Comparison of Clinicopathological Features and Survival Outcomes Associated with HER2-Zero and HER2-Low Breast Cancers: A retrospective, Observational Study

Mahmut UCAR[1], Mukaddes YILMAZ[1], Eda ERDIS[2], Birsen YUCEL[2]

[1] Sivas Cumhuriyet University, Faculty of Medicine, Department of Medical Oncology
[2] Sivas Cumhuriyet University, Faculty of Medicine, Department of Radiation Oncology

ABSTRACT

Despite being classified as HER2-negative, HER2-zero and HER2-low subtypes are considered distinct entities due to their varying clinicopathological features and survival outcomes. This study was designed to evaluate the sociodemographic, clinical, survival and prognostic differences between HER2-zero and HER2-low patients who were evaluated as HER2 negative. This retrospective single-center study included patients with HER2-negative non-metastatic breast cancer between 2003 and 2022. Patients were analyzed in two groups as HER2-zero and HER2-low. Of 680 patients, 484 (71%) were included in the HER2-zero group and 196 (29%) in the HER2-low group. Statistically significant differences were found between the groups in terms of histopathologic subtyping ($p< 0.001$), ER ($p< 0.001$) and PR status ($p= 0.005$), and presence of lymphovascular invasion ($p= 0.023$). When survival results were analyzed according to HER2 status, overall survival and disease-free survival were not statistically different for all patients. This result was also supported in luminal A, luminal B and triple negative patients ($p>0.050$). HER-2 status was not observed as a factor affecting OS and DFS in univariant and multivariant analyses ($p> 0.050$). There were no clinically and pathologically significant differences between HER2-low and HER2-zero, except that HER2-low patients had more ER and PR positivity, more luminal subgroups and more lymphovascular invasion. When evaluated together with histopathologic subgroups, no survival difference was detected between both groups. HER2 status could not be determined as a prognostic factor.

Keywords: Breast cancer, Epidermal growth factor receptor, Survival analysis, Overall, Disease-free survival

INTRODUCTION

Oncogenic amplification of the v-erb-b2 avian erythroblastic leukaemia viral oncogene homolog 2 (ErbB2) gene encoding the human epidermal growth factor receptor-2 (HER2) transmembrane protein is seen in almost 15 to 20% of all breast cancer patients.[1-3] Breast cancer patients with an immunohistochemistry (IHC) staining score of 3+ are categorised as HER2-positive patients. Breast cancer patients with an IHC staining score of 2+ are also categorised as HER2-positive patients unless they are found to have no ErbB2 amplification by fluorescence in situ hybridisation (FISH) testing.[1] HER2-positive breast cancer is associated with more severe clinical and biological features due to larger tumour sizes, higher histological grades, higher antigen Kiel 67 (Ki-67) levels, and more regional lymph node involvement. Therefore, a favourable prognosis requires developing monoclonal targeted therapies or first-generation antibody-drug conjugates.[1-4] In this context, the exact molecular typing of breast cancer regarding HER2 status is a vital prognostic factor that can be used in predicting the response to different treatment modalities.[2]

HER2-negative breast cancer patients may have different IHC staining scores (0, 1+, or 2+). Accordingly, breast cancer patients with an IHC staining score of 0, i.e., HER2-zero breast cancer patients, breast cancer patients with an IHC staining score of 1+, i.e., and breast cancer patients with an IHC staining score of 2+and who are found to have no ErbB2 amplification by FISH testing are categorised as HER2-low breast cancer patients.[1, 5] In the context of differences in the responses of breast cancer patients to HER2-targeted therapies, it has been proposed that in addition to being categorised as HER2-negative and HER2-positive, HER2-negative breast cancer patients should be further categorised as HER2-low and HER2-zero breast cancer patients.[6-8]

In the literature, data on the differences between HER2-low and HER2-zero breast cancer patients in terms of clinicopathological characteristics, responses to neoadjuvant chemotherapy, and survival outcomes are inconsistent.[2,5,6,9] Several studies suggested that HER2-low breast cancer is a potentially independent subtype of breast cancer that differs significantly from HER2-zero breast cancer.[10,11] Revealing the differences between these two breast cancer subtypes in terms of clinical and molecular features may help physicians better understand the underlying pathophysiology of breast cancer and thus develop treatment methods that will increase survival outcomes.[7,10]

Given the foregoing, this study was designed to evaluate the sociodemographic, clinical, survival and prognostic differences between HER2-zero and HER2-low patients who were evaluated as HER2-negative.

PATIENTS AND METHODS

Study Design

This investigation was structured as a retrospective, observational study based at a single centre.

Population and Sample

The study population consisted of all consecutive breast cancer patients followed up at the Oncology Center of the Faculty of Medicine of Sivas Cumhuriyet University in Turkey between 2003 and 2022. The research data were obtained from patient's medical records and the hospital information system. The study's inclusion criteria were being 18 years of age or older, being a female, and having non-metastatic early stage (stages I to III) breast cancer. On the other hand, the study's exclusion criteria were being younger than 18, being male, having metastatic breast cancer at admission, having a second primary cancer, having an IHC staining score of 3+, having an IHC staining score of 2+ and ErbB2 amplification as indicated by ISH testing, and not having adequate follow-up data. In the end, the study sample consisted of 680 consecutive adult female non-metastatic breast cancer patients, who were divided into two groups: HER2-zero group (n= 484, 71%) and HER2-low group (n= 196, 29%).

Data Collection

Patients' demographic (age), clinical [menopausal status, comorbidities, the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scale score], laboratory [carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) levels], and pathological [histopathological type and subtypes, grade, hormonal status in terms of estrogen receptor (ER) and progesterone receptor (PR), lymphovascular and perineuronal invasion, tumour necrosis, Ki-67 staining, TNM stages based on the American Joint Committee on Cancer (AJCC) AJCC staging system, 8th edition[12] characteristics were collected and recorded into a preprepared worksheet. All pathology samples were evaluated in the same centre by a team specialised in breast cancer. Patients with ER and/or PR positivity were regarded as hormone receptor (HR) positive. Details related to the administered treatments, including the type of breast and axillary surgery, the type of chemotherapy, i.e., neoadjuvant or adjuvant chemotherapy, and adjuvant radiotherapy protocols were recorded. The American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines were used to define the ER, PR and HER2 statuses of the patients.[3,13] HER2-negative patients were categorised as either HER2-zero (IHC 0) or HER2-low (IHC +1 or IHC +2 and a negative FISH test result). The quantification of HER2 status using IHC was performed by

a single team of experienced breast pathologists as described in the literature.[2]

Follow-up Procedure

All patients were followed up at six-month intervals in the Department of Oncology Center outpatient clinics. Recurrences, metastases, and types of metastases were recorded during the follow-up visits. The time from initiation of breast cancer treatment to the time of first breast cancer recurrence, metastasis, or death from breast cancer without any sign of cancer was defined as disease-free survival (DFS), whereas the time from breast cancer diagnosis to death or the last follow-up, regardless of recurrence or metastasis was defined as overall survival (OS).

Ethical Approval for the study protocol was granted by the local ethics committee (Sivas Cumhuriyet University, ethical approval: 2023-11/13 on November 16, 2023). The research was conducted in line with the ethical guidelines outlined in the Declaration of Helsinki. Due to the retrospective nature of the study and the anonymity of the data, written informed consent was not obtained from the participants.

Statistical Analysis

Descriptive statistics derived from the gathered data were presented as median with range for continuous variables and as frequencies and percentages for categorical variables. The normality of continuous variables was assessed using Shapiro-Wilk, Kolmogorov-Smirnov. For comparing categorical variables between groups, Pearson's chi-square test was employed for 2x2 tables with expected cell counts of five or more, Fisher's exact test for 2x2 tables with fewer than five expected cells, and the Fisher-Freeman-Halton test for RxC tables with fewer than five expected cells. In comparing two independent groups, the independent samples, t-test was utilised for numerical variables conforming to normal distribution and the Mann-Whitney U test for those not conforming. To determine the OS and DFS in patients with HER2-zero and HER2-low breast cancer, the Kaplan-Meier survival analysis and the log-rank test were applied. Cox regression analysis was also performed to determine prognostic factors.

Statistical analyses were conducted using Version 23 SPSS (IBMCorp., Armonk, NewYork, USA) program. A probability (p) value of ≤ 0.05 was considered statistically significant.

RESULTS

Of the 680 consecutive adult female non-metastatic breast cancer patients in the sample, 484 (71%) were included in the HER2-zero group, and 196 (29%) were included in the HER2-low group. The mean age of the overall sample was 52 (range 24-89) years. Most (82%) patients were younger than 65. More than half (58%) of the patients were postmenopausal, and the most common (74%) ECOG-PS scale score was zero. There were significant differences between the groups in the rates of patients with ER and PR status, molecular subtypes and lymphovascular invasion ($p< 0.050$) (Table 1). In the HER2-low group, the rates of ER and PR positivity and lymphovascular invasion were significantly higher. However, triple negative subtype was lower than in the HER2-zero group. There was no significant difference between the groups in other tumoral characteristics ($p> 0.050$). The distribution of patients' sociodemographic and clinical characteristics by the study groups is given in Table 1.

Although the treatments applied to the patients were similar, neoadjuvant chemotherapy and adjuvant hormonotherapy were used more in the HER2-low group than in the HER2-zero group. There was no significant difference between the groups in metastatic disease pattern, except for the rate of patients with skin metastasis. Accordingly, the rate of patients with skin metastasis was significantly higher in the HER2-low group than in the HER2-zero group ($p= 0.001$). There was no significant difference in the time to recurrence for all groups. The distribution of treatment modalities and recurrence patterns according to the study groups is shown in Table 2.

The 5-year, 10-year, 15-year and median OS of all patients according to the study groups were 86%, 74%, 62% and 244 months in the HER2-zero group

Table 1. Sociodemographic and clinical characteristics of the study groups

		Overall n= 680 (100%)	Group HER2-zero n= 484 (71%)	Group HER2-low n= 196 (29%)	p value
Age, year (median, min-max)	52 (24-89)	51 (24-89)	52 (26-83)	0.453	
Age	≤ 65 years	505 (82)	398 (82)	157 (80)	0.292
	> 65 years	125 (18)	86 (18)	39 (20)	
Menopause status	Premenopause	284 (42)	204 (42)	80 (41)	0.409
	Postmenopause	396 (58)	280 (58)	116 (59)	
ECOG performance status	0	503 (74)	365 (75)	138 (70)	0.062
	1	145 (21)	93 (19)	52 (27)	
	2 or more	32 (5)	26 (5)	6 (3)	
Histopathology	Ductal	508 (74)	358 (74)	150 (77)	0.234
	Lobuler	30 (6)	30 (6)	18 (9)	
	Mixed	46 (10)	46 (10)	14 (7)	
	Others	50 (10)	50 (10)	14 (7)	
Molecular subtypes	Luminal A	268 (39)	196 (41)	72 (37)	<0.001
	Luminal B*	278 (41)	176 (36)	102 (52)	
	Triple negative	134 (20)	112 (23)	22 (11)	
TNM Stage	Stage I	137 (20)	99 (21)	38 (19)	0.521
	Stage II	322 (47)	234 (48)	55 (45)	
	Stage III	221 (33)	151 (31)	70 (36)	
Estrogen receptor	Negative	162 (24)	134 (28)	28 (14)	<0.001
	Positive	518 (76)	350 (72)	168 (86)	
Progesterone receptor	Negative	202 (30)	158 (33)	44 (22)	0.005
	Positive	478 (70)	326 (67)	152 (78)	
Grade	Grade 1	216 (32)	163 (34)	53 (27)	0.184
	Grade 2	297 (44)	202 (42)	95 (49)	
	Grade 3	167 (25)	119 (24)	48 (25)	
Lymphovascular invasion (n= 604)	Negative	342 (57)	255 (59)	87 (50)	0.023
	Positive	262 (43)	175 (41)	87 (50)	
Perineural invasion	Negative	400 (68)	288 (69)	57 (34)	0.300
	Positive	187 (32)	130 (31)	112 (66)	
Tumor necrosis	No	371 (69)	260 (69)	111 (68)	0.442
	Yes	168 831)	116 (31)	52 (32)	
Intraductal component	No	192 (32)	144 (34)	48 (27)	0.055
	Yes	413 (68)	282 (66)	131 (73)	
Multicentricity/focality	No	551 (85)	384 (84)	167 (88)	0.107
	Yes	94 (15)	72 (16)	22 (12)	
Extracapsular extension	Negative	162 (41)	113 (41)	49 (41)	0.493
	Positive	230 (59)	159 (59)	71 (59)	
Ki-67, % (median, min-max)		20 (0-100)	20 (0-100)	20 (0-100)	0.975
CEA groups	Normal	440 (74)	321 (76)	119 (71)	0.167
	High	152 (26)	104 (24)	48 (29)	
CA15-3 groups (n= 600)	Normal	464 (77)	335 (78)	129 (76)	0.395
	High	136 (23)	96 (22)	40 (24)	

and 86%, 71%, 47% and 183 months in the HER2-low group, respectively (p= 0.214). The 5-year, 10-year, 15-year and median DFS of all patients according to the study groups were 81%, 68%, 59% and 244 months in the HER2-zero group and 68%, 65%, 38% and 178 months in the HER2-low group, respectively (p= 0.131). Figure 1 shows the OS curves of all patients according to HER2 status. When the survival curves were analysed, it was observed that the survival difference between the

Table 2. Comparison of treatment modalities and the patern of recurrence to the patients in each group

	Overall n= 680 (100%)	Group HER2-zero n= 484 (71%)	Group HER2-low n=196 (29%)	p value
Neoadjuvant chemotherapy	27 (4)	14 (3)	13 (7)	0.024
Breast surgery				
Mastectomy	365 (54)	269 (56)	96 (49)	0.070
Breast conserving	315 (46)	215 (44)	100 (51)	
Axillary intervention				
No	3 (1)	2 (0.4)	1 (1)	0.722
Sentinel lymph node biopsy	133 (19)	91 (19)	42 (21)	
Axillary dissection	544 (80)	391 (81)	153 (78)	
Adjuvant chemotherapy	562 (83)	402 (83)	160 (82)	0.366
Adjuvant radiotherapy	539 (79)	378 (78)	161 (82)	0.141
Adjuvant hormotherapy	541 (80)	369 (76)	172 (88)	<0.001
Recurrence	166 (24)	115 (24)	51 (26)	0.299
Bone	108 (16)	78 (16)	30 (15)	0.446
Lung/pleura	58 (9)	37 (8)	21 (11)	0.127
Liver	45 (7)	33 (7)	12 (6)	0.445
Central nervous system	39 (6)	26 (5)	13 (7)	0.317
Locoregional	21 (3)	14 (3)	7 (4)	0.317
Skin	6 (1)	–	6 (3)	0.001
The time to recurrence (median, month)				
All	42 (3-195)	41 (3-195)	43 (4-183)	0.680
Luminal A	51 (6-184)	60 (10-184)	25 (6-183)	0.064
Luminal B*	46 (4-165)	34 (4-145)	54 (12-165)	0.065
Triple negative	31 (3-195)	31 (3-195)	23 (4-70)	0.613

*Footnote: *Luminal B (HER2-negative)*

groups increased after 15 years, although it was not statistically significant in both OS and DFS curves.

The 5-year, 10-year, 15-year and median OS of HER2-zero and HER2-low patients in luminal A patients was 93% vs 96%, 80% vs 85%, 68% vs 60% and NR vs 184 months, respectively (p= 885). The 5-year, 10-year, 15-year and median DFS of HER2-zero and HER2-low patients in luminal A patients was 88% vs 90%, 73% vs 82%, 64% vs 41% and NR vs 183 months, respectively (p= 0.885). Figure 2 shows the OS curves of luminal A according to HER2 status. When the survival curves were analysed, it was observed that the survival difference between the groups increased after 15 years, although it was not statistically significant in both OS and DFS curves.

The 5-year, 10-year, 15-year and median OS of HER2-zero and HER2-low patients in luminal B patients was 84% vs 83%, 71% vs 66%, 60% vs 39% and 244 vs 165 months, respectively (p= 0.123). The 5-year, 10-year, 15-year and median DFS of HER2-zero and HER2-low patients in luminal B patients was 79% vs 76%, 69% vs 58%, 56% vs 38% and 244 vs 165 months, respectively (p= 0.054). Figure 3 shows the DFS curves of luminal B according to HER2 status. A result close to statistical significance was obtained in the DFS curve of Luminal B patients according to HER2 status. According to the curve, the DFS results of HER2-zero patients were better than HER2-low patients.

The 5-year, 10-year, 15-year and median OS of HER2-zero and HER2-low patients in triple-negative patients was 77% vs 68%, 62% vs 48%, 55% vs 0% and 205 vs 91 months, respectively (p= 0.252). The 5-year, 10-year, 15-year and median DFS of HER2-zero and HER2-low patients in triple-negative patients was 70% vs 59%, 59% vs 44%, 53% vs 0% and 195 vs 70 months, respec-

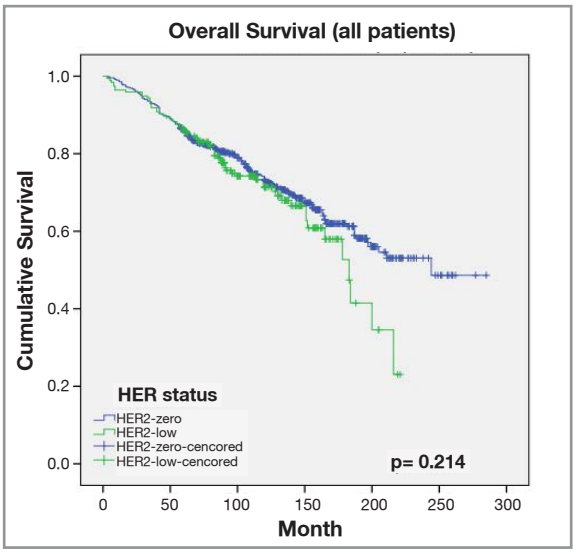

Figure 1. The Kaplan-Meier survival analysis with Log Rank test showing the overall survival outcomes of all patients according to HER2-zero and-low statuses

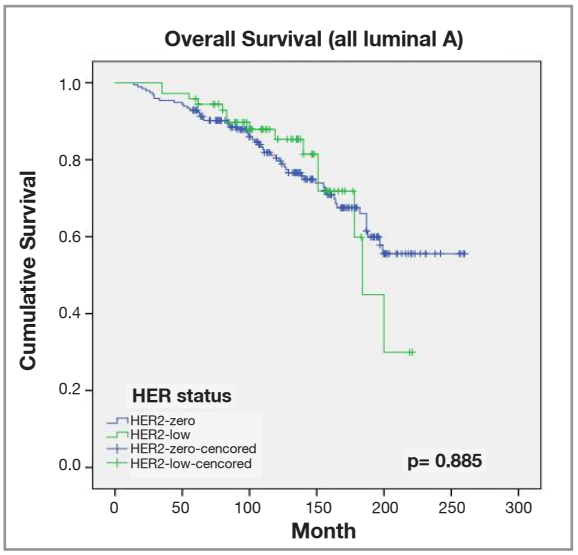

Figure 2. The Kaplan-Meier survival analysis with Log Rank test showing the overall survival outcomes of luminal A patients according to HER2-zero and-low statuses

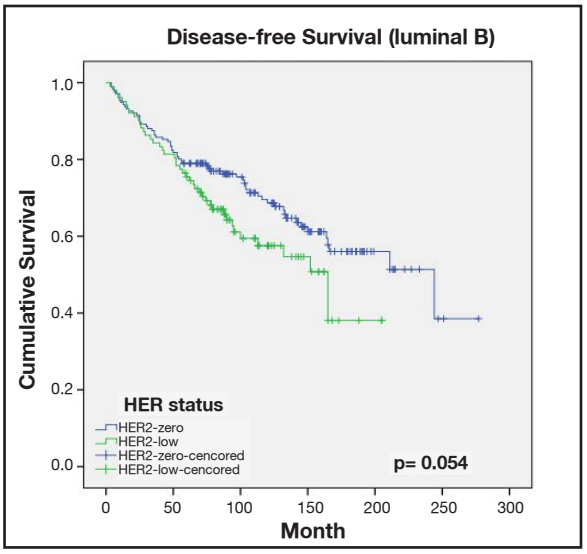

Figure 3. The Kaplan-Meier survival analysis with Log Rank test showing the disease-free survival outcomes of luminal B patients according to HER2-zero and-low statuses

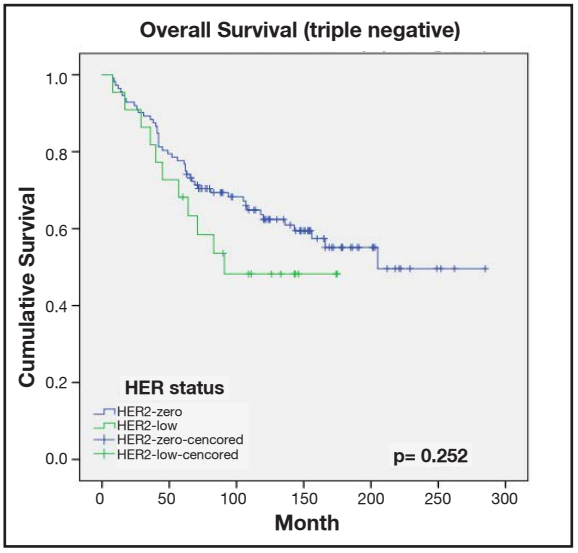

Figure 4. The Kaplan-Meier survival analysis with Log Rank test showing the overall survival outcomes of triple negative patients according to HER2-zero and-low statuses.

tively (p= 0.201). Figure 4 shows the OS curves of triple-negative according to HER2 status. What is remarkable in the survival curve of triple-negative patients is that 15-year OS and DFS are zero in the HER2-low patient group.

HER-2 status (HER2-zero vs HER2-low) was not observed as a factor affecting OS and DFS in univariant and multivariant analyses (p> 0.050). The prognostic factors affecting OS are given in Table 3. The prognostic factors affecting DFS are given in Table 4.

DISCUSSION

There was no significant difference between HER2-low and HER2-zero breast cancer patients in sociodemographic and clinical characteristics. ER and PR positivity, luminal like subgroup and

Table 3. Prognostic factors affecting OS of the study groups

Overall survival		Univarite analysis			Multivariate analysis		
		HR	95% CI	p value	HR	95% CI	p value
HER2 status	HER2-zero	1			1		
	HER2-low	1.20	1.08-1.62	0.216	1.28	0.92-1.77	0.140
Age	≤65 years	1			1		
	>65 years	2.06	1.53-2.78	<0.001	1.60	1.03-2.48	0.039
Menopause status	Premenopause	1					
	Postmenopause	1.51	1.14-1.99	0.004			
ECOG performance status	0	1			1		
	1	2.27	1.69-3.03	<0.001	1.69	1.14-2.53	0.009
	2 or more	5.80	3.76-8.95	<0.001	3.56	1.07-7.45	0.001
Molecular subtypes	Luminal A	1			1		
	Luminal B*	1.53	1.12-2.09	0.007	1.95	0.91-4.19	0.085
	Triple negative	1.92	1.34-2.72	<0.001	3.33		0.039
TNM Stage	Stage I	1			1		
	Stage II	1.36	0.88-2.12	0.164	1.67	0.38-1.18	0.173
	Stage III	3.49	2.27-5.36	<0.001	1.99	1.02-2.11	0.010
Estrogen receptor	Negative	1			1		
	Positive	0.65	0.49-0.86	0.003	0.63	0.42-0.93	0.023
Progesterone receptor	Negative	1			1		
	Positive	0.61	0.46-0.80	<0.001	0.59	0.44-0.79	0.001
Grade	Grade 1	1					
	Grade 2	1.20	0.87-1.66	0.255			
	Grade 3	1.62	1.14-2.30	0.007			
Lymphovascular invasion	Negative	1					
	Positive	1.64	1.23-2.17	0.001			
Perineural invasion	Negative	1					
	Positive	1.48	1.10-1.98	0.009			
Tumor necrosis	No	1			1		
	Yes	3.02	2.22-4.11	<0.001	2.20	1.53-3.17	<0.001
Extracapsular extension	Negative	1			1		
	Positive	2.39	1.83-3.13	<0.001	1.97	1.23-3.16	0.004
CEA groups	Normal	1			1		
	High	2.25	1.67-3.04	<0.001	1.47	1.02-2.11	0.038
CA15-3 groups	Normal	1			1		
	High	2.42	1.80-3.26	<0.001	1.70	1.14-2.53	0.009

*Footnote: *Luminal B (HER2-negative), CEA normal ≤ 2.5 ng/mL, CA 15-3 normal ≤ 25 U/mL*

lymphovascular invasion were more comman in the HER2-low group. The OS and DFS were the same in HER2-zero and HER2-low breast cancer patients. However in Kaplan Mayer survival graphs, both OS and DFS curves showed a divergence after 15 years, although not statistically significant. It was same when patients were categorised according to histopathological subtypes. A result close to statistical significance was obtained only in the DFS of luminal B subgroup patients. In patients with the Luminal B subgroup, the DFS of HER2-low patients was lower than HER2-zero patients. Furthermore, the findings of the study revealed that HER2-low and HER2-zero breast cancer patients have the same prognosis.

The crosstalk between HR and HER2 signalling pathways has been studied previously.[10] Accordingly, ER positivity and PR positivity may impact the biological characteristics and prognosis of HER2-negative breast cancer patients.[3] In a study using the PAM-50 test on a group of patients with HER2-low, it was found that the proportion of HER2-low was higher in HR-positive disease. Compared to HER2-negative patients, increased

Table 4. Prognostic factors affecting DFS of the study groups

Disease-free survival		Univarite analysis			Multivariate analysis		
		HR	95% CI	p value	HR	95% CI	p value
HER2 status	HER2-zero	1			1		
	HER2-low	1.23	0.93-1.62	0.133	1.33	0.98-1.08	0.066
Age	≤65 years	1					
	>65 years	1.84	1.39-2.45	<0.001			
Menopause status	Premenopause	1					
	Postmenopause	1.31	1.01-1.70	0.038			
ECOG performance status	0	1			1		
	1	2.26	1.72-2.98	<0.001	2.01	1.29-3.14	0.002
	2 or more	5.30	3.45-8.14	<0.001	3.06	1.39-9.28	0.008
Molecular subtypes	Luminal A	1					
	Luminal B*	1.49	1.11-1.99	0.007	1.46	0.89-2.39	0.130
	Triple negative	1.85	1.32-2.58	<0.001	2.25	1.21-4.19	0.010
TNM Stage	Stage I	1					
	Stage II	1.38	0.91-2.09	0.120	1.27	0.81-2.81	0.291
	Stage III	3.68	2.46-5.49	<0.001	3.58	2.32-5.54	<0.001
Estrogen receptor	Negative	1					
	Positive	0.68	0.51-0.89	0.006			
Progesterone receptor	Negative	1			1		
	Positive	0.58	0.45-0.75	<0.001	0.53	0.40-.070	<0.001
Grade	Grade 1	1					
	Grade 2	1.23	0.91-1.67	0.171			
	Grade 3	1.58	1.13-2.21	0.006			
Lymphovascular invasion	Negative	1					
	Positive	1.79	1.37-2.33	<0.001			
Perineural invasion	Negative	1					
	Positive	1.53	1.16-2.03	0.002			
Tumor necrosis	No	1			1		
	Yes	3.01	2.25-4.03	<0.001	2.46	1.63-3.73	<0.001
Extracapsular extension	Negative	1			1		
	Positive	1.98	1.42-2.75	<0.001	2.25	1.40-3.62	0.001
CEA groups	Normal	1			1		
	High	2.18	1.65-2.90	<0.001	2.07	1.37-.315	0.001
CA15-3 groups	Normal	1			1		
	High	2.48	1.87-3.29	<0.001	2.23	1.46-3.42	<0.001

*Footnote: *Luminal B (HER2-negative), CEA normal ≤ 2.5 ng/mL, CA 15-3 normal ≤ 25 U/mL*

expression of HER2 and luminal-related genes was observed in HER2-low patients. Furthermore, within the HER2-low group, ERBB2 levels were higher in HR-positive disease compared to triple-negative breast cancer (TNBC). Among HER2-negative breast cancer patients, studies reported higher rates of HER2-zero breast cancer patients than HER2-low breast cancer patients.[3,10] In this study, only 29% of the patients had HER2-low breast cancer compared to 71% of the patients who had HER2-zero breast cancer. Similar to our study, several studies reported higher rates of patients with ER and PR positivity in the HER2-low breast cancer patient group.[3,11,14,15] One of these studies also reported a significantly higher rate of patients with HR positivity in the HER2-zero breast cancer patient group than in the HER2-low breast cancer patient group (94.4% vs. 89.9%).[15] In the present study, ER positivity was 86% vs 72%, and PR positivity was 78% vs 67% in the HER2-low group compared to HER2-zero. Furthermore, the TNBC rate was observed at a higher rate in the HER2-low group than in the HER2-zero group.

The differences between the pathological characteristics of HER-low and -zero breast tumours have been reported in many studies. Zheng et al.[10] reported that HER2-low tumours were more likely to be high-grade tumours, had poorer differentiation, and had higher Ki-67 values than HER2-zero tumours. In contrast, Zhong et al.[14] reported significantly higher rates of patients with well or moderately differentiated tumours among HER-low breast cancer patients compared to HER-zero breast cancer patients. Similarly, other studies reported higher rates of patients with HR-positivity, low Ki-67 levels, and luminal-type tumours among HER-low breast cancer patients compared to HER-zero breast cancer patients.[11,16] On the other hand, Jin et al. found that the differences between HER2-low and HER2-zero breast cancer in terms of clinical and molecular phenotypes were only marginal after adjusting for HR expression. Consequently, Lu et al.[3] concluded that HER2-low and HER2-zero breast cancers are merely variations of HER2-negative breast cancer and not distinct molecular entities.[15] Li et al.[8] determined variations between HER2-low and HER2-zero breast cancer biomarker expressions. In our study, prognostic pathologic features such as necrosis, grade, level of Ki-67, CEA and Ca15,3, perineural invasion, and extracapsular extension were similar in both groups. Only lymphovascular invasion positivity was higher in the HER2-low group compared to the HER2-zero group. In addition, the presence of intraductal components was also observed at a higher rate in the HER2-low group than in the HER2-zero group, close to statistical significance.

The data on the survival outcomes of breast cancer patients with varying HER2 signalling in the literature are inconsistent.[3,10,14,19,20] While some studies reported significantly superior survival outcomes in HER2-low breast cancer patients than in HER2-zero breast cancer patients, regardless of HR status[14,19,21], others reported significantly superior prognostic outcomes adjusted for clinical characteristics and primary treatments, notably in HR-negative HER2-low breast cancer patients than in HR-negative HER2-zero breast cancer patients.[10,19,20,22] On the other hand, an improvement in relapse-free survival was observed only in HR-positive HER2-low breast cancer patients with HR.[16] Additionally, while several studies did not find any significant difference between the survival outcomes of HER2-low and HER2-zero breast cancer patients[10,15,23,24], others reported poorer survival outcomes in HR-negativeHER2-low breast cancer patients.[3] In a recent systematic review and meta-analysis, Li et al.[7] reported longer OS and DFS in the HER2-low breast cancer patient group than the HER2-zero breast cancer patient group, yet did not find any significant difference between the groups in prognostic outcomes. Several other systematic reviews and meta-analyses of different breast cancer characteristics reported comparable results.[9,18,25-28] Along these lines, in this study, there was no difference in DFS and OS between each of the HER2-low and HER2-zero groups, even when clinically divided into luminal A-like, luminal B-like and triple-negative subtypes. However, there were a few noteworthy points in this regard. One of them is that both the OS and DFS curves of all patients and Luminal A patients show an increasing survival difference between the groups after 15 years. Another result, which was close to statistical significance, was that the DFS of HER2-low patients in the Luminal B subgroup was lower than that of HER2-zero patients. Although statistically significant results were not obtained, when the survival curves of all patient groups were analysed, it was seen that patients with HER2-low had a worse outcome than those with HER2-zero.

Many known prognostic factors related to the disease and the patient affect survival in patients with breast cancer. Tumour grade, ER and PR expression, histological subtype, Ki-67 score, lymph node metastasis, lymphovascular invasion, tumour size, CA 15.3 level in relation to the disease, age, race, performance status in relation to the patient have been shown as prognostic factors in many studies.[29-31] In univariate and multivariate modelling performed to test whether HER-2 low status was an independent prognostic marker, as expected, low ECOG performance, triple-negative molecular subtype, advanced stage disease, progesterone receptor negativity, tumour necrosis, extracapsular spread in the lymph node, high tumour markers negatively affected both DFS and OS. In addition, advanced age and ER-negativity were identified as additional poor prognostic factors for OS. İn our study, HER-2 low status was not identified as a prognostic factor for OS and DFS in HER-2 nega-

tive disease. Some studies have speculated that the survival benefits of HER2-low tumours compared to HER2-zero tumours may be due to HER2-targeted therapies.[10,32] However, in our study, both groups were treated with similar treatment strategies and no HER2-targeted therapy was applied to any group in the study. These findings suggest that HR positivity is an important factor in determining the biological behaviour of her-2 low disease.

Limitations of the Study: This study has some limitations. The most important limitation is that the study was retrospective. In addition, although HER2 negativity was demonstrated by Insitu hybridisation methods in this study, a detailed genetic examination of the tumours could not be performed. However, the fact that the pathology of all patients was examined by professional pathologists in a single centre may be an advantage.

Conclusion

There were no clinically and pathologically significant differences between HER2-low and HER2-zero, except that HER2-low patients had more HR positivity, more luminal subgroups and more lymphovascular invasion. When evaluated together with histopathologic subgroups, no survival difference was detected between both groups. Furthermore, HER2 status could not be determined as a prognostic factor.

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Correspondence:

Dr. Mahmut UCAR

Sivas Cumhuriyet Universitesi,

Tip Fakultesi

Department of Medical Oncology

Yenisehir, Merkez

SIVAS / TURKIYE

Tel: (+90-505) 222 70 48

e-mail: dr.mahmutucar@gmail.com

ORCIDs:

Mahmut Ucar	0000-0002-3311-6152
Mukaddes Yilmaz	0000-0002-7927-8480
Eda Erdis	0000-0003-3003-8643
Birsen Yucel	0000-0002-0083-6866