

The impact of hormone receptor status on survival and recurrence of HER2-positive breast cancers in standard adjuvant setting: A retrospective study in Tehran, Iran

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Abstract

Objective: To evaluate hormone receptor status on survival and recurrence of the human epidermal growth factor receptor 2-positive breast cancer treated with Trastuzumab in the adjuvant setting.

Methods: The retrospective study was conducted in 2017 at the Breast Cancer Research Centre, Tehran University of Medical Sciences, Tehran, Iran, and comprised data of women aged >20 years with stage I-III of human epidermal growth factor receptor 2-positive breast cancer who were treated with Trastuzumab from 2008 to 2017. The patients were divided into two groups. Group P had patients who were triple positive for human epidermal growth factor receptor 2, oestrogen receptor and progesterone receptor. Group N had patients positive for only human epidermal growth factor receptor 2. All patients in group P were treated with hormone therapy. Overall survival, disease-free survival, and distant metastasis rates were measured. SPSS 22 was used for data analysis.

Results: Of the 263 patients, 169(%) were in group P with a mean age of 46.86 ± 10.92 years, and 94(%) were in group N with a mean age of 48.53 ± 12.33 years ($p > 0.05$). There were no unfavourable predictors for overall survival and disease-free survival except for stage ($p < 0.05$). The difference on both counts between the groups was not significant ($p > 0.05$ each).

Conclusion: The impact of hormone receptor positivity on survival and progression of human epidermal growth factor receptor 2-positive breast cancer remains an area of debate.

Keywords: Breast cancer, HER2, Hormone receptor, Trastuzumab, Survival. (JPMA 70: 11; 2020).

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Introduction

Breast cancer (BC) is a heterogeneous disease¹ which is in both developed and developing countries the most common cancer among women with a spike in incidence in Asia over the last 40-50 years.² Nowadays, BC therapy consists of surgery, radiotherapy, chemotherapy, and biological therapy as well as some other methods, whereas in the locally advanced stage, biological therapy, such as Trastuzumab therapy, is often the only effective method of all the human epidermal growth factor receptor 2-positive (HER2+) BC therapies.³ It is clear that receptor status information is much more readily available and can give us an extremely useful tool for obtaining information about the behaviour of the disease in patients in a clinical

setting.¹ The impact of hormone receptor (HR) status on disease-free survival (DFS), overall survival (OS) or the clinical outcome of patients treated with Trastuzumab is controversial.⁴⁻⁶ Data suggests that 45% of BCs with HER2-over-expression were HR-positive (HR+), and 43% were HR-negative (HR-).⁶ Approximately half of BCs that over-express HER2 also express HRs.⁷ Recurrent BC after initial treatments is usually associated with poor outcome.⁸ Over-expression and/or amplification of HER2 are associated with poor prognosis in BC and predict survival advantage to anti-HER2 therapy in BC.⁹

The current study was planned to evaluate the efficacy of HR status in stage I-III HER2+ BC patients.

Materials and Methods

The retrospective study was conducted in 2017 at the Breast Cancer Research Centre, Tehran University of Medical Sciences, Tehran, Iran, and comprised data of women aged >20 years with stage I-III of HER2+ BC who

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were treated with Trastuzumab from 2008 to 2017. The patients were divided into two groups. Group P had patients who were triple positive for HER2, oestrogen receptor (ER) and progesterone receptor (PR). Group N had patients positive for only HER2.

After approval from the ethics committee of Kermanshah University of Medical Sciences, Kermanshah, Iran, female patients with HER2+ (HER2 3+ or HER2 2+ and fluorescence in situ hybridization [FISH] positivity) were included. Those with stage 4 or those receiving Trastuzumab as adjuvant therapy for less than one year were excluded.

Clinicopathological and demographic details were extracted for patient files based on pathology and clinical reports. The median follow-up time had been 42 months (interquartile range [IQR]: 12-125 months).

OS was defined as the time from the diagnosis of breast cancer based on pathology report to death from any cause, and DFS was defined as the time from the diagnosis of breast cancer based on pathology report to recurrence and/or metastasis, whichever was the earliest. Breast tumour recurrence was defined as a come-back of cancer to the same place as the original (primary) tumour or to another place in the body. Distant metastasis was defined as recurrence at a distant site from primary cancer.

Data was analysed using SPSS 22. Categorical and continuous variables were analysed using chi-square and Mann-Whitney U test, respectively. Outcomes for this study were OS, DFS, and distant metastasis. The comparison between OS and DFS for the two groups was checked by GraphPad Prism 5 software while the log-rank test was used to compare the Kaplan-Meier curves for OS and DFS. Also, Cox's proportional hazard regression analysis was used to check the effects of various parameters on the primary analysis. A two-tailed $p < 0.05$ was considered statistically significant. In all analyses, confidence interval (CI) was 95%. A forest plot of random-effect was used by Comprehensive Meta-Analysis (CMA) software version 2.0 for hazard ratios (HRs).

Results

Of the 263 patients, 169(%) were in group P with a mean age of 46.86 ± 10.92 years, and 94(%) were in group N with a mean age of 48.53 ± 12.33 ($p > 0.05$). There were no significant differences in terms of age, lymph node metastasis, tumour size, stage, vascular invasion, laterality,

radiotherapy, Ki67 index, and chemotherapy between the two groups ($p > 0.05$). But grade and type of tumour pathology were different in the two groups ($p < 0.05$) (Table 1).

Table-1: Demographic and clinico-pathological variables in gastric patients with human epidermal growth factor receptor 2 (HER2) positivity.

Variables	Group P, n=169	Group N, n=94	p-value
Age: mean, Year \pm SD	46.86 \pm 10.92	48.53 \pm 12.33	0.277
Age group: year, n (%)			0.392
≥ 50	67 (39.6)	42 (44.7)	
< 50	102 (60.4)	52 (55.3)	
Grade: n (%)			0.045
1	11 (6.5)	2 (2.1)	
2	92 (54.4)	42 (44.7)	
3	66 (39.1)	50 (53.2)	
Lymph node involvement: n (%)			0.272
Yes	100 (59.2)	60 (63.8)	
No	69 (40.8)	34 (36.2)	
Tumour size group: cm			0.317
< 2	34 (20.1)	14 (14.9)	
2-5	120 (71)	67 (71.3)	
> 5	15 (8.9)	13 (13.8)	
Tumour size: mean, cm \pm SD	3.05 \pm 1.53	3.25 \pm 1.61	0.144
Type of tumour pathology: n (%)			0.031 [#]
IDC	158 (93.5)	95 (94.7)	
IDC and DCIS	3 (1.8)	5 (5.3)	
LC	8 (4.7)	0 (0)	
TNM Stage, n (%)			0.164
1	47 (27.8)	19 (20.2)	
2	75 (44.4)	39 (41.5)	
3	47 (27.8)	36 (38.3)	
Vascular invasion: n (%)			0.481
Yes	90 (53.3)	49 (52.1)	
No	79 (46.7)	45 (47.9)	
Laterality: n (%)			0.475
Right	86 (50.9)	49 (52.1)	
Left	83 (49.1)	45 (47.9)	
Radiotherapy: n (%)			0.512
Yes	139 (82.2)	78 (83)	
No	30 (17.8)	16 (17)	
Ki67 index group: n (%)			0.411
≤ 20	54 (41.5)	34 (44.2)	
> 20	76 (58.5)	43 (55.8)	
NA	39	17	
Ki67 index: mean, % \pm SD	27.89 \pm 18.29	30.54 \pm 21.92	0.600
Chemotherapy, n (%)			0.236
AB	123 (72.8)	73 (77.7)	
nAB	46 (27.2)	21 (22.3)	
Hormone therapy, n (%)			NA
LET	51 (30.2)	NA	NA
TAM + DECAV	100 (59.2)		
Aromasin	5 (3)		
LET + TAM	13 (7.6)		

*Bold values indicate significant p-value. #2 cells (33.3%) have expected count less than 5. The minimum expected count is 2.86. The p-value from likelihood ratio test is 0.009. Abbreviations: NA, not available; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; LC, lobular carcinoma; AB, anthracycline-based chemotherapy; nAB, non-anthracycline-based chemotherapy, LET, Letrozole; TAM, Tamoxifen; DECAV, Cisplatin-based chemotherapy regimen.

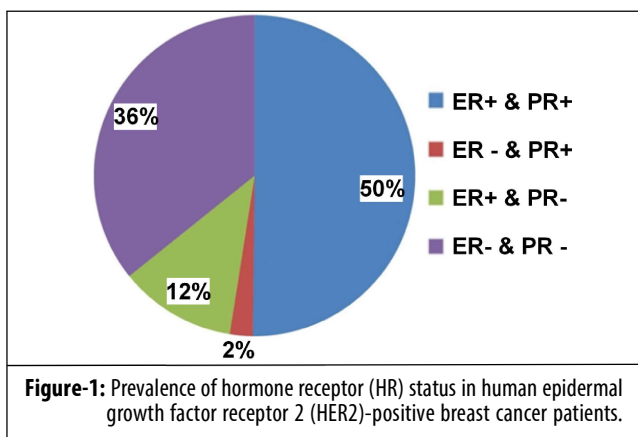


Figure-1: Prevalence of hormone receptor (HR) status in human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients.

Prevalence of HR status and study variables were noted (Figure 1).

There were no unfavourable predictors for OS and DFS except for stage ($p=0.023$; $p=0.034$) (Figures 2-3).

The means OS and DFS in group P were not significantly different from that of group N ($p=0.200$; $p=0.312$). No significant increased risk was seen in group P when compared with group N for either 5-year DFS or 5-year OS (Figure 4).

In terms of distant metastasis in the two groups, there was no significant difference for bone, brain, lung or liver metastases (Table 2).

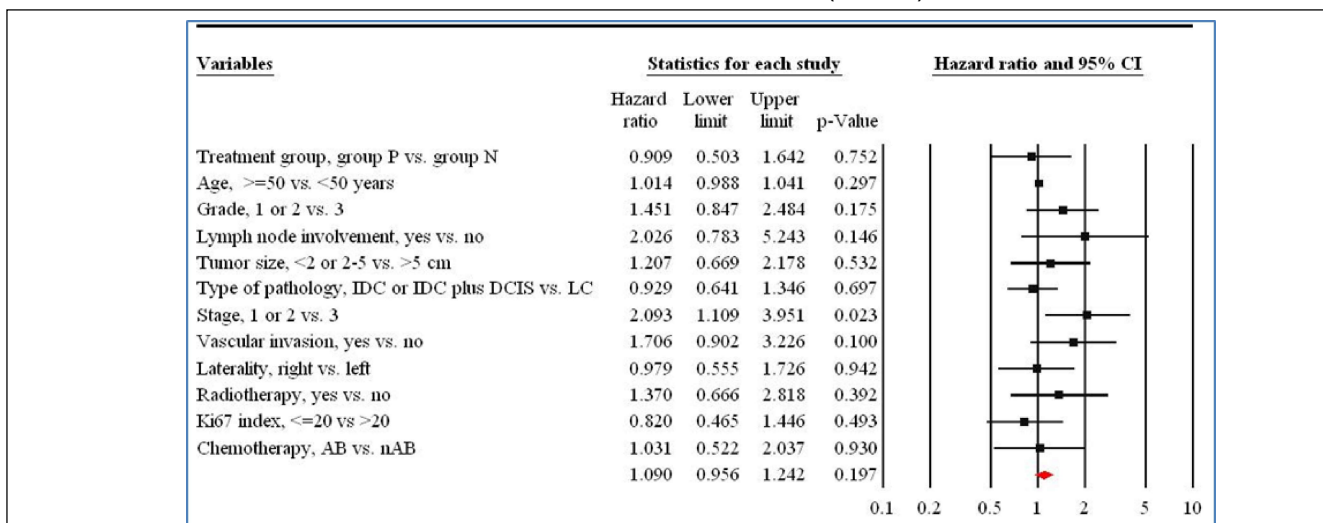


Figure-2: Forest plot of random-effect of hazard ratio of affecting variables on overall survival.*HRs (hazard ratios) are presented as the risk of the left-side category vs. the right-side category. Abbreviations: CI, confidence interval; NA, not available; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; LC, lobular carcinoma; AB, anthracycline based chemotherapy; nAB, non-anthracycline based chemotherapy. Group P=(HER2+) ER+ and/or PR+ group; Group N=(HER2+) ER- and PR-.

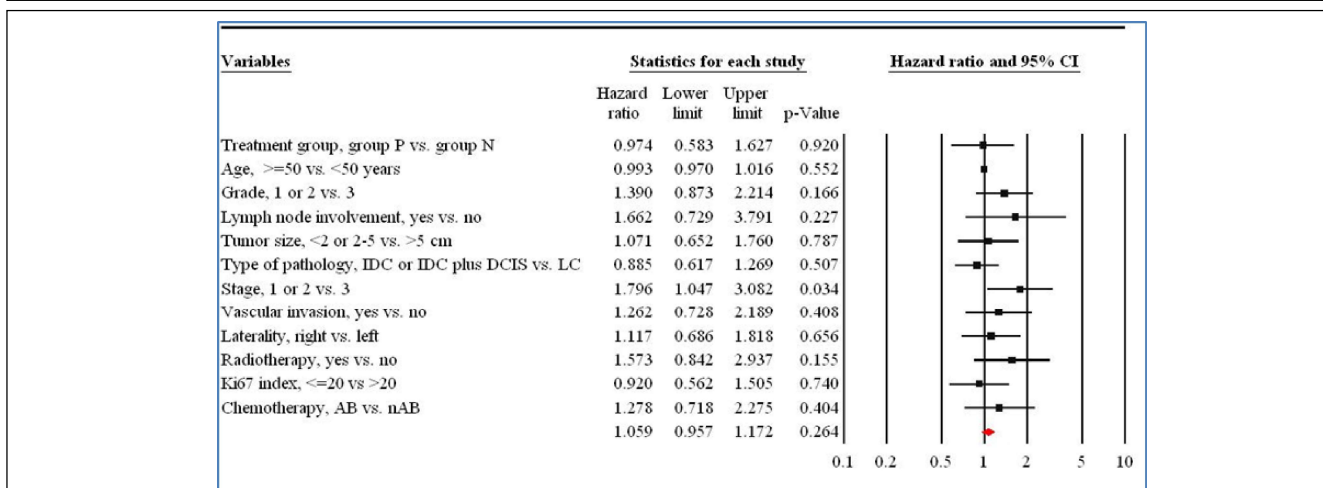
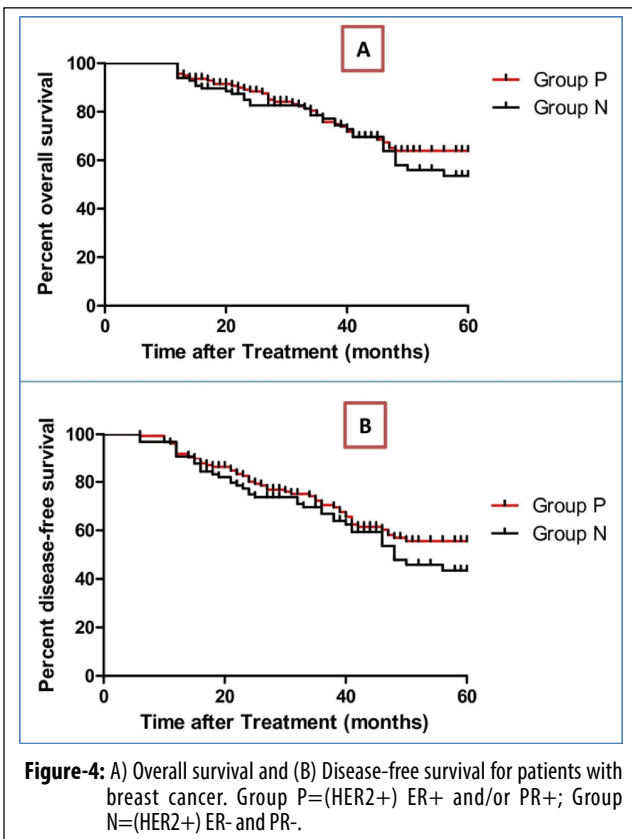


Figure-3: Forest plot of random-effect of hazard ratio of affecting variables on disease-free survival.*HRs (hazard ratios) are presented as the risk of the left-side category vs. the right-side category. Abbreviations: CI, confidence interval; NA, not available; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; LC, lobular carcinoma; AB, anthracycline-based chemotherapy; nAB, non-anthracycline-based chemotherapy. Group P=(HER2+) ER+ and/or PR+ group; Group N=(HER2+) ER- and PR-.

Table-2: Distant metastasis rates.

Metastasis site	Group P (n=169)	Group N (n=94)	p-value
Bone, n (%)	9 (5.3)	8 (8.5)	0.318
Brain, n (%)	6 (3.5)	4 (4.2)	0.775
Lung, n (%)	5 (3)	4 (4.2)	0.581
Liver, n (%)	5 (3)	3 (3.2)	0.916



Discussion

The study evaluated the impact of HR on the survival of HER2+ patients with stage I-III BC. BC is a chemo-sensitive tumour.¹⁰ Few previous studies have compared survival or recurrence rates between two HER2+ BCs (HR+/HER2+ and half were HER2+/ER-) with emphasis on Trastuzumab therapy.¹¹ One study¹² compared survival between the two HER2+ BCs and found at 4-year follow-up that HR status minimally influenced the response to Trastuzumab, although HR status was reported as a significant predictor in DFS.

A cohort of 469 HER2+ BCs was categorised by molecular subtype (HR+/HER2+ and HER2+/ER- subtypes) and Trastuzumab treatment. Overall, 299 patients were treated with Trastuzumab, and HR+ patients received hormone therapy. Trastuzumab treatment significantly improved

OS in both subtypes, but OS and DFS were similar in the two subtypes. Trastuzumab treatment induced a significant reduction in distant metastasis rates in both subtypes, with a greater reduction observed in HR+/HER2+ compared to HER2+/ER-.¹¹ The most favourable outcome was observed in the HR+/HER2+ subgroup treated with Trastuzumab,^{13,14} with a median OS of 48.3 months, compared to 40.9 months in the HR-/HER2+ subgroup treated with Trastuzumab in metastatic BC. The early recurrent HR+/HER2+ metastatic BC patients substantially benefitted from Trastuzumab, whereas the later recurrent ones didn't show similar benefits. The results confirmed that Trastuzumab-containing therapy substantially improved OS in HR+/HER2+ and HR-/HER2+ metastatic BC patients in China.¹³ Some studies suggested that anti-endocrine therapy for the metastatic disease does not appear to influence the overall response to Trastuzumab. The outcome was improved with the addition of Trastuzumab to chemotherapy as previously described.^{15,16}

The reports suggested that high ER expression ($\geq 30\%$) was associated with a reduced probability of tumour response to Trastuzumab plus chemotherapy.¹⁷ However, progression-free survival (PFS) was significantly improved when maintenance endocrine therapy was added to Trastuzumab in ER+ metastatic BC patients.¹⁸ The levels of expression of HR are directly correlated with response to hormone therapy.^{19,20} In patients with HR+ tumours ($\geq 1\%$ of tumour cells), maintenance endocrine therapy added to Trastuzumab upon the completion of chemotherapy was associated with a significant PFS benefit.¹⁷

Trastuzumab treatment improved OS in HR- patients only in the first 3 years, whereas in the HR+ group the effect of Trastuzumab was still apparent 5 years after diagnosis.²¹ The 10-year OS in the study cohort was 80.9% for HR-/HER2+, and 89.2% for HR+/HER2+ treated with Trastuzumab. Nevertheless, matching clinical factors between patients with HR- and HR+ tumours demonstrated that the survival effect of Trastuzumab was not affected by HR status. Trastuzumab treatment improves patients' survival regardless of HR status and should be offered to all HER2+ patients.²¹

A review showed that HER2 over-expression is an independent adverse prognostic factor regardless of the hormonal status of the tumour, indicating that patients with HR+/HER2+ breast tumours might not derive a benefit from single-agent hormonal therapy. Targeting

both HR and HER2 signalling pathways upfront might not be the most-effective therapeutic strategy in the management of HR+/HER2+ breast tumour.⁷ Non-metastatic patients with HR+/HER2+ disease treated with Trastuzumab had lower 5-year locoregional recurrence rate as patients who did not receive Trastuzumab, whereas patients with HR-/HER2+ disease had similar rates of locoregional recurrence regardless of Trastuzumab treatment.²²

Tumour samples from 596 patients were HER2-over-expressing by FISH; 45% of these were HR+ and 43% were HR-. HR status did not affect the clinical benefit of Trastuzumab given as a single agent or combined with chemotherapy.⁶ The addition of Trastuzumab to chemotherapy provides an improved clinical benefit compared to chemotherapy alone, regardless of HR status. Median OS of patients with HR- tumours was lower than that of patients with HR+ tumours, and it found that patients with HER2-over-expressing/HR+ or HER2-over-expressing/HR- tumours derive similar clinical benefit from treatment with Trastuzumab.⁶

One study obtained data from 299 patients with early HER2+ breast tumour (155 patients with HR+ and 144 with HR-) who underwent surgery and received standard adjuvant chemotherapy, hormonal therapy and/or radiation.²³ The two groups had similar characteristics except for histological grade and extra-capsular extension. Five-year DFS was statistically different between the two groups (65.0% for HER2+/HR- versus 74.6% for the HER2+/HR+ patients), but 5-year OS was not statistically different between the two groups (75.5% in HER2+/HR- patients versus 82.4% for the HER2+/HR+ patients).²³

Bone metastasis as the first location of recurrence was more common in the HR+ population.^{1,24} One study showed a shorter DFS for HER+/HR- versus HER +/HR+ status for 5-year survival, with rates of 52% and 87%, respectively.²⁴ One trial evaluated 1698 HER2+ early BC patients in the non-Trastuzumab (observational) arms, found a 3-year DFS of 70% and 78% for the absence and presence of HR, respectively.²⁵ Another point is the evidence that in patients over-expressing HER2, Trastuzumab achieved a modest benefit in HR+ patients compared with HR- patients, although this difference was not statistically significant.^{12,25}

Conclusion

In HER2+ tumours, OS and DFS rates were very similar for HR+ and HR- BC patients. The impact of HR+ on survival and progression of HER2+ BCs continues to be an area of debate.

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Conflict of interest: None.

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