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ORIGINAL RESEARCH

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Survival outcomes of HER2 low patients with metastatic breast cancer: a retrospective analysis

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Abstract

Background: HER2 low (human epidermal growth factor receptor 2) expression is found in around 50–60% of breast cancer cases and is associated with poorer prognoses in early-stage breast cancer. This study evaluates survival outcomes in HER2 low metastatic breast cancer and compares them with other groups. **Methods**: This retrospective analysis examined metastatic breast cancer patients diagnosed between 2010 and 2023. HER2 low was defined as immunohistochemistry (IHC) 1+ or 2+ with negative fluorescence *in situ* hybridization (FISH). The primary objective was to compare overall survival between HER2 low and HER2 0 groups using Kaplan-Meier survival analysis with *p*-values to assess statistical significance. **Results**: A-hundred and twenty-eight patients with metastatic breast cancer were evaluated. Fifty-seven patients were luminal A (44.7%), 46 patients were luminal B (35.9%), and 25 patients (19.5%) were triple negative. Eighty-eight patients (68.8%) were HER2 0+, while 40 patients (31.2%) were in HER2 low (1+, 2+) group. In terms of genetic subtypes, metastatic status at diagnosis, age, The Eastern Cooperative Oncology Group (ECOG), both the HER2 0 and HER2 low groups showed the same results. Median survival of all patients was 28 months, while it was 40 months for luminal A group, 25 months for luminal B group, and 19 months for triple negative group. In the luminal A ($p = 0.971$), luminal B ($p = 0.820$) and triple negative groups ($p = 0.444$), survival rates of the HER2 0+ and HER2 low groups did not differ statistically significantly. **Conclusions**: In our study, no relationship was found between being in HER2 low group and poor survival in patients with metastatic breast cancer.

Keywords

HER2 low; HER2 targeted therapies; Metastasis; Breast cancer; Triple negative; Overall survival

1. Introduction

Breast cancer is the most frequently diagnosed cancer among women [1]. Due to the greater likelihood of visceral organ metastasis and the 5-year survival rate of only 25–30% among individuals with metastatic disease, it ranks among the primary causes of death associated with cancer [2].

Breast cancer exhibits high heterogeneity, necessitating its classification into various molecular subtypes to optimize treatment strategies and predict clinical outcomes. Depending on the expression levels of hormone receptors (estrogen and progesterone) and HER2, it is categorized into four main histopathological subtypes, each possessing unique prognostic and predictive implications. The treatment strategies for breast cancer are determined by its molecular subtypes, such as luminal A, luminal B, HER2 positive, and triple-negative. Depending on the subtype, therapeutic options vary from endocrine therapy to HER2 targeted treatments or chemotherapy [3]. Accurate classification is essential as the molecular subtype affects both survival outcomes and the likelihood of response to specific treatments, thereby playing a critical role in personalized cancer management.

Approximately 15–20% of breast cancer cases belong to the HER2 positive subtype [4]. HER2, a transmembrane glycoprotein possessing tyrosine kinase activity, is part of the epidermal growth factor receptor (EGFR) family, which comprises four members. Proteins belonging to the EGFR family function by forming heterodimer receptors with HER2 as the result of ligand binding. HER2 receptors activate signal transduction pathways in cells, causing cellular differentiation and proliferation after that activation [5].

HER2 positive tumors usually have poor prognosis due to their higher grades and proliferation rates. The use of HER2 targeted therapies in these cases has improved survival outcomes. Such treatments are effective for patients with HER2 amplification and overexpression, but ineffective for others [6, 7].

A considerable number of individuals diagnosed with breast cancer, approximately 50–60%, are categorized as “HER2

low," characterized by IHC scores of 1+ or 2+ without gene amplification, as confirmed by FISH testing. These patients were traditionally grouped within the HER2 negative category alongside those with IHC scores of 0, and they were treated according to the established protocols for HER2 negative breast cancer [7, 8]. Recent research indicates that HER2 low tumors exhibit unique biological and clinical characteristics when compared to HER2 negative tumors (those with scores of 0). For instance, HER2 low patients have been observed to present with larger tumor sizes, higher histological grades, increased Ki-67 positivity, and a greater likelihood of axillary lymph node involvement. The results indicate that HER2 low tumors might form a distinct subgroup within HER2 negative breast cancers, highlighting the need for further exploration of personalized therapies, including HER2 targeted treatments [9–11].

This study aimed to assess the influence of HER2 low status on survival outcomes among patients with metastatic breast cancer. Our analysis also aimed to identify whether the clinical characteristics and survival trends of our HER2 low patients aligned more closely with HER2 0 or HER2 positive patients. Through this comparison, we aimed to contribute to the ongoing discussion on the clinical relevance of the "HER2 low" classification and its potential implications for personalized treatment strategies in metastatic breast cancer.

2. Materials and methods

A retrospective study analyzed 200 patients with metastatic breast cancer who were diagnosed at our oncology clinic between January 2010 and December 2023. Patients with incomplete paper-based or electronic medical records at the time of diagnosis were excluded from the study. As a result, a total of 128 patients were included in the analysis. Patients who were evaluated as HER2 1+ or 2+ but FISH-negative, as confirmed by IHC, were considered as HER2 low. The patients' demographic and clinicopathological data were gathered from both paper-based patient files and digital medical records.

Data were analyzed using IBM SPSS Statistics 20.0 for Windows (IBM Corp., Armonk, NY, USA). The normality of continuous variables was evaluated with the Kolmogorov-Smirnov test. Depending on the aim of the analysis, continuous variables were given as mean ± standard deviation or median (minimum–maximum). Categorical variables were examined using both the chi-square test and Fisher's exact test. Survival differences between HER2 low and HER2 0+ groups across breast cancer subtypes were analyzed using the Kaplan-Meier method with the log-rank test.

3. Results

A total of 128 diagnosed patients were analyzed, with an average age of 57 (34–98) years. Ninety-two patients (71.9%) were under 65 years of age. ECOG performance status (PS) score of 112 patients (87.5%) was 0 or 1 point, while 16 patients (12.5%) had ECOG PS scores of 2 or 3 points. Eighty-six patients (67.2%) were premenopausal. While 55 (43%) patients were metastatic at the time of diagnosis, 73 (57%) patients relapsed during follow-up. Fifty-seven patients had luminal A (44.5%), 46 patients had luminal B (35.9%), and 25 patients (19.5%) had triple-negative tumors. Eighty-eight patients (68.8%) were in the HER2 0+ group, while 40 patients (31.2%) were in the HER2 low (1+, 2+) group. The number of patients with an estrogen receptor (ER) positivity rate of 1–10% was 4 (3.9%), while the number of patients with 10–100% ER positivity was 98 (96.1%) (Table 1).

TABLE 1. Demographic and clinicopathologic characteristics of patients.

Variables	n (%)
Age (yr)	
<65	92 (71.9)
≥65	36 (28.1)
Genomic type	
Luminal A	57 (44.5)
Luminal B	46 (35.9)
Triple negative	25 (19.5)
HER2 status	
HER2 0	88 (68.8)
HER2 low	40 (31.2)
ER positivity rate	
1–10%	4 (3.9)
10–100%	98 (96.1)
Metastasis status	
De novo	55 (43.0)
Relapse	73 (57.0)
Menopause status	
Premenopausal	86 (67.2)
Postmenopausal	42 (32.8)
ECOG	
PS 0 or 1	112 (87.5)
PS 2 or 3	16 (12.5)

ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor-2; PS: Performance score.

There was no statistically significant association between HER2 0 and HER2 low groups regarding genomic subtypes ($p = 0.342$), metastasis at diagnosis ($p = 0.549$), age ($p = 0.916$), or ECOG PS ($p = 0.623$) (Table 2). The overall median survival for all patients was 28 months.

Among the 25 patients with triple-negative tumors, the median survival time was 19 months. Sixteen patients belonged to the HER2 0+ group, while the remaining nine were classified as HER2 low. The median survival for the HER2 low group was 19 months, compared to 18 months for the HER2 0+ group. In the metastatic triple-negative subgroup, no statistically significant difference in survival was observed between HER2 0+ and HER2 low patients ($p = 0.444$) (Fig. 1).

In the luminal A group, comprising 57 patients, the median survival was 40 months. Among these, 43 patients were

TABLE 2. The relationship between HER2 status and clinicopathologic characteristics.

Variables	HER2 0	HER2 low	*p* value
Metastasis status			
De novo	38 (43.2)	55 (43.0)	0.549
Relapse	50 (56.8)	23 (57.0)	
Subtype			
Triple negative	16 (18.2)	9 (22.5)	
Luminal A	43 (49.0)	14 (35.0)	0.342
Luminal B	29 (33.0)	17 (42.5)	
ER positivity rate			
1–10%	1 (1.4)	3 (10.0)	0.075
10–100%	71 (98.6)	27 (90.0)	
Age (yr)			
<65	63 (71.6)	29 (72.5)	0.916
≥65	25 (28.4)	11 (27.5)	
ECOG			
PS 0 or 1	77 (87.5)	35 (87.5)	0.623
PS 2 or 3	11 (12.5)	5 (12.5)	

ECOG: Eastern Cooperative Oncology Group; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor-2; PS: Performance score; p: significance.

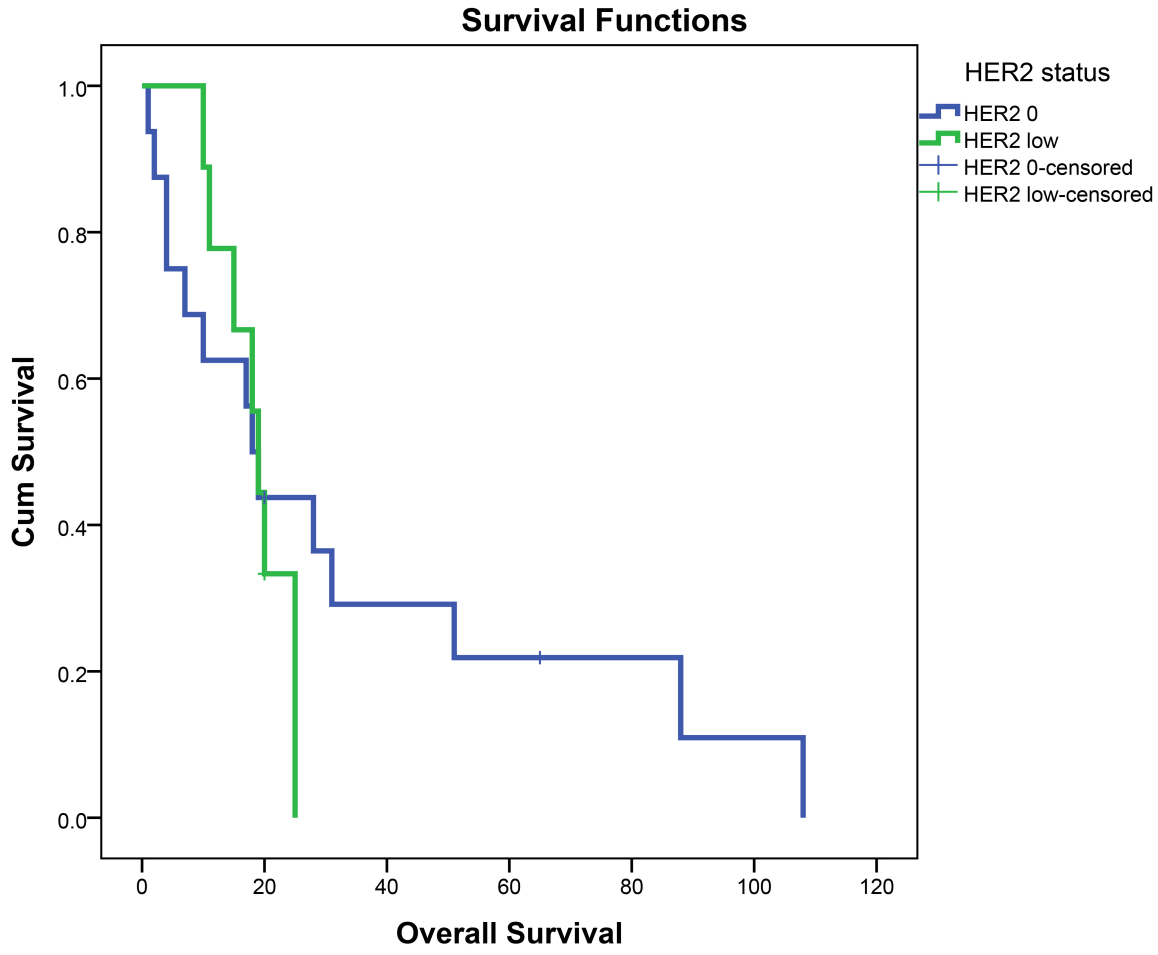

FIGURE 1. Kaplan-Meier Survival Curves for HER2 0+ and HER2 low Groups in triple negative patients. HER2: Human epidermal growth factor receptor 2.

classified as HER2 0+ and 14 as HER2 low. The median survival was 40 months for the HER2 0+ group and 38 months for the HER2 low group. No statistically significant difference in survival was found between the two groups (p = 0.971) (Fig. 2).

In the HER2 0+ group, the number of patients with an ER positivity rate of 1–10% was only 1, while 71 of these patients had positivity rates of 10–100%. Among the HER2 low group, the number of patients with ER positivity rates of 1–10% was 3, while 27 of these patients had positivity rates of 10–100% (p = 0.075) (Table 2).

For the 46 patients in the luminal B group, the median survival time was 25 months. Among these, 29 patients were classified as HER2 0+ and 17 as HER2 low. The median survival was 32 months for the HER2 0+ group and 17 months for the HER2 low group. Although a numerical difference was noted between the groups, it was not statistically significant (p = 0.820) (Fig. 3).

4. Discussion

This study examined the prognostic significance of HER2 low status in metastatic breast cancer patients. Survival rates did not differ significantly between the HER2 0+ and HER2 low groups. Across the luminal A, luminal B, and triple-negative subtypes, overall survival rates were comparable. These results indicate that the prognostic influence of HER2 low status in metastatic breast cancer appears to be minimal when compared to its role in early-stage disease.

In our analysis, no statistically significant differences were observed between the HER2 0+ and HER2 low groups regarding age at diagnosis, ECOG performance status, or the presence of metastasis at the time of diagnosis. Approximately 30% of the patients analyzed in this study belonged to the HER2 low group. These results suggest that while HER2 low expression is relatively frequent in metastatic breast cancer, it does not significantly influence survival outcomes.

However, these results differ from those of several studies in the literature that have identified HER2 low status as a prognostic factor in early-stage breast cancer. For example, in the study by Rossi *et al*. [12], patients with HER2 2+ but FISH-negative tumors showed similar characteristics to those with HER2 positive tumors, including larger tumor sizes, higher histological grades, higher Ki-67 expression levels, and higher rates of axillary lymph node involvement. Previous research identified a link between HER2 2+ status and poorer disease-free survival outcomes. However, in our study, no significant differences in survival outcomes were detected between HER2 low and HER2 0+ groups in metastatic breast cancer. These findings imply that the prognostic relevance of HER2 low status may be more evident in early-stage disease compared to metastatic cases.

In a study by Eggemann *et al*. [13], which included 9872 patients with early-stage breast cancer, it was reported that patients with HER2 2+ but FISH-negative status had poorer disease-free survival rates compared to those with hormone receptor-positive status. In contrast, our study revealed no significant survival differences between the HER2 low and HER2 0+ groups. This divergence might be attributed to other factors influencing survival in metastatic breast cancer, including the burden of metastatic disease, previous treatment

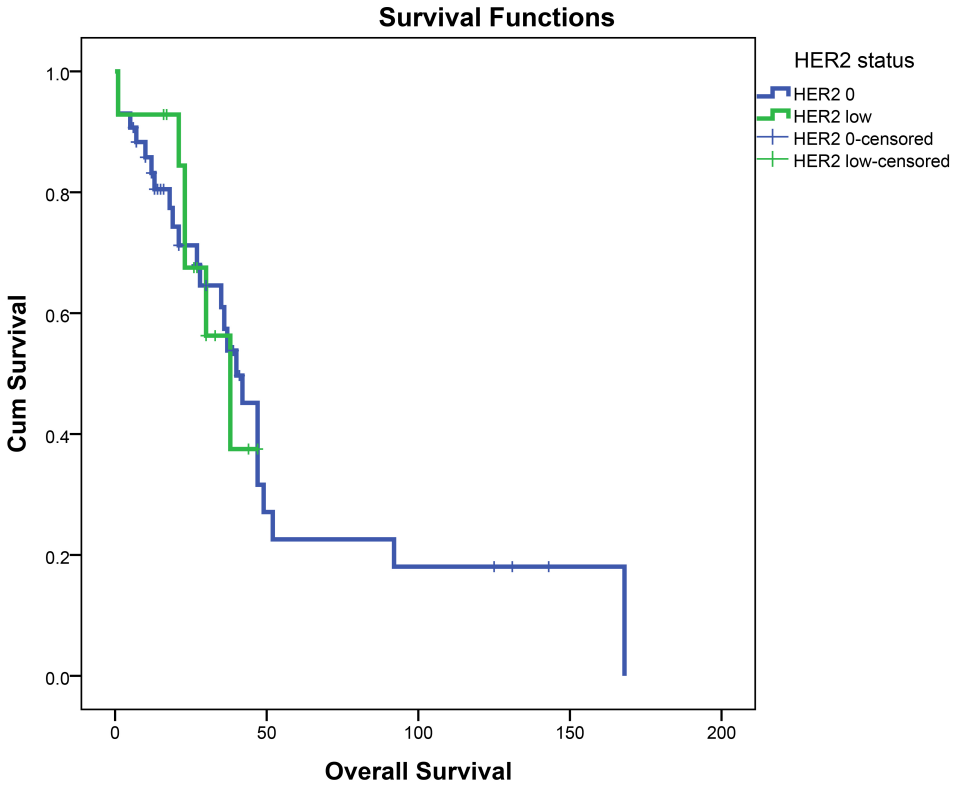

FIGURE 2. Kaplan-Meier Survival Curves for HER2 0+ and HER2 low Groups in Luminal A patients. HER2: Human epidermal growth factor receptor 2.

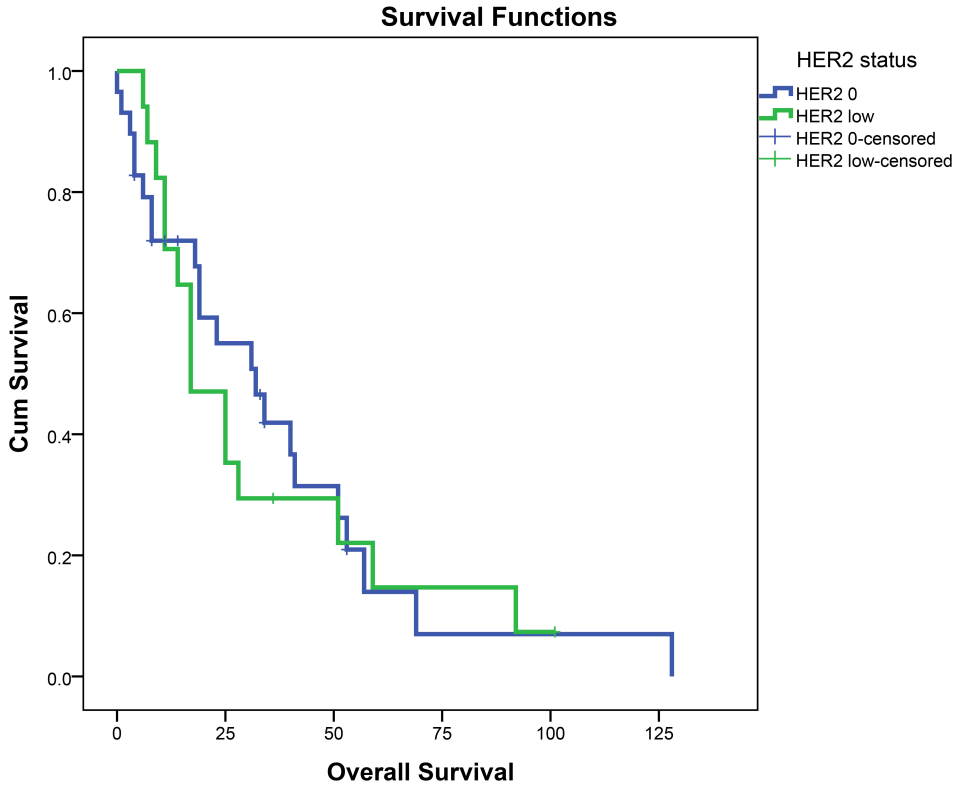

FIGURE 3. Kaplan-Meier Survival Curves for HER2 0+ and HER2 low Groups in Luminal B patients. HER2: Human epidermal growth factor receptor 2.

regimens, and patients' overall health conditions, which could diminish the prognostic significance of HER2 low expression.

A retrospective study by Gilcrease *et al.* [14] identified HER2 1+ or 2+ expression as a negative prognostic indicator in patients with breast cancer. That study suggested that HER2 low status was associated with poorer survival outcomes. However, since the study focused on early-stage breast cancer patients, its findings may not be directly applicable to our research, which centered on metastatic breast cancer. In our analysis, survival rates between the HER2 low and HER2 0+ groups were comparable, indicating that the prognostic significance of HER2 low expression might be less pronounced in metastatic cases.

The review and meta-analysis published by Molinelli *et al.* [10] in 2023 reported that patients with HER2 low metastatic breast cancer demonstrated better overall survival compared to those with HER2 0 tumors independently of hormone receptor status. This finding contrasts with our results, as no significant survival differences were observed between the HER2 low and HER2 0+ groups of our study. This discrepancy may be attributed to differences in study design, sample size or treatment protocols. Additionally, it is possible that other clinical factors in the metastatic setting, such as the extent of disease burden and prior treatments, may overshadow the potential prognostic value of HER2 low status, which could explain the divergent outcomes between studies.

Conversely, an analysis of the MBC-Registry of the Austrian Study Group of Medical Tumor Therapy (AGMT) reported that low HER2 expression did not significantly impact overall survival in metastatic breast cancer patients, irrespective of hormone receptor status [15]. These findings are consistent with our results, which showed no significant difference in survival outcomes between the HER2 low and HER2 0+ groups. The alignment between our study and the Austrian registry data suggests that, in the metastatic setting, HER2 low status may not serve as a strong prognostic factor. This consistency across different cohorts further highlights the need to explore additional factors that may influence survival in metastatic breast cancer patients, such as tumor burden, treatment history, and genetic mutations, which could potentially mask the impact of HER2 low expression.

In recent years, increasing attention has been directed toward the use of HER2 targeted therapies in patients with HER2 low expression. A key study in this area, the DESTINY-Breast04 trial, revealed that trastuzumab deruxtecan (T-DXd) provided a significant improvement in both progression-free survival and overall survival compared to conventional chemotherapy in HER2 low metastatic breast cancer patients who had undergone at least one prior treatment [16]. Likewise, subgroup analyses from various studies have indicated that HER2 targeted treatments, including trastuzumab-duocarmazine, may enhance response rates in patients with HER2 low expression [17]. In this study, patients with HER2 low expression were not treated with specific HER2 targeted therapies but rather followed standard treatment protocols for HER2 negative cases. This factor may have impacted the results and restricted our ability to evaluate the potential advantages of HER2 targeted treatments in this patient group.

The primary limitations of this study are its relatively small

sample size and its retrospective, single-center design, which may restrict the generalizability of the findings. Additionally, the reliance on medical records may have introduced selection bias and information bias due to incomplete or missing data. Variations in treatment protocols over the study period also constitute a potential source of heterogeneity, which could have affected survival outcomes. To confirm our findings and gain a deeper understanding of the prognostic impact of HER2 low status in metastatic breast cancer, further prospective multi-center studies with larger patient cohorts are required.

5. Conclusions

Our study found no significant link between HER2 low status and worse survival outcomes in patients with metastatic breast cancer. To confirm these findings and gain a deeper understanding of the prognostic significance of HER2 low expression, larger prospective studies are needed.

AVAILABILITY OF DATA AND MATERIALS

Raw data were generated at Health Sciences University Diskapi Training and Research Hospital. Derived data supporting the findings of this study are available from the corresponding author OD on request.

AUTHOR CONTRIBUTIONS

OD—took part in the planning, data collection, ethics committee application and writing of the manuscript. HS—contributed to the statistical analysis and writing of the data. EC—contributed to the planning and data collection of the manuscript. YD—contributed to data collection.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the principles of the Helsinki Declaration and was approved by the Ankara Etlik City Hospital Ethics Committee with protocol number 2023-052. Since this was a retrospective study, informed consent was obtained in accordance with the Ethics Committee's guidelines.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2024; 74: 229–263.

[2] Liang Y, Zhang H, Song X, Yang Q. Metastatic heterogeneity of breast cancer: molecular mechanism and potential therapeutic targets. Seminars in Cancer Biology. 2020; 60: 14–27.

[3] Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, *et al*. Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Archives of Pathology & Laboratory Medicine. 2020; 144: 545–563.

[4] Roy M, Fowler AM, Ulaner GA, Mahajan A. Molecular classification of breast cancer. PET Clinics. 2023; 18: 441–458.

[5] McLemore LE, Albarracin CT, Gruschkus SK, Bassett RL III, Wu Y, Dhamne S, *et al*. HER2 testing in breast cancers: comparison of assays and interpretation using ASCO/CAP 2013 and 2018 guidelines. Breast Cancer Research and Treatment. 2021; 187: 95–104.

[6] Corti C, Giugliano F, Nicolò E, Tarantino P, Criscitiello C, Curigliano G. HER2-low breast cancer: a new subtype? Current Treatment Options in Oncology. 2023; 24: 468–478.

[7] Kang S, Kim SB. HER2-low breast cancer: now and in the future. Cancer Research and Treatment. 2024; 56: 700–720.

[8] Nicolò E, Tarantino P, Curigliano G. Biology and treatment of HER2-low breast cancer. Hematology/Oncology Clinics of North America. 2023; 37: 117–132.

[9] Tarantino P, Viale G, Press MF, Hu X, Penault-Llorca F, Bardia A, *et al*. ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer. Annals of Oncology. 2023; 34: 645–659.

[10] Molinelli C, Jacobs F, Agostinetto E, Nader-Marta G, Ceppi M, Bruzzone M, *et al*. Prognostic value of HER2-low status in breast cancer: a systematic review and meta-analysis. ESMO Open. 2023; 8: 101592.

[11] Tarantino P, Hamilton E, Tolaney SM, Cortes J, Morganti S, Ferraro E, *et al*. HER2-low breast cancer: pathological and clinical landscape. Journal of Clinical Oncology. 2020; 38: 1951–1962.

[12] Rossi V, Sarotto I, Maggiorotto F, Berchialla P, Kubatzki F, Tomasi N, *et al*. Moderate immunohistochemical expression of HER-2 (2+) without HER-2 gene amplification is a negative prognostic factor in early breast cancer. The Oncologist. 2012; 17: 1418–1425.

[13] Eggemann H, Ignatov T, Burger E, Kantelhardt EJ, Fettke F, Thomssen C, *et al*. Moderate HER2 expression as a prognostic factor in hormone receptor positive breast cancer. Endocrine-Related Cancer. 2015; 22: 725–733.

[14] Gilcrease MZ, Woodward WA, Nicolas MM, Corley LJ, Fuller GN, Esteva FJ, *et al*. Even low-level HER2 expression may be associated with worse outcome in node-positive breast cancer. The American Journal of Surgical Pathology. 2009; 33: 759–767.

[15] Gampenrieder SP, Rinnerthaler G, Tinchon C, Petzer A, Balic M, Heibl S, *et al*. Landscape of HER2-low metastatic breast cancer (MBC): results from the Austrian AGMT_MBC-Registry. Breast Cancer Research. 2021; 23: 112.

[16] Modi S. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer: a plain language summary of the DESTINY-Breast04 study. Future Oncology. 2025; 21: 367–380.

[17] Banerji U, van Herpen CML, Saura C, Thistlethwaite F, Lord S, Moreno V, *et al*. Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study. The Lancet Oncology. 2019; 20: 1124–1135.

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