B^2 Prognostic Index in Determining Prognosis in Metastatic Breast Cancer

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ABSTRACT

Objective: To determine the relationship between the B^2 prognostic index (B^2PI) scoring method and prognosis in metastatic breast cancer, and to create a formula based on parameters that can be easily accessed in daily practice.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Medical Oncology, Dokuz Eylul University, Izmir, Turkiye, between May 2010 and June 2021.

Methodology: The clinicopathological characteristics of the patients were compared between the groups. All female breast cancer patients over the age of 18 years with *de novo* metastatic and non-metastatic breast cancers who developed metastasis during follow-up, were included in the study. Those with a second solid cancer or haematological malignancy and with a life expectancy of less than 3 months were excluded from the study. Chi-square and Fisher's exact tests were used to compare categorical data between the groups. Overall survival evaluations were made using the Kaplan-Meier analysis method and Log-Rank test. Risk factors for mortality were evaluated in Cox regression analysis. In all statistical tests, $p < 0.05$ was considered statistically significant.

Results: There were 176 patients in this study, out of which 111 (63.1%) were *de novo* metastatic. When the effect of B^2PI risk groups on overall survival in intrinsic subtypes was analysed, significant differences were found in the overall survival of B^2PI risk groups in all subtypes except HER2+ ER- (HER2 overexpression subtype). According to the B^2PI scoring system, the median overall survival was higher for both low-risk and moderate-risk patients compared to those in the high-risk category.

Conclusion: For metastatic breast cancer patients, the B^2PI can be used to determine prognosis and develop treatment strategies, as it is a clinical decision-making tool based on parameters that are easily accessible in daily practice.

Key Words: *Metastatic breast cancer, B^2 prognostic index, Prognosis, Survival.*

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INTRODUCTION

The most common cancer and the one that causes the most deaths in women is the breast cancer. In 2020, an estimated 2.26 million women are thought to have died from breast cancer.[1,2] Today, through advances in systemic therapies, supportive care, and early detection through modern screening techniques, mortality from breast cancer has decreased significantly.[1] Despite its high morbidity, breast cancer has a better prognosis than other aggressive cancers. The American Cancer Society estimates the chance of survival at two years is 91% and the chance of survival at 10 years is 84%. However, if distant metastasis develops, the survival rate is greatly reduced. Five-year survival has been reported as 99% in localised diseases, 86% in regional diseases, and 27% in advanced diseases.[3]

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The high two-year survival rate is good compared to other cancers, but the development of metastasis is the most dangerous situation for a breast cancer patient.

Breast cancer often metastasises to bone, lung, and liver. Treatment modalities used after metastatic disease develops include systemic chemotherapy, hormonotherapy, and targeted therapy. The differences in survival rate among patients with metastatic breast cancer are associated with various clinical indicators such as tumour pathological subtype, tumour volume, and nodal status.[4] They are effective predictors of survival.

The disease process of breast cancer is quite complex due to biological heterogeneity and receptor changes. While survival time in patients receiving standard treatment may be a few months in aggressive disease, this period may be of years in benign disease without a major limitation in quality of life. Survival exceeds 10 years in a small but significant percentage. Therefore, the determination of prognostic factors helps the authors classify patients according to their risks.[5] The B^2 prognostic index (B^2PI) is a clinical decision-making tool that provides risk classification for patients with metastatic breast

cancer, created using easily accessible routine parameters used in daily clinical practice. It is calculated based on a total of 10 parameters which include metastasis-free interval (MFI), hormone receptor status, lung metastasis, liver metastasis, brain metastasis, bone metastasis, bone marrow metastasis, soft-tissue metastasis, presence of malignant effusion, and the presence of all other metastatic sites. B^2PI is a validated scoring system. Hormone receptor status, specific metastasis sites, and MFI are found to be the most important prognostic factors. Patients are divided into three risk groups according to the B^2PI score. Patients with a score of eight or less were in the low, those with a score between 9 and 14 were in the moderate, and those with a score of 15 and above were in the high-risk category.[5]

The B^2PI scoring method has a very few similar research examples in the literature. The question appears to inquire whether a treatment plan can be established based on the risk classification of a patient immediately upon the diagnosis. The objective of this study was to determine the relationship between the B^2PI scoring method and prognosis in metastatic breast cancer, and to create a formula based on parameters that can be easily accessed in daily practice.

METHODOLOGY

Female breast cancer patients (176 patients) over 18 years of age, *de novo* metastatic and non-metastatic, who developed metastasis during the follow-up, were followed up in the Department of Medical Oncology at Dokuz Eylul University Hospital, between 2010 and 2021. The data collection was obtained retrospectively. Exclusion criteria were the presence of a second solid or haematologic malignancy other than breast cancer, follow-up of the patient in another oncology centre, life expectancy <3 months, inability to obtain healthy data from the hospital information system. B^2PI scoring system parameters were MFI, hormone receptor status, metastasis to the lungs, liver, brain, bone, bone marrow, soft tissue involvement, the presence of malignant effusion, and the presence of any other metastatic sites. B^2PI is a tool that provides risk stratification for metastatic breast cancer patients, created with simple parameters, that can be easily applied in clinical practices. It is calculated over a total of 10 parameters. Each parameter has different scoring points. Scorings were done as follows; time until metastasis developed week ≤2 years = 3, hormone receptor-negative = 8, liver metastasis = 7, effusion due to metastasis = 4, brain metastasis = 8, bone metastasis = 4, bone marrow metastasis = 10, soft tissue metastasis = 4, lung metastasis = 4, and other metastases = 0.

Analyses were performed with SPSS software v 22.0 (IBM, NY, USA). After descriptive statistics were performed, Shapiro-Wilk and Kolmogorov-Smirnov normality tests were used to determine whether continuous data were normally distributed or not. The demographical and clinical characteristics of the patients were compared between the groups. Kruskal-Wallis test was used to compare variables that were not normally distributed between the groups, and One-Way ANOVA test was used to compare normally distributed variables. The results of these analyses were presented as mean ± standard deviation, median, and minimum-maximum values. Chi-square and Fisher's exact tests were used to compare categorical data between the groups. The results are given as numbers and percentages (%). Overall survival evaluations were made using the Kaplan-Meier analysis method and Log-Rank test. Risk factors for mortality were evaluated in Cox regression analysis. Results are presented with 95% confidence intervals. In all statistical tests, p-value <0.05 was considered statistically significant.

Ethical approval for the research was given by the University's Ethics Committee (Decision no: 2022/04-19, File no: 6947-GOA, Dated: 02.02.2022).

RESULTS

There were 176 patients with an average age of 52.9 ± 13.6 years. The patients' ages were between 25 and 88 years. One hundred and twenty-six patients (71.6%) died during follow-up. One hundred and eleven (63.1%) of the patients were metastatic at the time of diagnosis, while 65 of the patients (36.9%) subsequently developed metastasis. Distribution of patients according to breast cancer intrinsic subtypes was such that, 25 (14.2%) patients had Luminal A, 77 (43.8%) patients had Luminal B HER2-, 36 (20.5%) had Luminal B HER2+, and 19 (10.8%) patients each had HER2+ ER- (HER2 extreme expression type), and triple-negative. Patients' characteristics are in described Table I.

The average B^2PI score of the patients was 12.1 ± 6.6. According to B^2PI, 67 (38.1%) of the patients were in the low-risk group, 51 (29%) were in the moderate-risk group, and 58 (33%) were in the high-risk group. A statistically significant difference was detected when comparing B^2PI risk score medians for breast cancer intrinsic subtypes. Triple-negative and Luminal A, triple-negative and Luminal B HER2+, triple-negative and Luminal B HER2-, Luminal A and HER2+ ER-, Luminal B HER2+, and HER2+ ER- B^2PI score median values were significantly different from each other (p <0.05). Statistical differences were also detected in the grouping of intrinsic subtypes according to B^2PI risk groups. There were no triple-negative patients in the low-risk group while in the luminal groups, the low-risk group was more common than the moderate- and high--risk groups. There was no statistical relationship between B^2PI score averages in pre-peri-postmenopausal groups (p = 0.626). There was a statistical relationship between B^2PI risk score and survival in the triple-negative patient group. Patients classified in the high-risk group exhibited a mortality rate 9.2 times higher than those in the medium-risk group (p = 0.035). As the B^2PI risk groups moved from the low-risk group to the high-risk group, the rate of metastasis to more than one of the metastatic sites included in the score increased statistically significantly. The differences between risk groups for lungs, brain, liver, bone marrow, and effusion metastases were found to be statistically significant (Table II).

Table I: The clinicopathological conditions of the patients.

Variables	Number of patients (n) (%)
Age mean ± SD (min-max)	52.9 ± 13.6 (25.0-88)
Age groups n (%)	
<40 years	26 (14.8)
40-65 years	117 (66.5)
>65 years	33 (18.8)
Menopause status	
Premenopausal	62 (35.2)
Postmenopausal	97 (55.1)
Perimenopausal	17 (9.7)
Histological type	
Invasive ductal carcinoma	80 (45.5)
Invasive lobular carcinoma	34 (19.3)
Mixed type	49 (27.8)
Other types	13 (7.4)
ER	
ER-	39 (22.2)
ER <50%	24 (13.6)
ER ≥50%	113 (64.2)
PR	
PR-	73 (41.5)
PR <20%	34 (19.3)
PR≥ 20%	69 (39.2)
HER2	
HER2-	120 (68.2)
IHC+	37 (21)
FISH+	19 (10.8)
Molecular subtype	
Triple-negative	19 (10.8)
Luminal A	25 (14.2)
Luminal B HER2+	36 (20.5)
Luminal B HER2-	77 (43.8)
HER2+ ER-	19 (10.8)
Bone metastasis	112 (63.6)
Lung metastasis	51 (29)
Brain metastasis	17 (9.7)
Liver metastasis	54 (30.7)
Bone marrow metastasis	7 (4)
Soft tissue metastasis	19 (10.8)
Effusion metastasis	19 (10.8)
Other metastases	82 (46.6)
MFI (%)	
≤2 years	143 (81.3)
>2 years	33 (18.8)
B²PI risk class	
Low-risk	67 (38.1)
Moderate-risk	51 (29)
High-risk	58 (33)

`ER: Oestrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2, IHC: Immunohistochemical, FISH: Fluorescence in situ hybridisation, MFI: Metastasis free interval.

Table II: Evaluation of metastasis sites in B²PI risk groups.

Sites of metastasis	B²PI low-risk (n = 67)	B²PI moderate-risk (n = 51)	B²PI high-risk (n = 58)	p-value
Metastasis group n (%)				<0.001*
Solitary	45 (67.2)	20 (39.2)	12 (20.7)	
Multiple	22 (32.8)	31 (60.8)	46 (79.3)	
Bone metastasis (%)	44 (67.2)	26 (51)	42 (72)	0.061*
Lung metastasis n (%)	8 (11.9)	9 (17.6)	34 (58.6)	<0.001*
Brain metastasis n (%)	2 (3)	3 (5.9)	12 (20.7)	0.002*
Liver metastasis n (%)	2 (3)	26 (51)	26 (44.8)	<0.001*
Bone marrow metastasis n (%)	0 (0)	1 (2)	6 (10.3)	0.009*
Soft tissue metastasis n (%)	8 (11.9)	4 (7.8)	7 (12.1)	0.722*
Effusion metastasis n (%)	0 (0)	2 (3.9)	17 (29.3)	<0.001*
Other metastases n (%)	25 (37.3)	27 (52.9)	30 (51.7)	0.153*

*B²PI: B² Prognostic Index, *Chi-square test and Fisher's exact test.*

In Luminal A group patients, the overall survival of the high-risk group according to the B²PI riskscore was lower than the low-risk group (p = 0.003). The risk of death in high-risk patients was 5.8 times higher than in the low-risk patients. In Luminal B (HER2+ and HER2-) patients, the overall survival of the high-risk group according to the B²PI risk score was lower than that of the low-risk group. The survival of the high-risk group was lower than that of the moderate-risk group. The risk of death in high-risk patients was 3.4 times higher than in the low-risk patients and 2.5 times higher than in moderate-risk patients. Median overall survival time showed a statistical difference between the groups (p <0.001). The overall survival of the low-risk group was significantly higher than the high-risk group, and the overall survival of the moderate-risk group was significantly higher than the high-risk group (p <0.001 and p = 0.002), respectively.

According to the B²PI score, the death risk of high-risk patients was 2.4 times higher than low-risk patients and 2.1 times higher than moderate-risk patients (p <0.001; p = 0.001). It was observed that the overall survival of moderate-risk patients and the low-risk patients was not statistically significantly different. Survival analysis according to B²PI risk groups is shown in Figure 1.

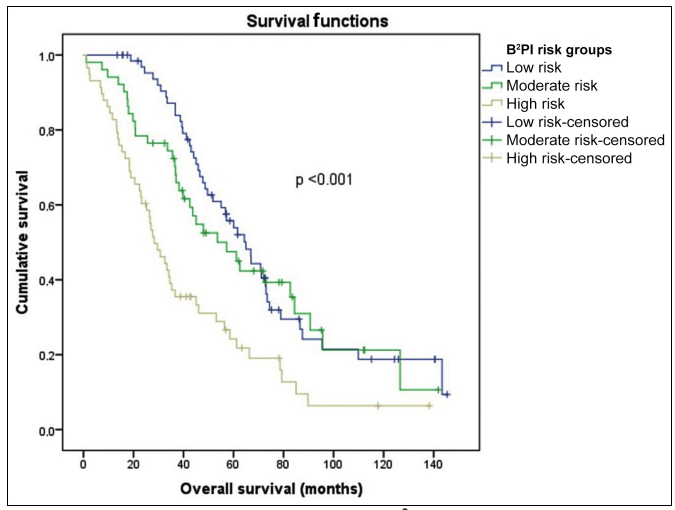

Figure 1: Evaluation of overall survival in B²PI risk groups.

DISCUSSION

B² prognostic index score is roughly composed of the following components: Hormone receptor status, specific metastasis site, and time until metastasis develops. This index is an easily applicable and practical method for the stratification of metastatic breast cancer patients into prognostic groups in the daily clinical practice. For survival prognosis, this score can be used as a useful tool for personalised treatment selection, as well as parameters such as molecular subtypes and comorbidity, which will guide the treatment of patients. Hormone receptor status has long been recognised as a very important prognostic and predictive factor in breast cancer. With the new molecular classification, this importance has been further strengthened.[6] Different subtypes of breast cancer differ not only in their risk of recurrence but also in their patterns of the recurrence. This may manifest itself as a local, distant or atypical site of metastasis.[7] Tumours that metastasise predominantly to the bone, show a clinically different course from those that metastasise to the liver, lung, or brain.[8,9] In terms of bone metastasis development rates, there were differences between breast cancer subgroups in this study's patient population.

The rate of lung metastasis development was statistically significantly different between the intrinsic groups. The higher lung

metastasis rate in triple-negative and Luminal B HER2- patients explains this difference. The rate of metastasis development in the "other group" and the development rates in the subgroups were different. This difference was due to the fact that the number of metastases in the Luminal A group was less than the other groups.

The preference of metastatic organ has shown to differ between subtypes of breast cancer. Bone is the single most frequent site for metastases and is involved in about 70% of all metastatic patients.[10] It is known that bone metastasis is higher in Luminal A, Luminal B HER2+, and Luminal B HER2- type breast cancer compared to the other molecular types (non-luminal types).[11,12]

It has also been shown that lung metastasis is higher in triple-negative type compared to other molecular subtypes.[12,13] The incidence of lung metastasis can reach up to 40% in triple-negative breast cancer compared with only 20% in non-triple-negative.[13] In this study, when examined in terms of metastasis locations between the risk groups, the presence of lung, brain, liver, bone marrow, and effusion metastasis showed a statistically significant difference.

As a result of this research, lung, brain, bone marrow, and effusion metastases increased from the low-risk score group to the high-risk score group.

Liver metastases were most common in the moderate-group, followed by the high-risk group, and least common in the low-risk group. In Regierer *et al.* and Stueber *et al.*'s studies, the distribution of lung, brain, bone marrow, and effusion metastases was similar among the risk groups, and liver metastases were more intense in those with moderate-risk than those with high-risk.[5,14] This situation was similar to this study. No significant difference was detected in the rate of bone and soft tissue metastasis between the risk groups.

Short MFI is an unfavourable prognostic marker in breast cancer. This short period is generally defined as 12 months or less than 24 months in the literature.[15] This period was accepted as 24 months in the present study. More aggressive treatment strategies are recommended in the patients with a very short MFI.[16] Triple-negative was divided into two groups: Moderate- and high-risk. There were no low-risk patients with triple-negative histology.

The median overall survival of patients with moderate-risk was higher than that of the patients with high-risk. According to B^2PI risk stratification of Luminal A patients, low-risk patients outlived the high-risk ones. In this study, there was no significant difference in median overall survival between the low-risk group and the moderate-risk group for Luminal A; however, in Stueber *et al.*'s study, the risk of death in moderate-risk patients was 1.49 times higher than in low-risk patients. For Luminal B HER2+ patients, low-risks had significantly longer overall survival time than high-risks. In Luminal B HER2- patients, those at low-risk had longer survival time than those at the high-risk, and median overall survival at the moderate-risk was significantly higher than at the high-risk. For Luminal B HER+ and HER- patients, the overall survival of those with low-risk was significantly higher than that of those with high-risk, and the median overall survival of moderate-risk patients was better than that of the high-risk patients. There was no significant difference in the median overall survival of HER2+ ER- and all non-luminal patients (When HER2+ ER- and triple-negative patients are included in the same group) according to B^2PI risk score. When triple-negative patients were evaluated alone, median overall survival was significantly different according to the B^2PI risk score. When all patients included in this study were grouped according to B^2PI risk groups, without any molecular subtype distinction, and median overall survival was analysed, median overall survival was found to be statistically different from each other. The median overall survival time of low, moderate, and high-risk group patients was 64.9, 53.6, and 28.3 months, respectively. Median overall survival was significantly higher in the low-risk group than in the high-risk group and in the moderate-risk group than in the high-risk group. The risk of death in high-risk patients was 2.4 times higher than in low-risk patients and 2.1 times higher than in moderate-risk patients. In the study by Regierer *et al.* in which the B^2PI risk score was defined, median overall survival was found to be 38, 31, and 16 months in the low, moderate, and high-risk groups, respectively.[14] The mean ages of breast cancer intrinsic subtypes were 55.0 ± 16.6 in triple-negative group, 54.1 ± 13.9 in Luminal A group, 47.7 ± 10.9 in Luminal B HER2+ group, 53.8 ± 13.5 in Luminal B HER2- group, and 56.0 ± 14.0 in HER2+ ER- group, and no statistical significance was detected between the groups. There are conflicting publications on this subject in the literature. In Al-Thoubaity's research, HER2+ and triple-negative tumour rates were less common in patients under 50 years of age.[17] In Setyawati *et al.*'s study, no relationship was found between patients' age and breast cancer molecular subtypes.[18]

The major limitation of the study is the retrospective analysis. Owing to the lack of data, especially adverse events, medicine compliance information may have been underestimated. Further studies may be necessary to determine whether risk groups may benefit from more intensive treatment options. Detailed molecular classification of tumours and analysis with prognostic indices, as in the present study, will lead to the selection of the correct treatment in patients with metastatic breast cancer.

CONCLUSION

For metastatic breast cancer patients, the B^2PI can be used to determine prognosis and develop treatment strategies, as it is a clinical decision-making tool based on parameters that are easily accessible in daily practice.

ETHICAL APPROVAL:

Approval for the study was granted by the Clinical Research Ethics Committee of Dokuz Eylul University of Health Sciences, Izmir, Turkiye (Decision no: 2022/04-19, File no: 6947-GOA, Dated: 02.02.2022).

PATIENTS' CONSENT:
Written informed consent was obtained from the participants.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MMC: Writing of the manuscript and data analysis.
MU: Design of the manuscript.
TY: Supervision of the manuscript.
All authors approved the final version of the manuscript to be published.

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