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" *Clinicopathologic Characteristics of Her2-low Breast Cancer in Egypt* "

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ABSTRACT:

Background: The emergence of Human epidermal growth factor receptor 2-Low (HER2-low) breast cancer as a distinct therapeutic category requires detailed characterization, particularly in understudied populations with unique clinical profiles, like Egypt.

Aim of this study: To determine the clinicopathological characteristics of HER2-Low breast cancer patients in Egypt.

Materials and Methods: A retrospective observational study was conducted on 309 invasive breast cancer patients classified as: HER2-Low (Immunohistochemistry 1+ or 2+/ In situ hybridization -; n=125) or HER2-zero (Immunohistochemistry (IHC) 0; n=184). Comprehensive data on demographics, presentation, pathology, treatment patterns, and survival were analysed using appropriate statistical methods. **Results:** Both groups showed similar demographic characteristics with median age of 50 years.

Clinicopathological features were largely comparable, though HER2-Low tumors showed significantly less extranodal extension (56.7% vs 87.5%, p=0.002) and numerically higher hormone receptor positivity (84.8% vs 77.7%, p=0.284). Treatment patterns and metastatic distribution were similar between groups. Survival analysis revealed no significant differences in median overall survival (59 vs 60 months, p=0.773), disease-free survival, or progression-free survival.

Conclusion/Recommendations: HER2-Low and HER2-zero breast cancers demonstrate remarkable clinicopathological similarity in Egyptian patients. The therapeutic relevance of HER2-low status appears more significant than its prognostic value. These findings highlight the critical need for standardized HER2 testing protocols to ensure accurate identification of patients eligible for novel treatments, particularly antibody-drug conjugate therapies.

Keywords: Antibody-drug conjugates (ADCs), HER2 Heterogeneity, HER2-0, HER2-Low, HER2-Negative

Introduction: Breast cancer remains the most frequently diagnosed malignancy and a leading cause of cancer-related mortality among women worldwide, accounting for 23.8% of all new cancer cases in women in 2022 **(Global Cancer Observatory (Globocan), 2022)**. The disease demonstrates considerable heterogeneity in its clinical presentation, pathological features, and prognosis, contributing to complex management challenges **(Venetis et al., 2022)**. Significant geographical disparities exist, with women in Arab nations, including Egypt, typically being diagnosed a decade earlier than their Western counterparts and presenting with more advanced-stage disease and more aggressive tumor biology, leading to poorer prognoses and lower survival rates **(Abdelaziz et al., 2020; Al-Shamsi et al., 2022)**.

The biological heterogeneity of breast cancer is classified through molecular subtyping based on the expression of key biomarkers: hormone receptors (ER and PR), human epidermal growth factor receptor 2 (HER2), and the proliferation marker Ki67. The main subgroups include hormone receptor-expressing Luminal cancers, HER2-enriched cancers characterized by HER2 overexpression, and triple-negative breast cancer (TNBC) that typically lacks all three markers **(Menon et al., 2024)**. The HER2 oncogene plays a pivotal role in regulating cell growth and survival, with gene amplification occurring in 20-30% of breast cancers, leading to massive HER2 protein overproduction and aggressive tumor behaviour **(Albagoush et al., 2024)**.

Historically, HER2 status was considered a binary biomarker determining eligibility for HER2-targeted therapies like trastuzumab, with tumors classified as HER2-positive (IHC 3+ or IHC 2+/ISH+) or HER2-negative (IHC 0, 1+, or IHC 2+/ISH-) **(Rubio, 2022; Bardia & Viale, 2023)**. This paradigm shifted with the development of novel antibody-drug conjugates (ADCs), particularly trastuzumab deruxtecan (T-DXd), which demonstrated significant survival advantages in patients with metastatic tumors exhibiting low HER2 expression in the landmark DESTINY-Breast04 trial **(Modi et al., 2022)**. This led to a fundamental reclassification into HER2-low (IHC 1+ or IHC 2+/ISH-) and HER2-zero (IHC 0) categories, expanding the population eligible for HER2-directed therapy and establishing HER2-low as a therapeutically relevant entity **(Venetis et al., 2022)**. This new category represents 31-51% of all primary breast cancers and exhibits distinct clinicopathological and molecular features compared to HER2-zero tumors (**Zhang & Peng, 2022; Neubauer et al., 2024)**. The prognostic significance of HER2-low status continues to be debated, with some evidence suggesting more favourable outcomes compared to HER2-zero tumors, potentially independent of hormone receptor status **(Ergün et al., 2023)**.

Material and Methods

This retrospective observational study was conducted at three Egyptian cancer centres (Oncology Centre Mansoura University, Damietta Cancer Center and Port Said El-Mabara Hospital) including Patients diagnosed with breast cancer from October 2020 to November 2021.

The study was applied on (309) subjects. As it was started with (480) subjects assessed for eligibility. Later, one hundred and fifty-one (151) of them were excluded [Ductal carcinoma In Situ (3), HER2 non conclusive (4) and HER2 positive (144)]. Out of the remaining (329) subjects, there were (20) with incomplete data (regarding IHC and HER2 status, lines of treatment or follow up data). So, final analysis was done on 309 breast cancer patients.

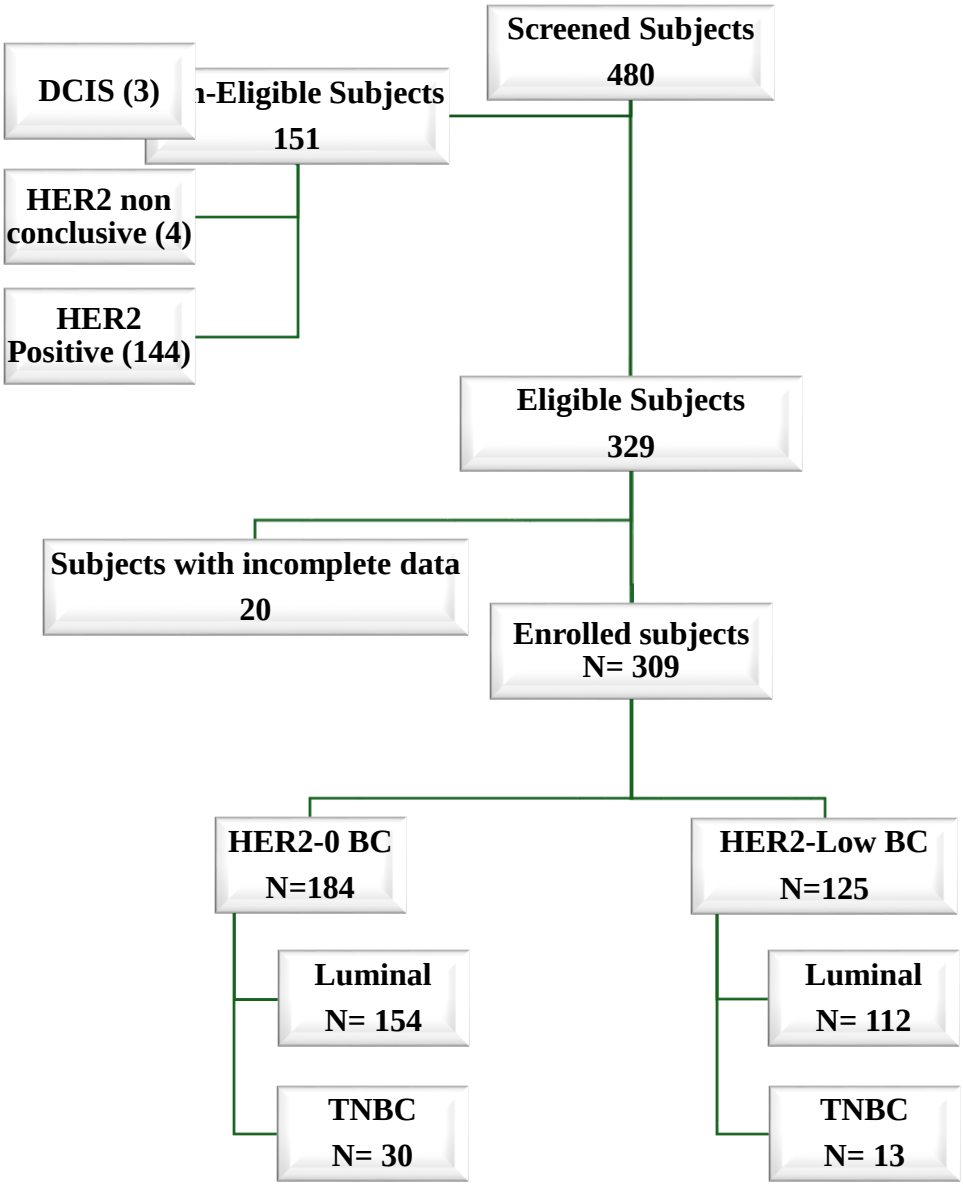


Figure (1): CONSORT diagram: Subjects Enrolment flow into the study

Groups of study and Case definitions: Patients were assigned into two groups based on Her2 status.

Group 1: HER2-Low BC Patients (whose test results were IHC 1+ or IHC 2+ with ISH-). **Group 2:** HER2-0 BC Patients (whose test results were IHC 0).

Inclusion Criteria: Breast cancer patients who were not assigned as HER2-positive, Patients whose IHC and ISH test results of HER2 status were available, Patients with invasive disease, and both genders.

Exclusion Criteria: HER2-positive BC, Patients whose data were unavailable or incomplete and patients with non-invasive diseases.

Exposures: Standard therapy according to routine clinical practice.

Follow up: Treatment, outcome and follow-up data were obtained from the patient's medical records. Follow up was done till December 2024.

End point/ Main Outcome Measure (Delgado & Guddati 2021):

The primary/ treatment outcomes were reported as:

(1) **Overall survival (OS):** was defined as the time from diagnosis till death, lost follow up or end of study.
(2) **Disease-free survival (DFS)** was calculated for all patients from the date of complete cure (date of surgery) till the date of recurrence, metastasis occurrence, death, lost follow up or end of study.
(3) **Progression-free survival (PFS)** was calculated only for metastatic patients from the date of diagnosis of the disease till the date of progression.

Data were collected from Hospital patients' medical records, including the following:

Patients' Characteristics: Age at diagnosis, Gender, Menopausal status, comorbidities (Diabetes, Hypertension), Family history of breast cancer, Hormonal Contraception use, Weight, Height, Eastern Cooperative Oncology Group (ECOG) performance status **(Bell & Di, 2024)**.

Clinical Presentation: Main complaint, Laterality of breast cancer, Site (quadrant), Number of breast masses, Primary Tumor size (cT), Regional lymph node (cN), Distant Metastases (M), Sites and Number of metastases, Prescence of visceral metastasis, Tumor markers: Cancer antigen CA15-3 9 (only in metastatic patients) and Overall clinical Stage -only in patients receiving neoadjuvant therapy- **(NCCN, 2025)**.

Pathological and Biological Characteristics: Type of Breast surgery [either Breast Conservation Surgery (BCS), or Mastectomy], Lymph Node Surgery [either Sentinel Lymph Node Biopsy (SLNB) or Axillary Clearance], Tumor histological type, grade, hormone receptor (progesterone and/or estrogen) quantitative status, human epidermal growth factor receptor 2 (HER2) status, Ki-67 status, Lymphvascular invasion (LVI), Perineural invasion (PNI), Extranodal Extension (ENE) and pathologic response status (pCR), Primary Tumor size (pT), Regional lymph node (pN) and Overall Pathological stage **(NCCN, 2025)**.

Systemic Therapy: included chemotherapy, hormonal therapy and ovarian function suppression in neoadjuvant, adjuvant and both first- and second-line metastatic treatment. Also include Endocrine Sensitivity and Best Objective Response Rate (ORR).

Survival data: Included disease free survival (DFS), progression free survival (PFS) and overall survival (OS).

HER2 Testing:

Immunohistochemical analysis was performed on tumor tissue specimens that had been fixed in 10% neutral buffered formalin for 6–72 hours, processed routinely, and embedded in paraffin. Staining was carried out on the VENTANA BenchMark GX automated platform (Roche) using the following monoclonal antibodies: (ER: anti-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Primary Antibody REF 790-4324, PR: anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody REF 790-2223, HER2/neu: anti- HER2/neu (4B5) Rabbit Monoclonal Primary Antibody REF 790-4493, Ki-67: anti-Ki-67 (30-9) Rabbit Monoclonal Primary Antibody REF 790-4286.). The staining protocol included automated epitope retrieval using the manufacturer's proprietary Cell Conditioning solution, followed by incubation with primary antibodies and detection using the standardized OptiView DAB detection system, all according to the manufacturer's defined protocols.

HER2 scoring was conducted in accordance with the latest ASCO/CAP guidelines, where tumors were categorized as HER2-0 (IHC 0), HER2-low (IHC 1+ or IHC 2+/ISH-negative), and HER2-positive (IHC 3+ or IHC 2+/ISH-positive). All slides were independently evaluated by two experienced breast pathologists, with discrepancies resolved through consensus review. This standardized and automated protocol ensured consistent and reproducible assessment of biomarker status across the cohort.

Data Management: Data were analysed using SPSS V.26. Descriptive statistics summarized the data, and associations between variables were tested using appropriate tests like chi-square, t-tests, and ANOVA. Survival was analysed with Kaplan-Meier curves and Log-Rank tests. A p-value < 0.05 was considered significant.

Ethical Considerations: The study was conducted in agreement with the standards of the Helsinki declaration. The study protocol was approved by the Institutional Review Board (IRB) of Port said Faculty of Medicine (code ERN: MED (1/1/2024) s.no (127) ONC 823a_001). Approval was obtained from Oncology Centre Mansoura University, Damietta Cancer Center, Port Said Health care authority and El-Mabara Hospital. Confidentiality and anonymity of the participants was assured by assigning a code number for each participant. Data was kept safe, and no personal data was published.

Results:

In this retrospective study, 309 breast cancer patients were included, with 184 (59.5%) patients had HER2-0 BC while 125 (40.5%) had HER2-Low BC. Patients' characteristics were largely similar when comparing the HER2-0 and HER2-low groups. Both cohorts had a median age of 50 years, with nearly all patients being female (99.5% vs. 97.6%). Premenopausal women represented the majority in each group (57.1% vs. 53.3%). Prevalence of comorbidities like diabetes and hypertension was comparable. Further analysis showed minor variations in certain factors. For instance, a family history of breast cancer was slightly less common in the HER2-0 group (17.3% vs. 22.7%). However, other characteristics, such as the use of hormonal contraception and obesity, were almost identical between the two groups. Ultimately, despite these minor differences, no statistically significant correlation was found between any of these characteristics and HER2 status. Details are shown in Table (1).

Table (1): Patients' Characteristics:

All patients		**HER2-0**		**HER2-Low**		**p**
		N	**%**	**N**	**%**	
Age (years)	Mean ± SD	50 ± 12		50 ± 11		0.996
Gender	Male	1	0.5%	3	2.4%	0.156
	Female	183	99.5%	122	97.6%	
Menopausal Status	Premenopausal	104	57.1%	65	53.3%	0.506
	Postmenopausal	78	42.9%	57	46.7%	
DM	Absent	134	74%	94	76.4%	0.637
	Present	47	26%	29	23.6%	
HTN	Absent	122	67%	88	71.5%	0.404
	Present	60	33%	35	28.5%	
Family History of Breast Cancer	Negative	143	82.7%	92	77.3%	0.257
	Positive	30	17.3%	27	22.7%	
Hormonal Contraception	Unexposed	47	49.5%	30	48.4%	0.894
	Exposed	48	50.5%	32	51.6%	
BMI	Normal	12	7.1%	14	11.6%	0.153
	Overweight	31	18.5%	25	20.7%	
	Obesity	89	53%	66	54.5%	
	Morbid Obesity	36	21.4%	16	13.2%	
PS (ECOG)	0	95	51.6%	59	47.2%	0.425
	1	68	37%	55	44%	
	2	18	9.8%	11	8.8%	
	3	3	1.6%	0	0%	

PS (ECOG, 0-1 vs 2-3)

The initial clinical presentation was remarkably similar between the HER2-0 and HER2-low patient groups. The overwhelming majority of patients in both cohorts presented with a breast lump as their primary complaint (89.6% vs. 89.5%, p= 0.961). Left-sided breast cancer was slightly more common (53.8% vs. 52.8%, p= 0.877), and tumors were most frequently located in the upper outer quadrant of the breast (53.8% vs. 59.2%, p= 0.353). A single breast lump was the most common presentation (59.9% vs. 58.4%, p= 0.750).

In terms of clinical staging, the disease profiles were also closely aligned. The T2 stage was the most common size for the primary tumor in both groups, followed by T4 (T2: 53.1% vs. 53.4%, T4: 30.6% vs. 38.4%, p= 0.566). For regional lymph node involvement, the N1 stage was predominant (63.6% vs. 68.5%, p= 0.641). The overall disease was most frequently classified as locally advanced (Stage III), with Stage II being the next most common (stage III: 48.5% vs. 45.2%, stage II: 38.4% vs. 35.6%, p= 0.512). A smaller proportion of patients presented with distant metastases (Stage IV) at diagnosis (12.1% vs. 19.2%).

Among those patients who were initially metastatic, the patterns of metastasis showed few differences. Prescence of Polymetastatic sites was common in both groups (75% vs. 64.3%, p= 0.369), and the presence of visceral metastases was nearly identical (58.3% vs. 57.1%, p= 0.951). Although the baseline CA 15-3 level was numerically higher in the metastatic HER2-0 group [(124 ± 102) U/mL vs. (85 ± 105) U/mL], this difference, like all others analysed, was not found to be statistically significant. Other details were summarized in Table (2).

Table (2): Initial Clinical Presentation and Clinical Staging:

All patients		**HER2-0**		**HER2-Low**		**p**
		N	**%**	**N**	**%**	
Main Complaint	Screening	2	1.2%	0	0%	0.961
	Lump	147	89.6%	102	89.5%	
	Pain	7	4.3%	4	3.5%	
	Skin Changes	3	1.8%	3	2.6%	
	Nipple Discharge	3	1.8%	2	1.8%	
	Symptoms of Mets	2	1.2%	3	2.6%	
Laterality of Breast Cancer	Right	81	44%	56	44.8%	0.877
	Left	99	53.8%	66	52.8%	

	Bilateral	4	2.2%	3	2.4%	
Site (quadrant)	Upper Outer	98	53.8%	74	59.2%	0.353
	Lower Outer	18	9.9%	16	12.8%	
	Upper Inner	35	19.2%	10	8%	
	Lower Inner	15	8.2%	11	8.8%	
	Retro-areolar	16	8.8%	14	11.2%	
Number of Breast Masses	No Evidence of Mass	1	0.5%	0	0%	0.750
	Single	109	59.9%	73	58.4%	
	Multifocal	39	21.4%	27	21.6%	
	Multicentric	33	18.1%	25	20%	
Primary Tumor (cT-Stage)	T1	6	6.1%	1	1.4%	0.566
	T2	52	53.1%	39	53.4%	
	T3	10	10.2%	5	6.8%	
	T4	30	30.6%	28	38.4%	
Regional lymph nodes (cN)	N0	15	15.2%	13	17.8%	0.641
	N1	63	63.6%	50	68.5%	
	N2	11	11.1%	9	12.3%	
	N3	10	10.1%	1	1.4%	
Distant metastasis (M)	M0	87	87.9%	59	80.8%	0.202
	M1	12	12.1%	14	19.2%	
Number of Mets Sites (metastatic from start)	≤ 3	1	8.3%	4	28.6%	0.369
	4-5	2	16.7%	1	7.1%	
	> 5	9	75%	9	64.3%	
Visceral Mets (metastatic from start)	Absent	5	41.7%	6	42.9%	0.951
	Present	7	58.3%	8	57.1%	
Baseline CA15-3 in Metastatic patients		124 ± 102		85 ± 105		0.386
Clinical Stage	Stage I	1	1.0%	0	0%	0.512
	Stage II	38	38.4%	26	35.6%	
	Stage III	48	48.5%	33	45.2%	
	Stage IV	12	12.1%	14	19.2%	

Main Complaint (Lump vs No Lump), Laterality of Breast Cancer (left vs right)
Site (left upper outer quadrant vs another site), Number of Breast Masses (single vs multiple)
Primary Tumor (T-Stage, T1-2 vs T3-4), Regional lymph nodes (N- vs N+)
Number of Mets Sites (single vs multiple)

The pathological characteristics of the HER2-0 and HER2-low groups demonstrated several similarities alongside one notable difference. Surgically, mastectomy was slightly more common than breast-conserving surgery in both cohorts (51.5% vs. 61.3%, p= 0.107), and axillary clearance was the predominant lymph node procedure for most patients (71.9% vs. 75%, p= 0.566). The most frequent histological type was

invasive ductal carcinoma (85.2% vs. 89.5%, p= 0.392), with Grade II tumors representing a similar, large proportion of cases in both groups (66.3% vs. 65.5%, p= 0.648).

A comparison of specific pathological features revealed that Lymphvascular invasion (LVI) was more common in the HER2-low group (68.9% vs. 75.6%, p= 0.304), while perineural invasion (PNI) was higher in the HER2-0 group (32.4% vs. 23.4%, p= 0.248); however, these differences were not statistically significant. In contrast, a significant difference was observed in extranodal extension (ENE), which was markedly more prevalent in the HER2-0 group (87.5% vs. 56.7%, p= 0.002). Additional results are detailed in Table (3).

Post-treatment outcomes and staging were largely comparable. The pathological complete response (pCR) rate was low in both groups (8.4% vs. 5.6%, p= 0.527). The pT2 stage was the most common for the primary tumor (56.2% vs. 59.5%, p= 0.411), pN0 stage (32.9% vs. 32.4%, p= 0.667), and pathological staging showed nearly half of all patients in both groups had Stage II disease (47% vs. 48.6%, p= 0.669). Aside from the significant finding regarding extranodal extension, no other statistically significant differences were identified between the groups in relation to HER2 status. Further details can be found in Table (3).

Table (3): Pathological Characteristics and Pathological Staging:

All patients		**HER2-0**		**HER2-Low**		**p**
		N	**%**	**N**	**%**	
Breast surgery	BCS	82	48.5%	43	38.7%	0.107
	Mastectomy	87	51.5%	68	61.3%	
LN surgery	SLNB	47	28.1%	27	25%	0.566
	Axillary Clearance	120	71.9%	81	75%	
Histological type	Ductal	156	85.2%	111	89.5%	0.392
	Lobular	13	7.1%	6	4.8%	
	Mixed Ductal and Lobular	8	4.4%	5	4%	
	Micropapillary	2	1.1%	1	0.8%	
	Metaplastic	1	0.5%	0	0%	
	Favourable Histology	3	1.6%	1	0.8%	
Tumor Histological Grade	G1	3	1.9%	0	0%	0.648
	G2	106	66.3%	74	65.5%	
	G3	50	31.3%	38	33.6%	
	G4	1	0.6%	1	0.9%	
LVI	Absent	33	31.1%	21	24.4%	0.304

	Present	73	68.9%	65	75.6%	
PNI	Absent	48	67.6%	49	76.6%	0.248
	Present	23	32.4%	15	23.4%	
Extra Nodal Extension	Absent	6	12.5%	13	43.3%	0.002
	Present	42	87.5%	17	56.7%	
Pathologic CR Status	Non-pCR	76	91.6%	51	94.4%	0.527
	pCR	7	8.4%	3	5.6%	
Primary Tumor (pT)	T0	12	7.1%	4	3.6%	0.411
	T1	42	24.9%	23	20.7%	
	T2	95	56.2%	66	59.5%	
	T3	17	10.1%	13	11.7%	
	T4	3	1.8%	5	4.5%	
Regional lymph nodes (pN)	N0	55	32.9%	35	32.4%	0.667
	N1	50	29.9%	39	36.1%	
	N2	41	24.6%	24	22.2%	
	N3	21	12.6%	10	9.3%	
pTNM Stage	Stage 0	7	4.2%	3	2.7%	0.669
	Stage I	16	9.5%	11	9.9%	
	Stage II	79	47%	54	48.6%	
	Stage III	63	37.5%	38	34.2%	
	Stage IV	3	1.8%	5	4.5%	

Tumor Histological Grade (G1-2 vs. G3-4)

The analysis of immunohistochemical markers revealed comparable biological profiles between the two groups (HER2-0 vs. HER2-Low). Hormone receptor (HR) positivity was highly prevalent, though it was more common in the HER2-low cohort (77.7% vs. 84.8%, p= 0.284). The proliferation index, as measured by Ki67, also showed near-identical mean levels between the groups (38 ± 24 vs. 40 ± 25, p= 0.492). Ultimately, neither HR status nor Ki67 levels demonstrated a statistically significant association with HER2 status. The data are presented in Table (4).

Table (4): Biological Markers by IHC:

All patients		**HER2-0**		**HER2-Low**		**p**
		N	**%**	**N**	**%**	
HR	Negative	30	16.3%	13	10.4%	0.284
	Low	11	6%	6	4.8%	
	Positive	143	77.7%	106	84.8%	
Ki67%	Mean ± SD	38 ± 24		40 ± 25		0.492

Treatment patterns were highly similar between the HER2-0 and HER2-low groups across all settings. In the neoadjuvant setting, nearly half of all patients received chemotherapy (46.2% vs. 49.6%, p= 0.556), while only a small minority received neoadjuvant endocrine therapy (7.6% vs. 6.4%, p= 0.685). For adjuvant treatment, approximately half of the patients in each group did not receive chemotherapy. The Anthracycline-Taxane regimen was the most common chemotherapy choice (45.7% vs. 38.4%, p= 0.393), and a small portion received adjuvant capecitabine (14.4% vs. 12.5%, p= 0.725).

Endocrine therapy (ET) was widely used and comparable between groups. Aromatase inhibitors were more frequently administered than tamoxifen in both the HER2-0 and HER2-low cohorts (62.9% vs. 56.5%, p= 0.339 and 44.7% vs. 48.9%, p= 0.534, respectively). Most premenopausal patients received ovarian function suppression (70.3% vs. 67.3%, p= 0.731), and most tumors in both groups were classified as endocrine-sensitive (82.6% vs. 77.2%, p= 0.523).

In the metastatic setting, chemotherapy was a more common first-line choice for the HER2-0 group (73% vs. 58.3%, p= 0.284) compared to ET, with anthracycline-based regimens being the most frequent selection in both cohorts (37% vs. 30%, p= 0.536). For first-line endocrine therapy, aromatase inhibitors were predominant (54.5% vs. 66.7%, p= 0.530). Second-line treatment choices were evenly split between chemotherapy and endocrine therapy for both groups, with Taxane-based chemotherapy (38.5% vs. 36.4%, 0.061) and aromatase inhibitors (70% vs. 72.7%, p= 0.890) being the most utilized options. No significant differences were found in any treatment strategy based on HER2 status. More details about systemic treatment are provided in Table (5).

Table (5): Systemic Therapy in neoadjuvant, adjuvant and metastatic setting:

All patients		**HER2-0**		**HER2-Low**		**p**
		N	**%**	**N**	**%**	
Neoadjuvant Chemotherapy	Absent	99	53.8%	63	50.4%	0.556
	Present	85	46.2%	62	49.6%	
Neoadjuvant ET	Absent	170	92.4%	117	93.6%	0.685
	Present	14	7.6%	8	6.4%	
Adjuvant chemotherapy	None	93	50.5%	70	56%	0.393
	Anthracycline-Taxane	84	45.7%	48	38.4%	
	Anthracycline-Free	7	3.8%	7	5.6%	
	Absent	89	85.6%	56	87.5%	0.725

Adjuvant Capecitabine	Present	15	14.4%	8	12.5%	
Adjuvant Tamoxifen	Absent	73	55.3%	47	51.1%	0.534
	Present	59	44.7%	45	48.9%	
Adjuvant AI	Absent	49	37.1%	40	43.5%	0.339
	Present	83	62.9%	52	56.5%	
Ovarian Function Suppression	Absent	22	29.7%	16	32.7%	0.731
	Present	52	70.3%	33	67.3%	
Endocrine Sensitivity (in Adjuvant setting)	Sensitive	109	82.6%	71	77.2%	0.523
	Secondary Resistant	7	5.3%	8	8.7%	
	Primary Resistant	16	12.1%	13	14.1%	
First Line Metastatic	Chemotherapy	27	73%	21	58.3%	0.284
	ET	10	27%	15	41.7%	
First Line Metastatic Chemotherapy	GemCarbo	2	7.4%	5	25%	0.536
	Taxane	7	25.9%	5	25%	
	Capecitabine	5	18.5%	2	10%	
	Anthracycline	10	37%	6	30%	
	Vinorelbine	3	11.1%	2	10%	
First Line Metastatic ET	AI	6	54.5%	10	66.7%	0.530
	Fulvestrant + CDK4/6	5	45.5%	5	33.3%	
Second Line Metastatic	Chemotherapy	13	56.5%	11	50%	0.661
	ET	10	43.5%	11	50%	
Second Line Metastatic Chemotherapy	GemCarbo	6	46.2%	2	18.2%	0.061
	Taxane	5	38.5%	4	36.4%	
	Capecitabine	0	0%	4	36.4%	
	Anthracycline	0	0%	1	9.1%	
	Vinorelbine	2	15.4%	0	0%	
Second Line Metastatic ET	AI	7	70%	8	72.7%	0.890
	Fulvestrant + CDK4/6	3	30%	3	27.3%	

The pattern of metastatic disease was comparable between the HER2-0 and HER2-low groups. Bone was the most common site of metastasis in both cohorts, though it was numerically more frequent in the HER2-0 group (77.5% vs. 67.5%, p= 0.317). The incidence of liver metastasis was identical between the two groups (42.5% vs. 42.5%, p= 1.000). Other common sites, including lung (35% vs. 47.5%, p= 0.256), soft tissue (30% vs. 42.5%, p= 0.245), and brain (25% vs. 25%, p= 1.000), showed numerical but statistically insignificant differences. The rates of pleural effusion (20% vs. 30%, p= 0.302) and skin metastasis (2.5% vs. 7.5%, p= 0.305) were also similar. No metastatic

site demonstrated a statistically significant association with HER2 status. The corresponding data are summarized in Table (6).

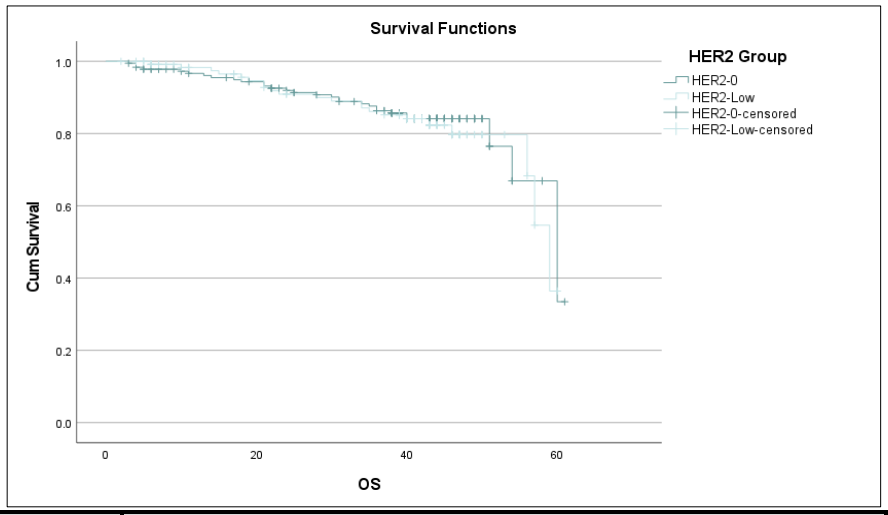
Table (6): Metastatic Sites both Initially and on Disease Progression:

All patients		HER2-0		HER2-Low		p
		N	%	N	%	
Bone Mets	Absent	9	22.5%	13	32.5%	0.317
	Present	31	77.5%	27	67.5%	
Liver Mets	Absent	23	57.5%	23	57.5%	1.000
	Present	17	42.5%	17	42.5%	
Lung Mets	Absent	26	65%	21	52.5%	0.256
	Present	14	35%	19	47.5%	
Pleural Effusion	Absent	32	80%	28	70%	0.302
	Present	8	20%	12	30%	
Brain Mets	Absent	30	75%	30	75%	1.000
	Present	10	25%	10	25%	
Skin Mets	Absent	39	97.5%	37	92.5%	0.305
	Present	1	2.5%	3	7.5%	
Soft Tissue Mets	Absent	28	70%	23	57.5%	0.245
	Present	12	30%	17	42.5%	

Among 309 evaluable patients, the median follow-up was 41 months (95% CI: 40-42) using the reverse Kaplan-Meier method. Patient retention decreased over time, with 155 patients remaining at risk at the median follow-up timepoint.

The Median OS for all studied patients was 59 months (95% CI 55.7-62.3). The median OS for HER2-0 group was 60 months (95% CI 51.5-68.5), while for HER2-Low group was 59 months (95% CI 55.7-62.3). The difference was not statistically significant (P= 0.773) as shown at Figure (2) and Table (7). The Median DFS for all studied patients was 57 months (95% CI 53.5 - 60.5). The median DFS for HER2-0 group was 57 months (95% CI 44.4 - 69.6), while for HER2-Low group was 55 months (95% CI 53.2 - 56.8). The difference was not statistically significant (P= 0.55) as shown at Figure (3) and Table (7). The Median PFS for all studied patients was 5 months (95% CI 0.7-9.3). The median PFS for HER2-0 group was 5 months (95% CI 0-10.4), while for HER2-Low group was 8 months (95% CI 2.6-13.4). The difference was not statistically significant (P= 0.39) as shown at Figure (4) and Table (7).

Table (7): Survival analysis of HER2-Low and HER2-0 groups:



All Patients		HER2-0				HER2-Low	p
		Median (months)	**95% CI**	**Median (months)**	**95% CI**		
Overall Survival	HER2 Groups	60	51.5 - 68.5	59	55.7 - 62.3	0.77	
	Overall	**Median:** 59 months		**95% CI** 55.7 - 62.3			
Disease Free Survival	HER2 Groups	57	44.4 - 69.6	55	53.2 - 56.8	0.55	
	Overall	**Median:** 57 months		**95% CI** 53.5 - 60.5			
Progression Free Survival	HER2 Groups	5	0 - 10.4	8	2.6 - 13.4	0.39	
	Overall	**Median:** 5 months		**95% CI** 0.7 - 9.3			

Figure (2): Overall Survival for all patients (HER2-Low versus HER2-0 groups).

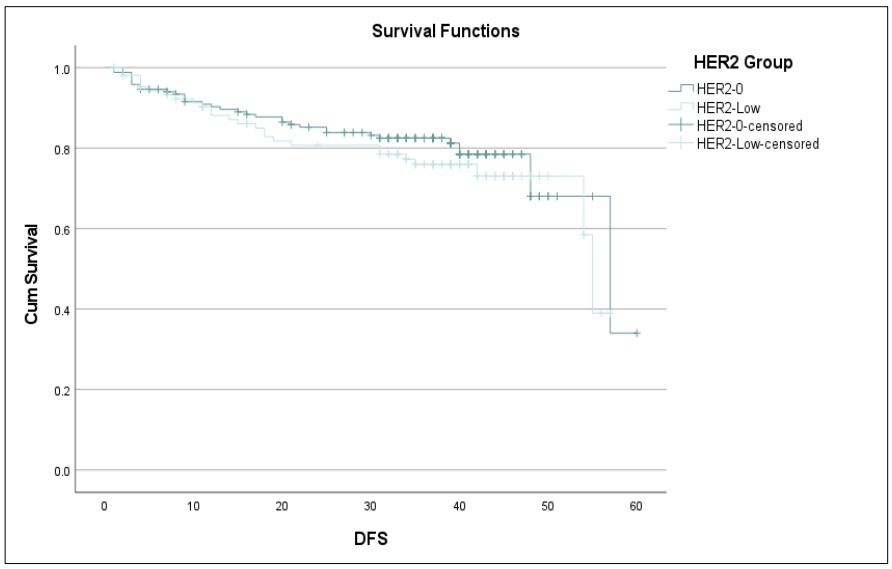


Figure (3): Disease free Survival for all patients (HER-Low versus HER-0 groups).

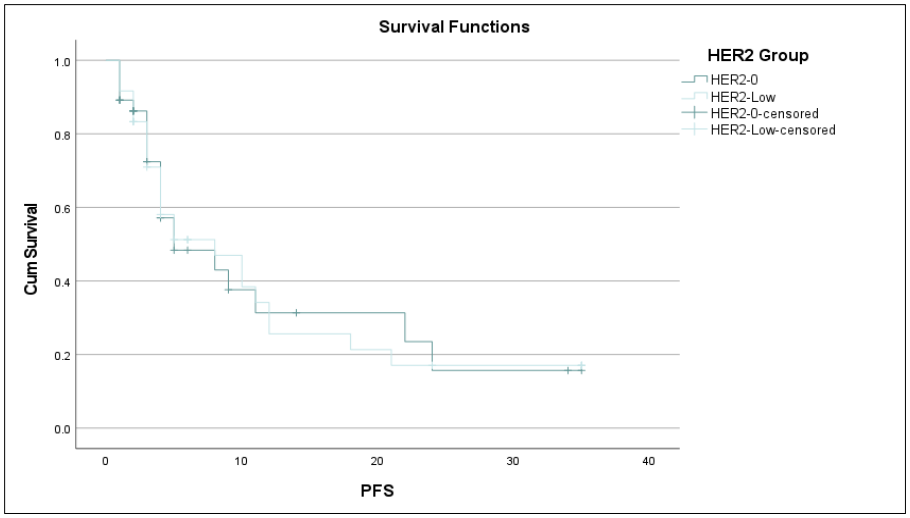


Figure (4): Progression Free Survival for all patients (HER-Low versus HER-0 groups).

Discussion:

Breast cancer is the most common malignancy in females worldwide, with molecular subtyping based on hormone receptor and Human Epidermal Growth Factor Receptor 2 (HER2) status **(Elkum et al., 2025)**. Historically, HER2 classification was binary: positive (IHC 3+ or IHC 2+/ISH+) tumors were eligible for anti-HER2 therapies like trastuzumab, while negative tumors (IHC 0, 1+, or IHC 2+/ISH−) were not **(Ardor et al., 2023; Bardia & Viale, 2023; Rubio, 2022)**. This paradigm shifted with the DESTINY-Breast04 trial, which demonstrated the efficacy of the antibody-drug conjugate trastuzumab deruxtecan (T-DXd) in metastatic tumors expressing low levels of HER2, leading to its FDA approval and a new classification of "HER2-low" (IHC 1+ or IHC 2+/ISH−) **(Ko et al., 2023)**. This reclassification from the previous HER2-negative category has revealed potential prognostic and predictive differences between HER2-low and HER2-zero (IHC 0) disease, though further research is needed to establish if HER2-low constitutes a distinct clinical entity **(Venetis et al., 2022; Neubauer et al., 2024; Ko et al., 2023)**.

This retrospective study was therefore designed with a primary objective to determine the clinicopathological characteristics of HER2-low breast cancer, including patient demographics, clinical presentation, staging, and treatment patterns. Secondary endpoints included a comparison with HER2-0 patients and an analysis of overall, disease-free, and progression-free survival. The study cohort consisted of 309 breast cancer patients, of which 125 (40.5%) were classified as HER2-low and 184 (59.5%) as HER2-0.

Demographic characteristics

The current study found that the clinicopathological profiles of these two groups (HER2-Low and HER2-0) were remarkably balanced, with few statistically significant differences. A key demographic finding was an identical median age at diagnosis of 50 years in both cohorts. This is significantly younger than the average age of 63 years typically reported in Western nations but aligns closely with epidemiological data from Asian and Arab countries, where averages are 48.8 years in Saudi Arabia, 51.9 years in South India, and 47.5 years in Pakistan **(Malik et al., 2025)**. This underscores the profound impact of geographical location, ethnicity, and associated patient characteristics—such as age at menarche, parity, age at first birth, menopausal age, and breastfeeding duration—on the demographic profile of breast cancer patients and, consequently, on the results of studies conducted in different regions.

Pathological and Biological Markers

The analysis of biological markers revealed a higher proportion of hormone receptor-positive (HR+) tumors in the HER2-low group compared to the HER2-0 group (89.6% vs. 83.7%, p=0.284). Although this difference was not statistically significant in the current cohort, this trend is strongly supported by multiple large-scale international studies, albeit with varying percentages that reflect differences in cohort size and composition. A large retrospective analysis by **Schettini et al. (2021)** of 3,689 patients found that 88.2% of HER2-low tumors were HR+ compared to 69.6% in the HER2-0 group ($p < 0.001$). Similarly, a study **by Zhang et al. (2022)** on 523 Chinese women reported HR+ rates of 87.4% for HER2-low versus 66.7% for HER2-0 ($p < 0.001$). **Rey-Vargas et al. (2024)**, in a study of Colombian women, found that intrinsic subtyping showed 96% of HER2-low tumors were Luminal A-like or B-like compared to 79.7% in the HER2-0 group (p=0.001). The variability in exact percentages between these studies and the current one is attributed to factors such as vastly different sample sizes, the reversed ratio of HER2-low to HER2-0 patients, ethnic diversity, technical factors in HER2 testing, and the significant confounding effect of HR status itself.

In contrast to HR status, the proliferation marker Ki-67 showed near-identical mean levels between the groups (40 ± 25 vs. 38 ± 24, p=0.492). This finding is consistent with the analysis by **Schettini et al. (2021)**, which found no significant difference in Ki-67 expression using either a 20% or 14% cutoff. However, this contrasts with a large South Korean study by **Kim et al. (2024)** on 11,416 patients, which reported a statistically significant difference, with a higher proportion of low-Ki-67 tumors in the HER2-low group. This discrepancy highlights how larger sample sizes, geographical location, and tumor heterogeneity can influence results.

Pathological examination showed the most common histological type was invasive ductal carcinoma in both groups (89.5% vs. 85.2%, p=0.392), with a slightly lower proportion of lobular carcinoma in the HER2-low group (4.8% vs. 7.1%). This finding stands in direct contrast to the results of **Li et al. (2023)**, whose large Chinese study reported a significantly higher proportion of invasive lobular cancers in the HER2-low group (28.7% vs. 13.9%). Such big difference is a prime example of how histological patterns can be influenced by ethnicity and sample type (e.g., core biopsy vs. surgical specimen). Furthermore, the distribution of histological grade was nearly equal between the groups, with Grade II tumors representing about 66% of cases in

both (p=0.648). This aligns with **Li et al. (2023)** but contrasts with **Schettini et al. (2021)**, who reported a higher prevalence of Grade III tumors and a significant difference in grade distribution, potentially due to inter-observer variability among pathologists.

Tumor Staging, Response to Therapy, and Metastatic Patterns

An extensive comparison of clinical (cT) and pathological (pT) tumor staging revealed highly balanced results. The majority of tumors in both groups were staged as cT1-T2 (approximately 55 vs. 59%) and pT2 (59.5% vs. 56.2%, p=0.411). These results are consistent with several studies, including **Chen Y et al. (2023)** and a Turkish single-center study by **Akay et al. (2025)**, which found no significant differences in T-stage. However, other studies, such as one by **Bergeron et al. (2023)** in France, reported that HER2-low tumors were significantly larger on average (2.8 cm vs. 2.5 cm, p=0.013). This disagreement is often attributed to the suboptimal reproducibility of distinguishing IHC 0 from IHC 1+, which can lead to tumor misclassification and skew results.

Lymph node involvement (cN and pN) also showed no significant differences. Interestingly, the current study found a lower rate of extranodal extension (ENE) in the HER2-low group (56.7% vs. 87.5%, p=0.002), a significant finding that, after review of existing literature, a notable gap was revealed. No prior studies have directly compared the frequency of ENE specifically between HER2-low and HER2-zero breast cancer subtypes. The foundational study by **Ma et al. (2021)**, which established the prognostic significance of ENE, reported that 39.3% of their 402-patient cohort was positive for this feature but did not perform an analysis stratified by HER2-low status. However, concluded ENE as an independent predictor of poorer prognosis in breast cancer. Lymphvascular invasion (LVI) was higher in the HER2-low group (75.6% vs. 68.9%, p=0.304), while perineural invasion (PNI) was lower (23.4% vs. 32.4%, p=0.248); neither reached significance, a finding regarding LVI that is supported by **Li et al. (2023)**.

A critical finding was the response to neoadjuvant chemotherapy. The pathological complete response (pCR) rate was lower in the HER2-low group (5.6% vs. 8.4%, p=0.527). While not significant in this cohort, this trend is confirmed as statistically significant in large meta-analyses and registry studies. A meta-analysis by **Molinelli et al. (2023)** found pCR rates of 15.6% for HER2-low vs. 22.6% for HER2-0 ($p < 0.001$), and a German registry study by **Lacruz et al. (2025)** reported rates of

30% vs. 39% ($p < 0.001$), highlighting how larger sample sizes can power these comparisons.

In the metastatic setting, the current study found a numerically higher incidence of stage IV disease at diagnosis in the HER2-low group (19.2% vs. 12.1%, p=0.202). However, the patterns of metastatic spread were broadly similar. The most common site was bone (67.5% vs. 77.5%, p=0.317), followed by equal rates of liver metastasis (42.5% in both groups). Lung, soft tissue, and pleural metastases were numerically more common in the HER2-low group, while brain metastasis was identical (25% in both). These patterns are consistent with the prospective German study by **Hein et al. (2021)** and the large cohort analyzed by **Lacruz et al. (2025)**, suggesting that HER2 expression level alone does not dictate a unique metastatic pattern.

Survival Outcomes: OS, DFS, and PFS

The most comprehensive analysis revealed no significant differences in survival outcomes between the two groups. The median Overall Survival (OS) was nearly identical at 59 months for HER2-low and 60 months for HER2-0 (p=0.773). This aligns with the large German cohort study by **Lacruz et al. (2025)**, which, after adjusting for confounders, found no significant differences in OS, with 1- and 5-year rates being similar (94% and 68%) for both groups. This finding, however, contrasts with a large meta-analysis by **Molinelli et al. (2023)** that reported a statistically significant but very slight OS benefit for HER2-low disease in both early and metastatic settings. Similarly, the median Disease-Free Survival (DFS) was 55 months for HER2-low and 57 months for HER2-0 (difference not significant). This result is supported by **Chen Y et al. (2023)** and **Zhang et al. (2022)** but contrasts with a Moroccan study by **Gamrani et al. (2023)** that found HER2-low patients had significantly poorer DFS. For Progression-Free Survival (PFS) in the metastatic setting, the current study found a median of 8 months for HER2-low vs. 5 months for HER2-0, a difference that was not statistically significant. This lack of difference is consistent with the meta-analysis by **Molinelli et al. (2023)** and other reports **(Agostinetto et al., 2021)**.

Conclusion and Recommendations

The extensive review of the current data alongside the existing literature reveals a consistent theme, while trends exist (e.g., higher HR+ rates in HER2-low), significant differences in clinicopathological features and survival outcomes between HER2-low and HER2-0 breast cancer are highly inconsistent across studies. The current study's

null findings on most endpoints, contrasted with the significant results of larger studies, underscore that observed differences are not inherent to the biology of HER2-lowness itself but are profoundly influenced by a multitude of factors. These include study population ethnicity, genetic and molecular profiles, sample size and composition, technical aspects and inter-observer variability in HER2 testing, differences in study design (e.g., inclusion of all stages vs. only metastatic), and the powerful confounding effect of hormone receptor status. Therefore, the assertion that HER2-low breast cancer constitutes a distinct clinical entity separate from HER2-0 remains supported by its response to novel antibody-drug conjugates but is not consistently substantiated by its natural history and baseline clinicopathological characteristics.

Moving forward, optimizing management requires standardized testing protocols incorporating automated platforms and artificial intelligence to reduce diagnostic variability, alongside prospective research with centralized testing. The current guidelines emphasize the need for standardized testing protocols and inter-observer agreement assessment, especially following the 2023 ASCO/CAP updates for HER2-low testing. Health provider education and infrastructure improvements are needed to reduce care delays, while national registries should be established to accurately track epidemiological patterns and clinical outcomes.

Limitations of the study

This study has several limitations. First, the accrual period coincided with the COVID-19 pandemic, which may have introduced biases. Diagnostic delays could potentially inflate the proportion of advanced-stage cases at presentation, while treatment modifications (e.g., adjustments in surgical planning) could impact pathological response rates and survival outcomes. Future studies comparing pre-pandemic, pandemic, and post-pandemic cohorts will be essential to disentangle these temporal effects."

Moreover, being retrospective design and few-regions Egyptian cohort, which may limit the generalizability of results. The small sample size that may lack the power to detect subtle differences in outcomes or rare characteristics. Absence of centralized HER2 testing and inter-observer variability among pathologists represents a significant constraint in HER2 classifications. These factors collectively highlight the need for future prospective, multi-center studies with standardized testing to validate its results.

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