Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.202412138-46

The Impact of Prognostic Factors on Survival in Patients with Non-Metastatic Invasive Breast Cancer: A Single-Center Experience

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ARTICLE INFO

Received:
31 July 2024
Revised:
29 October 2024
Accepted:
16 November 2024

Keywords:
Breast cancer, prognostic factors, survival, Metastasis

ABSTRACT

Background: Breast cancer (BC) is the most prevalent and lethal cancer in women. Prognostic factors are used to guide treatment and predict the prognosis. This study aimed to assess the influence of prognostic factors on the survival of patients with non-metastatic invasive BC.

Methods: Data from invasive BC patients admitted to Medical Oncology Department of Süleyman Demirel University between October 2002 and October 2013 were retrospectively reviewed. Clinicopathologic features, treatment information, and follow-up data were noted. The Kaplan-Meier method was used to estimate survival functions. Multivariate Cox regression analysis was performed to identify prognostic factors for disease-free survival (DFS) and overall survival (OS), with P-values <0.05 for univariate results

Results: A total of 717 patients entered the study. The median follow-up time was 41 months. Recurrence was detected in 17.4% of the patients, and 111 (15.5%) patients died. The 5- and 10-year DFS rates were 78% and 61%; OS rates were 86% and 70%, respectively. In multivariate analyses, DFS and OS were associated with axillary lymph node involvement (P<0.001 and P<0.05, respectively), tumor size (P<0.05), and histologic grade (P<0.05), whereas human epidermal growth factor receptor 2 positivity had only a statistically significant effect on poor OS (P=0.004).

Conclusion: Consistent with previous studies, traditional prognostic factors had an important impact on prognosis in invasive BC patients. In the current era, where more conservative surgical approaches and new, effective systemic neoadjuvant and adjuvant therapies are widely used, the importance of the traditional prognostic factors highlighted in our study needs to be established by further studies.

INTRODUCTION

Breast cancer (BC) is the most frequently diagnosed and fatal malignancy in women worldwide.[1] Similar to the global data, BC is the most common female cancer in Turkey.[2] Due to its heterogeneous nature, clinicopathologic characteristics and the natural course of BC can vary among patients. Prognostic and predictive factors are used to determine the natural history of the tumor, predict survival, and guide the treatment.[3,4] All factors present at the time of diagnosis and surgery that affect disease-free survival (DFS) and overall survival (OS) regardless of treatment are called prognostic factors. Traditional clinicopathologic prognostic factors are commonly used in patient management in developing countries due to their accessibility and practicality.[5] The most important clinicopathologic prognostic factor in BC is the presence and number of axillary lymph node (ALN) involvement.[4] In addition to the number of ALN metastases, tumor size and grade are crucial in establishing prognosis.[5] The amplification and/or high expression of human epidermal growth

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factor receptor 2 (HER2) has been shown to have prognostic and predictive significance in BC.[3,5] While nationwide studies are scarce, some regionally based studies evaluating the epidemiologic features and prognostic factors of BC in Turkey have been published.[6-8] A single-center study found that stage at presentation was associated with OS and grade impacted DFS.[6] However, the inclusion of metastatic patients in this study could potentially alter the outcomes. In another study, excluding patients with metastatic disease, tumor grade, and ALN involvement were associated with survival.[7] This study involved a relatively small patient cohort and the analysis was primarily conducted to assess the histologic grade. The aim of our study is to determine the impact of prognostic factors on survival among patients with non-metastatic invasive BC in a tertiary healthcare unit in Turkey that stands out by admitting a larger and varied patient population in its region.

METHODS

Study design and data collection

In this single institutional retrospective cohort study, data from 1014 patients with a BC diagnosis who were admitted to the Medical Oncology Department of Süleyman Demirel University between October 1st, 2002 and October 1st, 2013, were collected. The inclusion criteria for the study were as follows: patients with a pathologically proven diagnosis of invasive BC, and those aged at least 18 years and with complete follow-up information. All information was obtained from the archive file records or the hospital computer system. The data on demographics (gender, age at diagnosis, menopausal status), baseline clinicopathologic features (histology, grade, hormone receptor [HR] status, HER2 status, tumor size, ALN status, stage, lympovascular invasion [LVI], perineural invasion [PNI]), and the treatment received (type of surgery and systemic treatment modalities) were recorded. The initial diagnosis date, first recurrence date and region, the last control time, and the time of death were also noted.

Prognostic factors and endpoints

Patients with estrogen receptor (ER) or progesterone receptor of 1% or more by immunohistochemistry (IHC) were considered hormone-positive. HER2 positivity was defined as a CerbB2 IHC score of 3+ or 2+ with positive in situ hybridization. The histological grade was determined in accordance with the modified Scarff-Bloom-Richardson scale. All patients were staged using American Joint Committee on Cancer (AJCC TNM) 7th edition.

DFS was defined as the time from the date of initial diagnosis to the date of first recurrence (local recurrence and/or distant metastasis). OS was defined for surviving patients as the time from the first diagnosis to the date the files were scanned (October 2013) and for deceased patients as the time from the first diagnosis to death.

Treatments and follow-up

The patients underwent breast-conserving surgery or modified radical mastectomy, along with sentinel lymph node dissection or axillary dissection. Patients were treated following international guidelines, which included chemotherapy (neoadjuvant or adjuvant), radiotherapy, hormonal therapy, and trastuzumab, considering HR and HER2 status, along with other risk factors. During the follow-up period, patients were routinely checked every three months for the first two years, every six months up to five years, and then annually thereafter.

Statistical analysis

Statistical analyses were performed using IBM© SPSS© Statistics Version 15.0 for Windows. All patients meeting eligibility criteria within the defined period were included in the study, and thus, no sample calculation was made. Continuous variables were expressed as median (interquartile range [IQR] and/or range), while categorical variables were presented as numbers and percentages. The Kaplan–Meier method was used to estimate survival curves, and the comparisons were made using the Log-rank test. Multivariate Cox regression analysis using the backward LR method was performed to identify prognostic factors for survival, with P-values <0.05 for univariate results.

RESULTS

We analyzed data from 1014 BC patients retrospectively and 717 eligible patients were included in the study (Figure 1). The main demographic and clinicopathologic characteristics of the patients are summarized in Table 1. The median diagnosis age was 52 (IQR: 12; range 24-85), and 5.9% of the patients were below 35 years old. There were only 3 (0.5%) males. Of all patients, 51 (7.1%) had a first-degree family history of BC. The most common location was determined as the upper outer quadrant (49.8%).

Treatment and follow-up data are given in Table 2. The majority of patients (85%) underwent upfront mastectomy. Of these patients, 103 (16%) were diagnosed with stage I, 342 (53%) with stage II and 192 (30%) with stage III disease. A total of 304 patient (42.4%) received a combination of chemotherapy (CT), radiotherapy, and hormone

therapy. Of 591 patients who received at least one cycle of CT, 281 (47.5%) received an anthracycline plus taxane regimen, 269 (45.5%) received an anthracycline-based regimen, 38 (6.5%) received an anthracycline-free regimen, and 3 (0.5%) received taxane-based CT only. Considering 125 HER2-positive patients, 76 (60.8%) of them were detected to receive anti-HER2 (trastuzumab) treatment. Fifty-six (73.6%) of these patients were followed up to complete one year of trastuzumab treatment.

Table 1. Demographic and clinicopathologic characteristics of patients with non-metastatic invasive breast cancer

Characteristics (n=717)	No. of patients (%)
Median age at diagnosis, years (range)	52 (24-85)
Age groups	
<35	42 (5.9)
35-50	289 (40.3)
>50	386 (53.8)
Menopausal status	
Premenopausal	282 (39.5)
Postmenopausal	394 (55.2)
Perimenopausal	24 (3.3)
Undefined	14 (2)
Histology	
Invasive ductal carcinoma	538 (75)
Invasive lobular carcinoma	69 (9.6)
Mixt (invaziv ductal + invaziv lobular)	54 (7.5)
Others	56 (7.8)
Grade	
I	129 (18)
II	303 (42.3)
III	195 (27.2)
Undefined	90 (12.6)
Hormone profile*	
ER/PR positive and HER2 negative	394 (54.9)
ER/PR positive and HER2 positive	88 (12.2)
ER and PR negative and HER2 positive	37 (5.1)
Triple-negative	53 (7.3)
T stage	
T1	184 (25.7)
T2	382 (53.3)
T3	86 (12)
T4	41 (5.7)
Tx	24 (3.3)
N stage	
N0	292 (40.7)
N1	221 (30.8)
N2	100 (13.9)
N3	84 (11.7)
Nx	20 (2.9)
Stage at diagnosis** (AJCC-7th edition)	
I	111 (15.5)
II	358 (49.9)
III	234 (32.6)

ER=Estrogen receptor; PR=Progesteron receptor; HER2=Human epidermal growth factor receptor 2; AJCC=American Joint Committee on Cancer *The remaining 145 patients' hormone receptor status could not be evaluated from pathology reports **Fourteen patients did not have tumor size/lymph node status on medical records but known to be nonmetastatic at registration

Table 2. Treatment and follow-up data of patients with non-metastatic invasive breast cancer

Variables	No. of patients (%)
Surgery type	
Mastectomy	610 (85.1)
Breast-conserving surgery	98 (13.7)
None	9 (1.2)
Treatment type	
CT	55 (7.7)
RT	2 (0.3)
HT	73 (10.2)
CT + RT	93 (13)
RT + HT	21 (2.9)
CT + HT	139 (19.4)
CT + RT + HT	304 (42.4)
No treatment	30 (4.2)
Chemotherapy	
Adjuvant	644 (89.8)
Neoadjuvant	11 (1.5)
Neoadjuvant + Adjuvant	32 (4.5)
No treatment	30 (4.2)
Recurrence site	
Local recurrence	14 (11.2)
Visceral*	41 (32.8)
Bone and/or soft tissue	33 (26.4)
At least two sites	37 (29.6)

CT=Chemotherapy; RT=Radiotherapy; HT=Hormonotherapy; *Liver, lung, brain, etc. Data were presented as number and percentages (%).

The median follow-up time was 41 months (range 0.8-295), and 258 patients (36%) were followed up for at least 60 months. Recurrence developed in 125 patients (17.4%) during follow-up. The median time to recurrence was 28.8 months (range 5.6-167.2). Among the patients who underwent upfront surgery, 11 (1.7%) presented with only local recurrence and 85 (13.2%) with distant metastasis. The 5- and 10-year DFS rates of all patients were 78% and 61%, respectively (Figure 2).

It was observed that 111 (15.5%) patients died during the follow-up period. The 5- and 10-year OS rates were 86% and 70%, respectively (Figure 3). Kaplan-meier survival curves estimated that a larger number of ALN (P<0.001), increased tumor size (P<0.001), higher stage (P<0.001), higher grade (P=0.001), ER negativity (P=0.037), HER2 positivity (P=0.025),

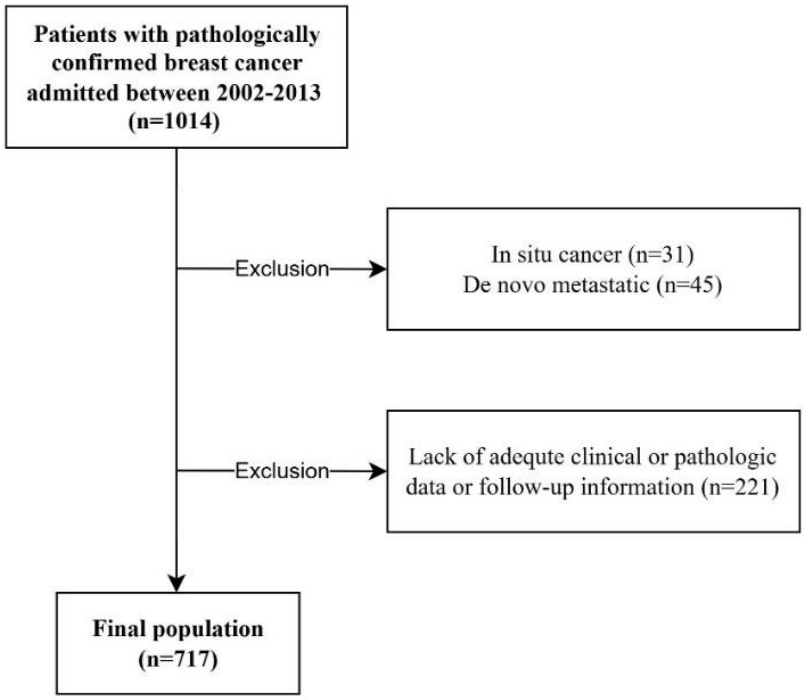

Figure 1. Flow-chart of the inclusion of patients in final analysis

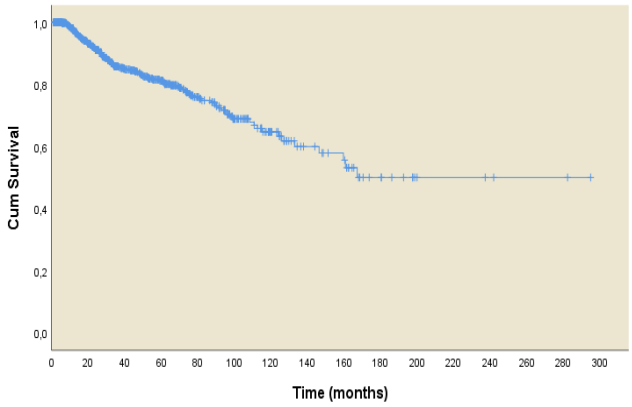

Figure 2. Kaplan-Meier survival curve for disease-free survival in patients with non-metastatic invasive breast cancer

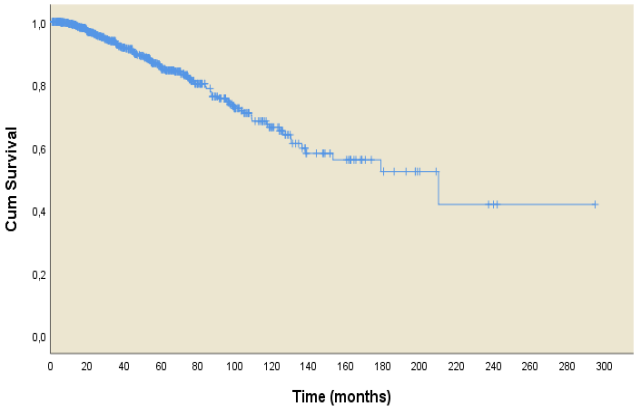

Figure 3. Kaplan-Meier survival curve for overall survival in patients with non-metastatic invasive breast cancer

and positive LVI (P=0.021) were associated with worse DFS rates. A larger number of ALN (P<0.001), increased tumor size (P<0.001), higher stage (P<0.001), higher grade (P<0.001), HER2 positivity (P<0.001), positive LVI (P<0.001), and positive PNI (P=0.022) were associated with worse OS rates (Supplementary file 1).

The results of univariate and multivariate Cox regression analyses for DFS and OS are shown in Table 3 and Table 4, respectively. Multivariate analyses revealed that DFS was statistically associated with N3 ALN involvement (P<0.001), tumor size (P<0.05), and histologic grade (P<0.05); OS rates were associated with N2 and N3 ALN involvement (P<0.05), tumor size (P<0.05), and histologic grade (P<0.05).

In addition, HER2 positivity was found to be a poor prognostic factor for OS (P=0.004).

DISCUSSION

BC is the most common cancer and the leading cause of death in women.[1] There is an increase in the incidence in parallel with the widespread use of screening methods worldwide and in Turkey.[9] Although there is a decrease in BC-related mortality in developed countries, BC is still an important public health problem, especially for developing countries, including Turkey.[10,11] Prognostic factors are used to determine the natural history of the tumor, predict survival, and guide treatment and follow-up. These factors are parallel to the natural course of the disease and are generally indicative of tumor growth, invasion, and metastatic potential.[12] Our retrospective

single-center study highlighted the prognostic importance of traditional clinicopathologic prognostic factors such as ALN involvement, tumor size and grade. HER2 positivity was also found to be associated with poor OS.

The clinical prognostic factor that we evaluated was age at diagnosis. Previous studies have indicated that younger age is an independent predictor of poor survival.[13,14] However, contradictory results have been found in other studies. In a study evaluating patients under 35 years of age, when adjusting for all prognostic variables, age was not significantly related to mortality from BC.[15] Similarly, another study reported that there was no significant difference in survival when controlling for confounding factors.[16]

Table 3. Cox regression analyses for the predictors of disease-free survival in patients with non-metastatic invasive breast cancer*

	Univariate			Multivariate		
	HR	CI (95%)	*P* value	HR	CI (95%)	*P* value
Age (<35 vs ≥35)	0.68	0.35-1.30	0.247			
Histologic subtype (IDC vs non-IDC)	0.94	0.62-1.40	0.940			
ER (positive vs negative)	1.62	1.10-2.38	0.014**	1.19	0.73-1.93	0.479
PR (positive vs negative)	1.58	1.06-2.34	0.023**	1.21	0.63-2.33	0.561
HER2 (positive vs negative)	0.50	0.32-0.79	0.003**	0.72	0.45-1.17	0.144
T stage						
T1 (ref.)	1			1		
T2	2.14	1.21-3.78	0.009**	1.95	1.09-3.51	0.020**
T3	3.91	2.04-7.51	<0.001**	2.51	1.28-4.93	0.007**
T4	9.62	4.95-18.69	<0.001**	6.4	3.19-12	<0.001**
ALN involvement	1			1		
N0 (ref.)	1			1		
N1	1.3	0.77-2.18	0.312	1.01	0.60-1.72	0.090
N2	2.24	1.29-3.88	0.004**	1.65	0.93-2.91	0.080
N3	5.10	3.13-8.33	<0.001**	3.41	2.02-5.75	<0.001**
Stage						
I (ref.)	1			1		
II	2.13	0.95-4.75	0.640	1.50	0.48-4.65	0.482
III	5.94	2.73-12.93	<0.001**	1.39	0.35-5.42	0.633
Grade						
I (ref.)	1			1		
II	3.59	1.63-7.88	<0.001**	2.95	1.32-6.59	0.008**
III	4.48	2.01-10	<0.001**	3.86	1.70-8.72	0.014**
LVI (positive vs negative)	0.55	0.36-0.84	0.021**	0.88	0.53-1.46	0.636
PNI (positive vs negative)	0.58	0.36-0.93	0.024**	0.80	0.48-1.35	0.420

HR=hazard ratio; CI=confidence interval; ref=referent; IDC=Invasive ductal carcinoma; ER=Estrogen receptor; PR=Progesterone receptor; HER2=Human epidermal growth
factor receptor 2; ALN=Axillary lymph node; LVI=Lymphovascular invasion PNI=Perineural invasion. *Backward LR method was performed. ** Statistically significant.

To explain these conflicting findings, it was postulated that the impact of younger age on survival is a result of overrepresentation of other established adverse clinicopathologic prognostic factors such as grade, ALN status, tumor size, HR status, and HER2 status.[17] We observed no survival difference in patients younger than 35 years in our study. The difficulty in commenting on this issue could be due to the relatively small sample of patients under the age of 35.

The histologic subtype of the tumor was another prognostic factor that we analyzed. We compared invasive ductal carcinoma (IDC) to non-IDC due to the heterogeneity and the limited number of cases for subtypes other than IDC and found no significant difference in terms of survival. In general, IDC has been compared with invasive lobular carcinoma in the literature, with inconsistent results for survival.[18-20] The discrepancy may be attributed to the patient selection criteria and the characteristics of the patients in these studies. In fact, our study was not primarily designed to evaluate histologic types and the patients were not selected for this purpose.

The presence and number of ALN involvement is still the most important independent prognostic factor in BC patients.[4] Regardless of tumor size, there is a direct relationship between the number of ALN metastases and the risk of distant metastasis.[21] In the

NSABP study, one of the oldest studies evaluating ALN involvement, a significant decrease in 5-year survival was observed as the number of metastatic ALNs increased.[22] Not surprisingly, our study showed that ALN involvement was a strong independent prognostic factor for DFS and OS, consistent with previous studies.[21,22] However, the majority of patients in our study underwent upfront surgery. Currently, neoadjuvant treatment is more commonly and effectively performed. Investigating the impact of axillary pCR or the number of residual ALNs after neoadjuvant treatment on survival, as well as their potential interaction with other strong prognostic factors, could be a more relevant research topic today.

Table 4. Cox regression analyses for the predictors of overall survival patients with non-metastatic invasive breast cancer*

	Univariate			Multivariate		
	HR	CI (95%)	*P* value	HR	CI (95%)	*P* value
Age (<35 vs ≥35)	1.02	0.44-2.33	0.957			
Histologic subtype (IDC vs non-IDC)	1.19	0.78-1.80	0.406			
ER (positive vs negative)	1.65	1.09-2.50	0.016**	1.41	0.91-2.20	0.119
PR (positive vs negative)	1.24	0.80-1.94	0.327			
HER2 (positive vs negative)	0.56	0.35-0.91	0.021**	0.64	0.49-0.83	0.004**
T stage						
T1 (ref.)	1			1		
T2	1.90	1.08-3.33	0.025**	1.5	0.86-2.78	0.140
T3	3.39	1.74-6.62	<0.001**	1.74	1.01-3.53	0.040**
T4	9.37	4.82-18.22	<0.001**	4.21	2.05-8.67	0.002**
ALN involvement						
N0 (ref.)	1			1		
N1	1.20	0.71-2.03	0.487	1.14	0.66-1.98	0.620
N2	1.94	1.06-3.52	0.030**	1.67	1.02-2.97	0.010**
N3	4.65	2.80-7.73	<0.001**	2.95	1.69-5.13	<0.001**
Stage						
I (ref.)	1					
II	1.44	0.69-2.99	0.329	0.92	0.30-2.81	0.885
III	4.55	2.25-9.18	<0.001**	1.66	0.42-6.56	0.468
Grade						
I (ref.)	1			1		
II	3.59	1.53-8.41	0.003**	2.59	1.08-6.18	0.030**
III	5.29	2.24-12.49	<0.001**	3.84	1.60-9.22	0.012**
LVI (positive vs negative)	0.40	0.25-0.64	<0.001**	0.64	0.38-1.07	0.095
PNI (positive vs negative)	0.54	0.33-0.87	0.012**	0.74	0.43-1.26	0.278

HR=hazard ratio; CI=confidence interval; ref=referent; IDC=Invasive ductal carcinoma; ER=Estrogen receptor; PR=Progesterone receptor; HER2=Human epidermal growth
factor receptor 2; ALN=Axillary lymph node; LVI=Lymphovascular invasion PNI=Perineural invasion. * Backward LR method was performed. ** Statistically significant.

Tumor size is the most important independent prognostic factor after ALN involvement. The prognosis decreases significantly as the tumor size increases.[21,23] Carter *et al.* found that 5-year survival was 99% in patients with tumors smaller than 1 cm and 86% in patients with tumors of 3-5 cm.[21] The prognostic significance of tumor size remains even when evaluated together with ALN involvement.[24] In addition, they provide prognostic insight when included in TNM staging. A single-center study from Turkey reported that OS statistically decreased with increasing TNM stage in patients with non-metastatic BC.[8] Our study demonstrated the statistical relationship between either tumor size or ALN involvement and survival, in line with previous studies. On the other hand, we found no statistical association between TNM stage and both DFS and OS in multivariate analyses. One potential explanation for this result is that TNM stage loses its significance, particularly when considered together with other strong prognostic factors such as tumor size and ALN. Additionally, as a selection criterion, the exclusion of metastatic patients from our study might have weakened the statistical association between TNM stage and survival.

Histologic grade was found to be an independent prognostic factor for both DFS and OS in our study. Grade is determined by scoring the three morphologic features of the tumor (tubule formation, nuclear pleomorphism, and number of mitoses) and the prognosis worsens as the grade increases.[25,26] It has been identified as an independent factor when

analyzed in conjunction with other significant prognostic factors.[8] Furthermore, Schwartz *et al.* showed that grade remains a prognostic factor despite changes in tumor size and the number of positive ALNs.[27] Histologic grade, in conjunction with ALN status and tumor size, should be essential parameters in pathology reports in BC.

BC patients with high expression of ER benefit more from endocrine therapy.[28] By considering this predictive value, large database studies and meta-analyses have also highlighted the prognostic significance of ER-positivity in BC.[28,29] However, these studies have certain limitations, such as inadequate data on adjuvant hormone therapy and/or CT, absence of HER2 status, lack of assessment of the impact of HER2-targeted therapies, and potential publication bias in meta-analyses. In our study, while ER positivity showed a prognostic effect in univariate analyses, this effect was not observed when combined with other significant prognostic factors. Considering the potential limitations of our study, our results may not definitively indicate that ER-positivity is not prognostic. Instead, our data suggest that evaluating the prognostic significance of ER-positivity as a single factor is challenging.

HER2/neu (Cerb-B2) is a protooncogene with approximately 20% amplification and/or high expression in BC that has both prognostic and predictive importance.[30] High levels of expression have been associated with poor prognosis in ALN-positive patients.[31] Although the results were variable in ALN-negative BC, in a study involving 2026 patients, HER2 was also found to be an important prognostic factor for survival in ALN-negative patients.[32] Anti-HER2 treatment has altered the natural biology of HER2-positive BC. Following evidence of survival benefit in patients with metastatic disease, the use of trastuzumab in the adjuvant setting has been demonstrated in major randomized trials. In 2005, a 52-week adjuvant trastuzumab treatment was found to significantly improve survival rates in the HERA study, subsequently being licensed in Turkey.[33] Nevertheless, not all HER2-positive patients in our country were able to access trastuzumab. One survey identified potential barriers to adjuvant trastuzumab use, including availability, cost, patient comorbidities, clinical data, insurance coverage, and guideline adherence.[34]

Another factor to consider is that, based on the promising results of the 2009 FinHER trial, where a nine-week treatment regimen was employed, some physicians in our country have decided to administer a nine-week course of trastuzumab.[35] In our study, 40% of the patients were not able to receive trastuzumab. We observed that patients admitted prior to 2008 represented the majority of patients who were unable to receive trastuzumab. In contrast, following the increased accessibility after 2008, the primary reasons for failure to receive trastuzumab were treatment refusal and comorbidities. Multivariate analyses in our study revealed that HER2-positivity is an important poor prognostic factor for OS but not for DFS. Although anti-HER therapies have enhanced survival rates, the fact that some HER2-positive patients have not received trastuzumab for the aforementioned reasons may have contributed to our study being correlated with historical data associating HER2-positivity with worse survival outcomes. In addition, the poor prognostic value of HER2-positivity may be explained by the absence of anti-HER2 treatment in the neoadjuvant setting and possible challenges with access to anti-HER2 therapies after recurrence, an issue that was beyond the scope of our study.

The last pathologic parameters evaluated for prognostic significance were LVI and PNI, which are routinely included in BC pathology reports. Although both parameters showed considerable results in our univariate analysis, neither was found to be a significant predictor of survival in the multivariate analysis. LVI has been associated with local recurrence, distant metastases, and a worse prognosis for BC patients.[36,37] Regarding PNI, there were few reports investigating its correlation with prognosis, and the results were inconsistent.[38,39] In addition, the frequency of LVI or PNI varies widely in different studies. The reported variation may be primarily due to interobserver variability and the challenges associated with diagnostic techniques.[40] Prospective studies designed with special attention to histopathologic evaluation of LVI or PNI are needed.

In a global report, BC survival at 5 years was found to be 81% in Europe and 84% in America.[41] According to a recent study evaluating 20000 BC patients in Turkey, the 5- and 10-year OS rates were 86% and 76%, respectively.[11] The survival rates in our study were comparable to these studies.

Our study had some limitations. The first one was the retrospective nature of the study. Second, we could not include the effect of CT on prognosis in our analysis as the CT regimens were exceedingly heterogeneous. Third, some of the HER2-positive patients did not receive anti-HER2 treatment as mentioned above. Fourth, upfront mastectomy was mostly preferred over neoadjuvant therapy for locally advanced patients during our screening period, which might have affected the outcomes. Despite all these limitations, we believe that such region-based studies with a large number of patients are important for contributing demographic and survival data to the literature.

CONCLUSION

Since BC is a heterogeneous disease that can vary from patient to patient, prognostic factors should be determined after diagnosis, and patients should be addressed individually before treatment. The prognostic importance of ALN involvement, tumor size, and histologic grade, which are among the strongest independent prognostic factors known for a long time, were also demonstrated in our study. In addition, the prognostic effect of HER2 has been emphasized. In the current era, where more conservative surgical approaches and new, effective systemic neoadjuvant and adjuvant therapies are widely used, the importance of the prognostic factors highlighted in our study needs to be established by further studies.

ACKNOWLEDGEMENTS

Non.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

ETHICAL CONSIDERATIONS

This study was accepted as an internal medicine specialization thesis of the corresponding author and was approved by the Ethics Committee of Süleyman Demirel University Faculty of Medicine, dated 31.07.2013, and numbered 173. The requirement for informed consent was waived due to its retrospective nature.

FUNDING

None.

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How to Cite This Article

Arici MO, Kocer M. The Impact of Prognostic Factors on Survival in Patients with Non-Metastatic Invasive Breast Cancer: A Single-Center Experience. Arch Breast Cancer. 2025; 12(1):37-46.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/1007