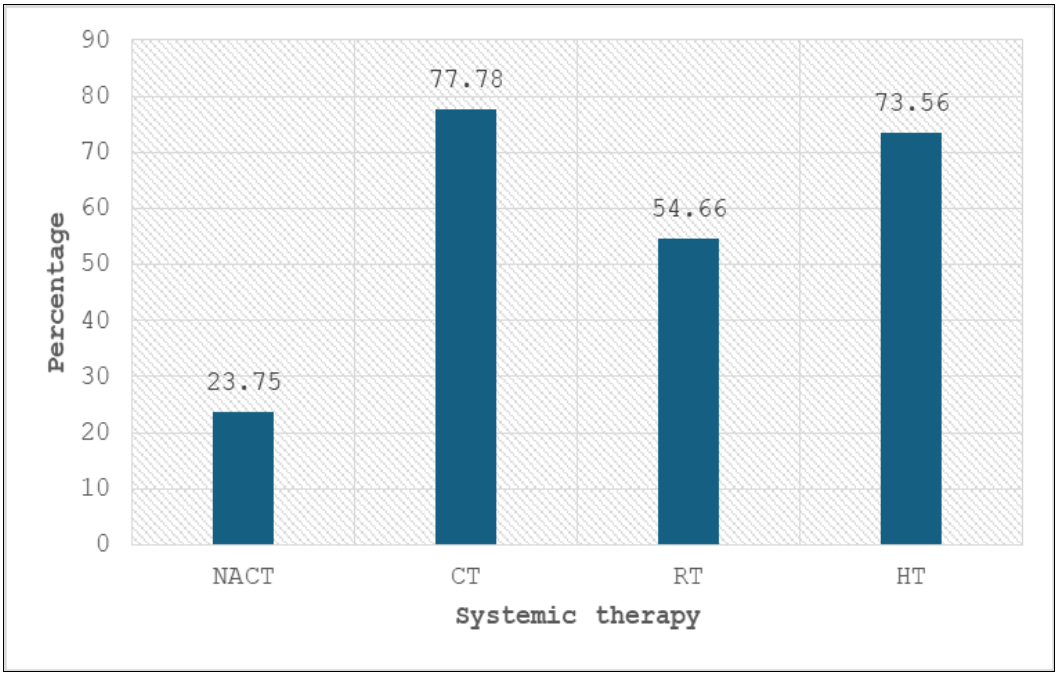

Fig 7: Systemic therapy given to the cohort

Hormone receptor positivity was significantly more common in HER2-low tumors than in HER2-zero tumors (81.76% vs. 67.62%, p<0.0001). HER2-low cancers show significantly more lymphovascular invasion (LVI), (72.34% vs 59.25%, P=0.0001) and revealed more frequent association with nodal involvement, (67.47% vs 56.60%, P=0.002). HER2-low tumors are more frequently associated with a higher stage at presentation (44.07% vs 34.8%, P=0.008) according to this study.

In this study, the HER2-low and HER2-zero groups showed comparable distributions with respect to age, tumor size and tumor grade.

Median follow-up period was of 51 months (ranging from 10 months to 104 months), over which 55 total disease-free survival events were recorded. Amongst these, 5 patients experienced local-regional recurrence and 50 patients developed metastasis at distant sites. Of these 55 events, 26 were recorded in HER2-zero group and 29 were recorded in HER2-low group.

Only one death occurred during the follow-up period and it was due to breast cancer. This event occurred in the HER2-low group.

Table 3: Clinical and pathological features comparison between HER2 low and HER2 zero tumors

		Her 2 zero		Her 2 low		Total		P-Value
		Number	Percentage	Number	Percentage	Number	Percentage	
Age group (in years)	<=65	397	87.44	289	87.84	686	87.61	0.867
	>65	57	12.55	40	12.15	97	12.38	
Hormone receptor status	Negative	147	32.37	60	18.23	207	26.43	<0.0001
	Positive	307	67.62	269	81.76	576	73.56	
Lymphovascular invasion	No	185	40.74	91	27.65	276	35.24	0.0001
	Yes	269	59.25	238	72.34	507	64.75	
Nodal status	N0	197	43.39	107	32.52	304	38.82	0.002
	N1/2/3	257	56.60	222	67.47	479	61.17	
Grade Group	1	35	7.70	20	6.07	55	7.02	0.378
	2+3	419	92.29	309	93.92	728	92.97	
Size Group (in cms)	<=5	350	77.09	255	77.50	605	77.26	0.891
	>5	104	22.90	74	22.49	178	22.73	
Stage	I+II	296	65.19	184	55.92	480	61.60	0.008
	III	158	34.80	145	44.07	303	38.69	

Kaplan-Meier analysis of disease-free survival (DFS) revealed no significant difference between tumors with low and zero HER2 expression overall (P=0.113; Fig. 8). Further on stratifying this cohort according to hormone receptor status, a similar lack of significance was observed among hormone receptor-positive (HR+) patients (P=0.643; Figure 9). However, in hormone receptor-negative (HR−) patients, those with HER2-low tumors demonstrated poorer DFS compared to those with HER2-zero tumors (P=0.0079, Figure 10).

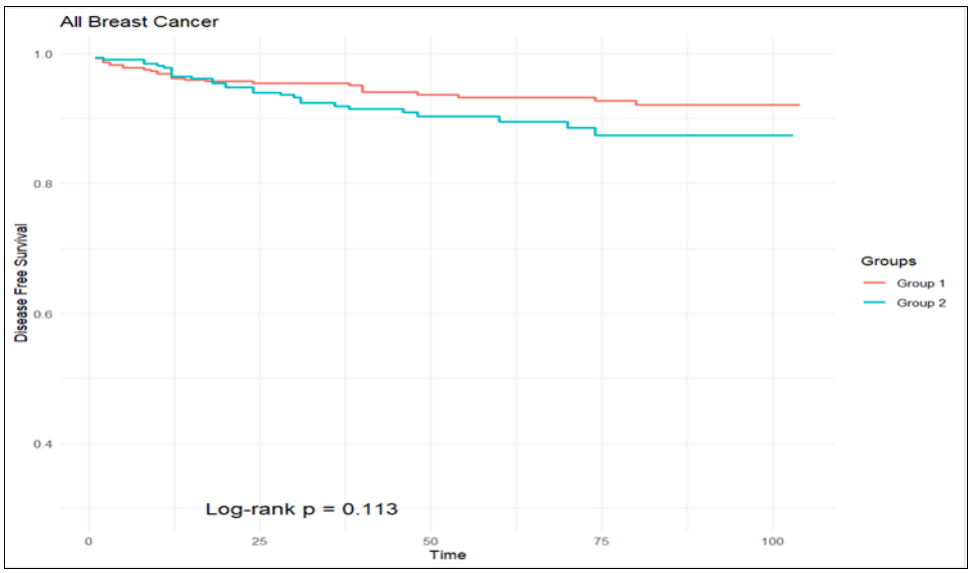

Fig 8: DFS HER2 low vs. HER2 zero in this cohort

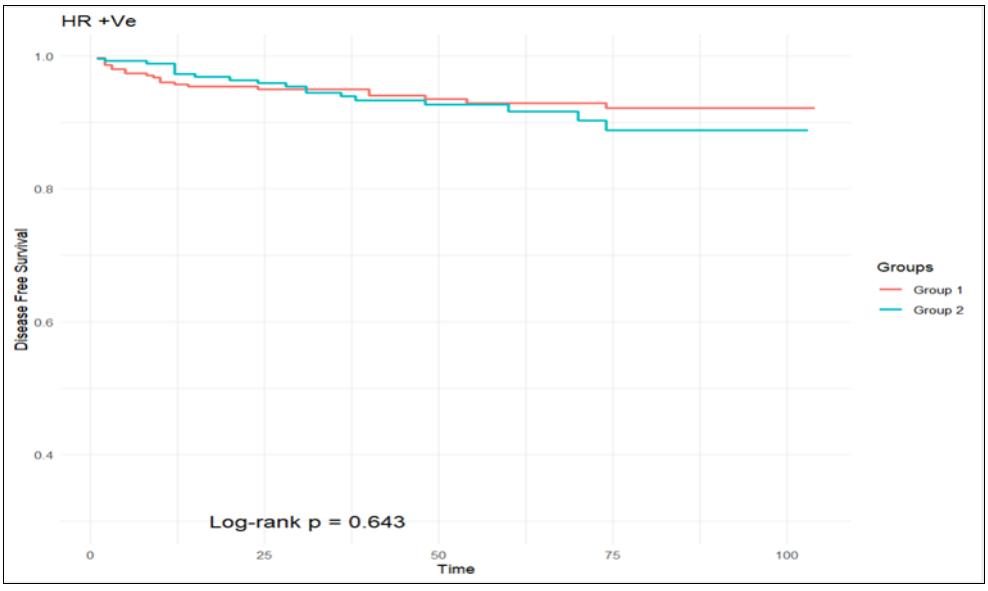

Fig 9: DFS in HR+ HER2 low vs. HER2 zero in this cohort

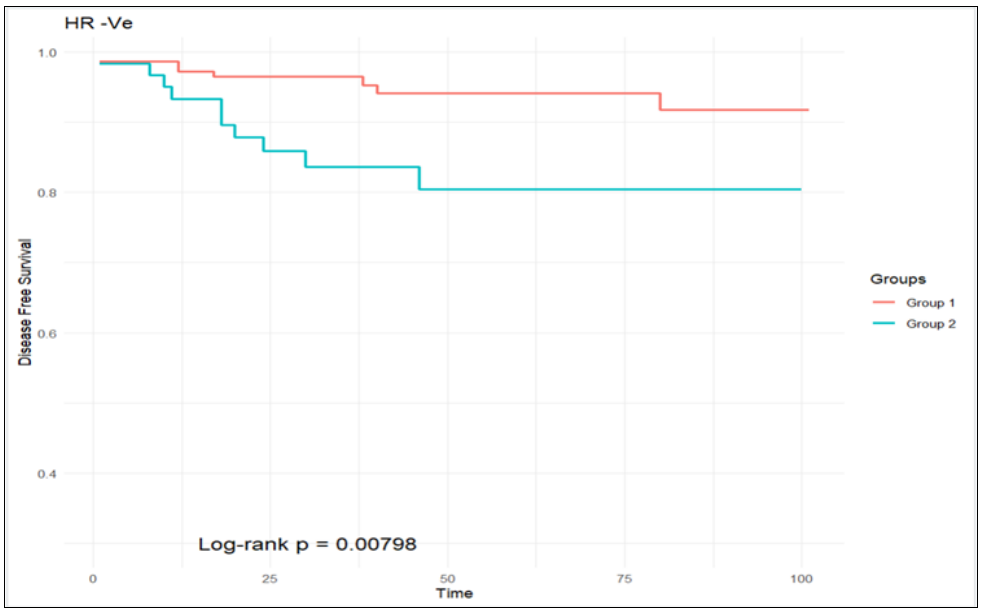

Fig 10: DFS in HR neg HER2 low vs. HER2 zero in this cohort

To assess the impact of various factors on disease-free survival (DFS), both univariate and multivariate Cox proportional hazards models were studied.

Absence of lymphovascular invasion (Hazard ratio: 0.4379, 95% Confidence interval: 0.2268-0.8454, P=0.0139), tumors of size ≤ 5cm (Hazard ratio: 0.5753, 95% Confidence interval: 0.331-0.998, P=0.049) and stage1+2 (Hazard ratio: 0.589, 95% Confidence interval: 0.3502-0.9907, P=0.046) were associated with good DFS in univariate analysis.

Table 4: Univariate analysis

Univariate			
Variables	**Hazard ratio**	**95% Confidence interval:**	**P-Value**
Age (≤ 65 years vs. >65 years)	1.766	0.639-4.88	0.273
Hormone receptor status (Negative vs. Positive)	1.325	0.757-2.317	0.323
HER2 expression (Zero vs. low)	0.661	0.3934-1.114	0.12
Grade (1 vs 2+3)	0.465	0.113-1.906	0.287
Lymphovascular invasion (Not seen vs. seen)	0.4379	0.2268-0.8454	0.0139
Maximum tumor Size (≤ 5.0cm vs >5.0cm)	0.5753	0.331-0.998	0.049
Stage (1+2 vs. 3)	0.589	0.3502-0.9907	0.046

In multivariate analysis, hormone receptor-negative tumors were significantly associated with poorer disease-free survival (DFS) (Hazard Ratio: 2.4762; 95% Confidence Interval: 1.1363-5.396; P=0.0225), as were HER2-low tumors (Hazard Ratio: 5.3772; 95% Confidence Interval: 1.3740-21.043; P=0.0157). Additionally, the presence of lymphovascular invasion was independently associated with reduced DFS (Hazard Ratio: 2.8765; 95% Confidence Interval: 1.0440-7.926; P=0.041).

Table 5: Multivariate analysis

Multivariate			
Variables	**Hazard ratio**	**95% Confidence interval**	**P-Value**
Age (≤ 65 years vs. >65 years)	1.5109	0.5529-4.294	0.4084
Hormone receptor status (Negative vs. Positive)	2.4762	1.1363-5.396	0.0225
HER2 expression (Zero vs. low)	5.3772	1.3740-21.043	0.0157
Grade (1 vs 2+3)	0.6054	0.1445-2.536	0.4924
Lymphovascular invasion (Not seen vs. seen)	2.8765	1.0440-7.926	0.041
Maximum tumor Size (≤ 5.0cm vs >5.0cm)	0.6517	0.3775-1.222	0.1821
Stage (1+2 vs. 3)	0.928	0.4896-1.759	0.8189

Other factors studied included age and grade.

Discussion

There has been an increasing interest in tumors with breast tumors with low HER2 expression because of emergence of antibody-drug conjugates (ADCs) that have shown significant efficacy in the treatment of metastatic breast cancers with low HER2 expression [15, 16]. A landmark Phase 3 clinical trial (DESTINY-Breast04) [17] was conducted that involved 557 breast cancer patients with low HER2 expression. They were randomized, where one group received trastuzumab deruxtecan and another group received physician's choice of chemotherapy. In mentioned study, the group that received antibody drug conjugate revealed significantly improved outcomes i.e. prolonged median progression-free survival (10.1 months vs. 5.4 months; Hazard ratio=0.51; p<0.001) and overall survival (23.9 months vs. 17.5 months; Hazard ratio=0.64; P=0.003)

among HR-positive patients and prolonged median progression-free survival (9.9 months vs 5.1 months, Hazard ratio=0.50 ; p<0.001) and overall survival (23.4 months vs 16.8 months, Hazard ratio=0.64 ; P=0.001) amongst all patients [2].

These findings have led to increased interest in exploring the clinical and pathological characteristics and survival outcomes of breast tumors with low HER2 expression, such as in the present study, because of their alleged anticipated therapeutic relevance in future clinical practice [18]. Ours was a retrospective study and included 783 HER2-negative breast cancer cases. This study aimed to compare and analyze the differences between HER2-zero and HER2-low tumors.

The results from our cohort demonstrated that tumors with low HER2 expression revealed significantly higher proportion of hormone receptor (HR) positivity and were more often associated with lymphovascular invasion (LVI), nodal involvement and a higher stage at presentation. Importantly, tumors with low HER2 expression were found to be linked with poorer disease-free survival (DFS), especially in the hormone receptor negative subgroup.

Among the 783 HER2-negative cases, 42.01% were identified as tumors with low HER2 expression. This proportion is slightly lower than that reported in other studies. A study by Schettini *et al*. revealed that in a cohort of 3,689 HER2-negative cases, 59.4% tumors revealed low HER2 expression. Another study by Agostinetto *et al*. reported 61% HER2 low tumors in a cohort of 804 patients HER2-negative cases [19]. In Asian populations, the prevalence appears even higher. A Japanese retrospective study involving 4,918 HER2-negative patients found 79.1% to be HER2-low [2, 20]. Another Chinese study with 12,467 patients reported a 72.6% prevalence of HER2-low tumors[21]. These differences can be attributed to differences in size of cohort studied and variability in HER2 testing practices and quality control.

In our cohort, tumors which revealed low HER2 expression were significantly more likely to be positive for hormone receptors as compared to tumors with zero HER2 expression (81.76% vs. 67.62%, p<0.0001). This is in concordance with other studies, including 90.2% HR positivity in a Japanese cohort and 88.2% in data from the cBio Cancer Genomics Portal [20, 22], as well as in the study by Yang *et al*. [2]. However, other clinical and pathological features have shown inconsistent trends across studies. A study by Horisawa *et al*. has reported that tumors with low HER2 expression usually had smaller tumor size and lower histological grade [18, 20]. A study by Jacot *et al*. revealed similar findings in triple-negative breast cancers [23]. Another study by Schettini *et al*. revealed that tumors with low HER2 expression were associated with worse T stage, N stage and histological grade compared to tumors with zero HER2 expression [22]. No such associations were observed in our study.

Prognostically, the evidence remains mixed. One retrospective study which involved 91 node-positive patients demonstrated that tumors with low HER2 expression correlate with shorter disease-specific survival, especially in HR-positive cases [24]. In contrast, our study showed a significant correlation between low HER2 expression and poorer disease-free survival in HR-negative tumors. Notably, Jacot *et al*. found worse outcomes in tumors with equivocal HER2 i.e. +2 on immunohistochemistry, lacking ERBB2 gene amplification by in-situ hybridization compared to tumors with zero +1 expression of HER2 on immunohistochemistry combined [23]. These discrepancies could result from variations in study design, including inclusion criteria (e.g., TNBC, early vs. advanced breast cancer) and lack of standardized treatment information.

Age which is a well-recognized factor that influences prognosis of breast cancer, remains poorly explored in breast tumors with low HER2 expression. In our study, no significant association was observed between HER2 expression and age stratified at 65 years.

Cox regression analysis further revealed that tumors with low HER2-low expression, negative for hormone receptors and with presence of lymphovascular invasion were associated with shorter disease-free survival, while those with absence of lymphovascular invasion and smaller tumor size (≤ 5.0 cm) were predictive of better disease-free survival outcomes.

However, the findings of this study are also followed by certain limitations. Firstly, this was a single-center retrospective study. Secondly, some cases which showed equivocal HER2 expression on immunohistochemistry but did not undergo in-situ hybridization for any reason, were excluded from analysis. Hence, further multicenter studies with larger sample sizes and standardized testing protocols are warranted to validate these observations.

Conclusion

Our data shows poor prognosis in tumors with low HER2 low expression especially in those tumors with negative hormone receptor status, however more research is called for. Understanding the clinical and pathological differences between breast cancers with low or absent/ zero HER2 expression is crucial for refining treatment strategies and improving patient outcomes. As the clinical importance of tumors with low HER2 expression becomes clearer, further research is needed to better characterize these tumors and identify whether they represent a unique breast cancer subtype with specific clinical behavior and therapeutic implications.

Conflict of Interest

Not available

Financial Support

Not available

References

1. Bray F, Laversanne M, Sung H, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263. DOI: 10.3322/caac.21834
2. Yang X, Li Y, Lu X, Ren X, Hua B. Clinicopathological features and prognosis of patients with HER2-low breast cancer. BMC Cancer. 2023;23(1):914. DOI: 10.1186/s12885-023-11421-0
3. Marchiò C, Annaratone L, Marques A, Casorzo L, Berrino E, Sapino A. Evolving concepts in HER2 evaluation in breast cancer: Heterogeneity, HER2-low carcinomas and beyond. Semin Cancer Biol. 2021;72:123-135. DOI: 10.1016/j.semcancer.2020.02.016
4. Karamouzis MV, Karatza LE, Ravazoula P, *et al*. Non-palpable breast carcinomas: Correlation of mammographically detected malignant-appearing

microcalcifications and molecular prognostic factors. Int J Cancer. 2002;102(1):86-90. DOI: 10.1002/ijc.10654
5. Von Minckwitz G, Huang CS, Mano MS, *et al*. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-628. DOI: 10.1056/NEJMoa1814017
6. Slamon D, Eiermann W, Robert N, *et al*. Adjuvant Trastuzumab in HER2-Positive Breast Cancer. N Engl J Med. 2011;365(14):1273-1283. DOI: 10.1056/NEJMoa0910383
7. Geyer CE, Forster J, Lindquist D, *et al*. Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer. N Engl J Med. 2006;355(26):2733-2743. DOI: 10.1056/NEJMoa064320
8. 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. Arch Pathol Lab Med. 2018;142(11):1364-1382. DOI: 10.5858/arpa.2018-0902-SA
9. Cheng X. A Comprehensive Review of HER2 in Cancer Biology and Therapeutics. Genes. 2024;15(7):903. DOI: 10.3390/genes15070903
10. Slamon DJ, Jones LB, Shak S, *et al*. Use of Chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783-792. DOI: 10.1056/NEJM200103153441101
11. Pusztai L, Harbeck. HER2-targeted therapies in HER2-negative breast cancer. Lancet Oncol. 2020;21(12):1602-1615.
12. Sparano JA, Gray RJ, Makower DF, *et al*. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med. 2015;373(21):2005-2014. DOI: 10.1056/NEJMoa1510764
13. 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
14. Delgado A, Guddati AK. Clinical endpoints in oncology-a primer. Am J Cancer Res. 2021;11(4):1121-1131.
15. Franchet C, Djerroudi L, Maran-Gonzalez A, *et al*. [2021 update of the GEFPICS' recommendations for HER2 status assessment in invasive breast cancer in France]. Ann Pathol. 2021;41(6):507-520. DOI: 10.1016/j.annpat.2021.07.014
16. Eiger D, Agostinetto E, Conde SR, Azambuja DE. The Exciting New Field of HER2-Low Breast Cancer Treatment. Cancers. 2021;13(5):1015. DOI: 10.3390/cancers13051015
17. Cortés J, Kim SB, Chung WP, *et al*. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med. 2022;386(12):1143-1154. DOI: 10.1056/NEJMoa2115022
18. Yang M, Sun J, Liu L, *et al*. Clinicopathological characteristics of HER2-low breast cancer: A retrospective study. Sci Rep. 2023;13(1):12382. DOI: 10.1038/s41598-023-39372-3
19. Agostinetto E, Rediti M, Fimereli D, *et al*. HER2-Low Breast Cancer: Molecular Characteristics and Prognosis. Cancers. 2021;13(11):2824. DOI: 10.3390/cancers13112824
20. Horisawa N, Adachi Y, Takatsuka D, *et al*. The frequency of low HER2 expression in breast cancer and a comparison of prognosis between patients with HER2-low and HER2-negative breast cancer by HR status. Breast Cancer. 2022;29(2):234-241. DOI: 10.1007/s12282-021-01303-3
21. Shui R, Liang X, Li X, *et al*. Hormone Receptor and Human Epidermal Growth Factor Receptor 2 Detection in Invasive Breast Carcinoma: A Retrospective Study of 12,467 Patients From 19 Chinese Representative Clinical Centers. Clin Breast Cancer. 2020;20(1):e65-e74. DOI: 10.1016/j.clbc.2019.07.013
22. Schettini F, Chic N, Maristany BF, *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
23. Jacot W, Maran-Gonzalez A, Massol O, *et al*. Prognostic Value of HER2-Low expression in non-metastatic triple-negative breast cancer and correlation with other biomarkers. Cancers. 2021;13(23):6059. DOI: 10.3390/cancers13236059
24. Gilcrease MZ, Woodward WA, Nicolas MM, *et al*. Even Low-level HER2 Expression may be associated with worse outcome in node-positive breast cancer. Am J Surg Pathol. 2009;33(5):759-767. DOI: 10.1097/pas.0b013e31819437f9

All Author's Name and Details

Samiksha R Shindegalwekar
(MBBS, MD Pathology), Fellow in Oncopathology, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Yogesh M Mistry
Consultant Pathologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Bhawana Chaudhari
Consultant Pathologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Ajay Junnarkar
Consultant Pathologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Bhumi Chhatbar
Consultant Pathologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Dipayan Nandy
Consultant Surgery, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Ghanish Panjwani
Consultant Surgery, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Pramod Patil
Consultant Radiation Oncologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Samarth Chhatbar
Consultant Radiation Oncologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Himanshu Mekap
Consultant Radiation Oncologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Amrendra Kumar
Consultant Radiation Oncologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Santosh Vandanasetti
Consultant Medical Oncologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Dr. Ameya Koranne
Consultant Medical Oncologist, Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

Malik Jamadar
Kailash Cancer Hospital and Research Centre, Vadodara, Gujarat, India

How to Cite This Article
Shindegalwekar SR, Mistry YM, Chaudhari B, Junnarkar A, Chhatbar B, Nandy D, *et al*. Clinicopathological and prognostic comparative study of HER2-low versus HER2-zero breast cancer. International Journal of Clinical and Diagnostic Pathology. 2025;8(3):26-35.