B^2 Prognostic Score: External Validation of a Clinical Decision-making Tool for Metastatic Breast Cancer

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Abstract

The B^2 Prognostic Score (B^2PS) is a decision-making tool in metastatic breast cancer. A total of 641 patients treated between 2001 and 2009 were classified into risk groups based on the B^2PS, and survival parameters were compared. Intermediate- and high-risk groups showed decreased survival, and the distribution of risk groups varied within the intrinsic subtypes. The B^2PS helps in counseling patients with metastatic breast cancer.

Background: The B^2 Prognostic Score (B^2PS) is a clinical decision-making tool in metastatic breast cancer (MBC) that provides risk classification based on routine parameters. This study validates the B^2PS in an independent series of MBC for the whole study group and for each intrinsic subtype. **Patients and Methods:** We analyzed 641 metastasized patients, treated in 17 German certified breast cancer centers between 2001 and 2009. They were classified into low, intermediate, and high-risk groups according to B^2PS. Overall survival (OS) curves for the various B^2PS groups were compared with Kaplan-Meier method. **Results:** According to the B^2PS formula, 42.3% of patients were classified as low risk, 25.4% as intermediate risk and 32.3% as high risk. Intermediate- and high-risk patients had a statistically significant decreased OS compared with B^2PS low-risk patients: (intermediate-risk: hazard ratio, 1.36; 95% confidence interval, 1.04-1.77; $P = .023$; high-risk: hazard ratio, 2.62; 95% confidence interval, 2.06-3.32; $P < .001$). The 5-year survival rates of low-, intermediate-, and high-risk patients were 41.3%, 26.9%, and 10.2%, respectively. The distribution of B^2PS risk groups varied significantly within the intrinsic subtypes. For each intrinsic subtype, B^2PS gives an additional risk classification. **Conclusions:** This study demonstrates the reproducibility of the B^2PS based on routinely assessable parameters and confirms its prognostic value in an independent entire cohort of MBC as well as in the separate intrinsic subtypes. It therefore can help in counseling and individualizing the therapeutic regimens of those patients.

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Introduction

Breast cancer continues to be the most frequent cancer among women. In Germany, the incidence amounts to 72,000 cases. The overall 5- and 10- year survival rates were 88% and 82% in 2016, but this differs according to the tumor stage (5-year survival rate for stage I, 98%-100%; stage II, 90%-95%; stage III, 70%-85%; and stage IV, 30%).[1]

Although prognoses have improved over the past decades, a relevant number of women develop metastatic breast cancer (MBC).[2] A survey of precise data is challenging, but using the back calculation method, one could estimate that up to 25% of women in Germany developed MBC in 2017.[3,4]

Individualized therapeutic strategies comprise hormonal, chemotherapeutic, or targeted therapies but should focus on quality of life and low toxicity. Lately, the combination of CDK4/6 inhibitors with endocrine therapy has been reported to improve progression-free survival (PFS) and overall survival (OS) of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative MBC.[5-8] In the case of

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progression under endocrine therapy or in cases that are not life threatening, monochemotherapy is indicated and might comprise taxanes, anthracyclines, vinorelbine, or capecitabine. No difference in efficacy has yet been demonstrated between these agents, but therapy resistance has to be considered because women are currently mostly heavily pretreated with several chemotherapeutic lines of treatment. In cases of threatening aggressive disease, polychemotherapy might be indicated, even if the influence on OS is still doubtful. Moreover, many scientific efforts have been recently made in the development of anti-HER2 directed substances.[9,10]

Despite all the scientific progress, the clinical behavior of MBC is more or less unpredictable, reflecting the biologic heterogeneity and receptor changes. Survival may range from a few months with a very aggressive course of the disease to several years without major limitations in the quality of life, and even for a small but meaningful percent of these patients, to more than 10 years. This underlines the importance of defining prognostic factors to develop risk-adopted treatment strategies.

The B^2 Prognostic Score (B^2PS) is a clinical decision-making tool for patients with MBC that provides risk classification based on routine parameters easily accessible in daily clinical care.[11,12] This score was evaluated in 942 patients by developing a Cox regression model, which showed HR status, specific sites of metastasis, and metastasis-free interval (MFI) to be the most significant prognostic factors. The score underwent an internal and external validation on 2 independent validation samples.[11] This study aimed to validate the B^2PS in an independent series of MBC from BRENDA (Breast Cancer Care under evidence-based Guidelines)[13,14] for the whole study group as well as for intrinsic subtypes.

Materials and Methods

Patients

The BRENDA collective included patients with breast cancer from the Department of Gynaecology and Obstetrics at the University of Ulm and from 16 partner clinics in Germany for the period of 2001 through 2009. The exact conditions and inclusion criteria of BRENDA have been described previously.[13] For this retrospective study, we extracted data from 641 patients with MBC. All patients participated after written and informed consent.

All metastatic sites that were identified by x-ray, computed tomography, or magnetic resonance imaging were coded as bone, lung, liver, any effusion, bone marrow, brain, skin, or soft tissue.

If any information in the database was missing or conflicting, a verification using the original patient file was done. Initial tumor staging and annual follow-up were carried out according to usual recommendations. Histologic verification of metastasis was not required.

Metastatic-free survival (MFS) was measured as the time from primary diagnosis to the occurrence of metastases. OS from occurrence of metastases was calculated from the date of diagnosis of MBC until death or the date of the last follow-up. If the patient was lost to follow-up, data were censored at the date of the last known contact. Adjuvant treatments were checked for guideline adherence. Guideline adherence was defined based on a systematic analysis of the guideline recommendations and statements of the interdisciplinary consensus S3 guideline issued by the German Cancer Society in 2008. A comparison of the treatment recommendations of the S3 guideline and other national breast cancer guidelines from the United States (National Comprehensive Cancer network [NCCN], American Society of Clinical Oncology [ASCO]), Canada (Cancer Care Ontario [CCO]), Australia (National Breast and Ovarian Cancer Centre [NBOCC]), and the United Kingdom (The National Institute for Health and Care Excellence [NICE], Scottish Intercollegiate Guidelines Network [SIGN]) showed that these guidelines differ only marginally.[15]

Surrogate Definition of Intrinsic Subtypes

To define the intrinsic breast cancer subtypes, HR expression, HER2 expression, and cell proliferation marker Ki67 are used.[16] As Ki67 was not available in the BRENDA database, we used grade as a surrogate parameter to include cell proliferation, as described before by Parise et al,[17] von Minckwitz et al,[18] and Lips et al.[19] The 5 intrinsic subtypes are defined as follows: luminal A ($HR^+/HER2^-$/grade 1 or 2), luminal B-HER2−negative-like ($HR^+/HER2^-$/grade 3), luminal B-HER2−positive-like ($HR^+/HER2^+$, all grades); HER2-overexpressing (non-luminal, $HR^-/HER2^+$), and triple-negative (basal-like, $HR^-/HER2^-$).

B^2PS

For each patient, we first calculated the corresponding prognostic index (B^2PI), which was derived by summing the item points of the prognostic factors: $B^2PI = \gamma_1 \times \text{covariate } A_1 + \gamma_2 \times \text{covariate } A_2 + \ldots + \gamma_n \times \text{covariate } A_n$, where $\gamma_1, \gamma_2, \ldots, \gamma_n$ denote the item points of the B^2PI (Table 1).

The 3 risk groups of the B^2PS are defined as follows: low-risk $B^2PI \leq 8$; intermediate-risk B^2PI: 9 to 14, and high-risk $B^2PI \geq 15$.

Statistics

All categorical data were described using numbers and percentages. Quantitative data were presented using median and range or mean and standard deviations. Survival distributions and median survival times were estimated using the Kaplan-Meier product-limit method and were compared using the generalized Wilcoxon test, including the number of patients, the number of events, median survival, and 95% confidence interval (CI). When no information was available, the status was coded as missing data. Statistical comparisons were carried out using the χ^2 test or the Fisher exact

Table 1 Item Points of the B2 Prognostic Index (B2PI)

Parameter	Item Points
MFI ≤ 2 years	3
HR-negative	8
Liver metastases	7
Effusion metastases	4
Brain metastases	8
Bone metastases	4
Bone marrow metastases	10
Soft tissue metastases	4
Lung metastases	4
For all other values	0

Abbreviations: HR = hormone receptor; MFI = metastasis-free interval.

Table 2 Basic Characteristics

	Total	Low-risk	Intermediate-risk	High-risk	
	N = 641 (%)	N = 271 (42.3%)	N = 163 (25.4%)	N = 207 (32.3%)	*P* Value
Age at Diagnosis of Advanced Breast Cancer, y					.096
Median	66	67	66	64	
Min-max	27-97	33-97	31-87	27-88	
Nodal Status					.025
Negative or unknown	205 (32.0)	101 (37.3)	51 (31.3)	53 (25.6)	
Positive	436 (38.0)	170 (62.7)	112 (68.7)	154 (74.4)	
Grading					<.001
1	20 (3.1)	13 (4.8)	5 (3.1)	2 (1.0)	
2	299 (46.8)	161 (59.9)	81 (49.7)	57 (27.5)	
3	320 (50.1)	95 (35.3)	77 (47.2)	148 (71.5)	
Intrinsic Subtypes					<.001
Luminal A	249 (38.8)	157 (57.9)	68 (41.7)	24 (11.6)	
Luminal B/HER2$^-$	147 (22.9)	77 (28.4)	41 (25.2)	29 (14.0)	
Luminal B/HER2$^+$	86 (13.4)	37 (13.7)	29 (17.8)	20 (9.7)	
TNT	96 (15.0)	0 (0.0)	17 (10.4)	79 (38.2)	
HER2 overexpressing	63 (9.8)	0 (0.0)	8 (4.9)	55 (26.6)	
Adjuvant Guideline Adherence (M0-Pat)					.423
No	389 (68.2)	167 (69.3)	88 (63.8)	134 (70.2)	
Yes	181 (31.8)	74 (30.7)	50 (36.2)	57 (29.8)	
Lung					< .001
No	454 (70.8)	224 (82.7)	120 (73.6)	110 (53.1)	
Yes	187 (29.2)	47 (17.3)	43 (26.4)	97 (46.9)	
Liver					<.001
No	420 (65.5)	262 (96.7)	67 (41.1)	91 (44.0)	
Yes	221 (34.5)	9 (3.3)	96 (58.9)	116 (56.0)	
Effusion					.168
No	594 (92.7)	225 (94.1)	153 (93.9)	186 (89.9)	
Yes	47 (7.3)	16 (5.9)	10 (6.1)	21 (10.1)	
Brain					<.001
No	553 (86.3)	264 (97.4)	152 (93.3)	137 (66.2)	
Yes	88 (13.7)	7 (2.6)	11 (6.7)	70 (33.8)	
Bone					.022
No	251 (39.3)	92 (33.9)	77 (47.2)	83 (40.1)	
Yes	390 (60.7)	179 (66.1)	86 (52.8)	124 (59.9)	
MFI					.273
Median	15	17	16.0	13.0	
Min-max	0-197	0-97	0-71	0-92	
MFI, mos					<.001
>24	209 (32.6)	109 (40.2)	57 (35.0)	43 (20.8)	
≤24	432 (67.4)	162 (59.8)	106 (65.0)	164 (79.2)	

Abbreviations: HER2 = human epidermal growth factor receptor; MFI = metastatic-free survival; TNT = triple-negative type.

test for categorical data and the log-rank test for censored data. The item points of the B^{2}PS denote the rounded estimates of beta coefficients for covariates with respect to 95% CI of betas multiplied by 10 in the corresponding adjusted Cox regression.

The primary endpoint was OS. Survival distributions and median survival times were estimated using the Kaplan-Meier product-limit method. The log rank-test was used to provide a formal statistical assessment of the differences between treatment arms with respect to OS. The Cox proportional hazards model with adjustment and interactions of covariates was used to estimate the hazard ratio (HR) and 95% CIs. Proportional hazards were tested for all entered variables using statistical and graphical methods (Schoenfeld residuals and log−log plot of cumulative hazard). *P*-values of < .05 were considered as statistically

significant. Statistical analyses were 2-sided and carried out using SPSS 24, NCSS 10, and R 3.5.

Results

Basic Characteristics

The median age of the 641 patients at MBC diagnosis was 66 years (range, 27-97 years). There are significant differences for nodal status, grading, intrinsic subtypes, lung, liver, brain, and bone metastases as well as MFI $\leq$ 24 months between the risk groups. Basic characteristics of the whole study group, as well as of the risk groups, are shown in Table 2. The median MFS was 15 months and did not significantly differ between the risk groups ($P = .273$). Of the high-risk patients, 79.2% had a MFI of less than 24 months.

Patients in the high-risk group showed positive lymph node status significantly more often (74.4%) and with higher grading (grade 3 in 71.5%) than patients in the low-risk or intermediate-risk group. Overall, only 32% of all 570 primarily M0 patients with later recurrent MBC received guideline-adherent treatment in the adjuvant situation.

OS of Risk Groups

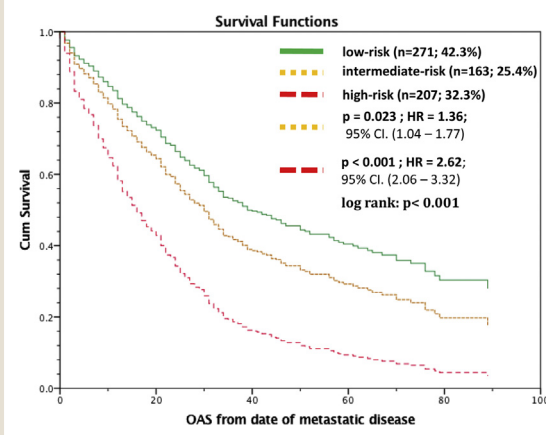
Survival was significantly decreased in the intermediate- or high-risk groups compared with the low-risk group. The 5-year survival rates were 41.3% in the low-risk, 26.9% in the intermediate-risk, and 10.2% in the high-risk group. The median survival rate was 27 months (95% CI, 24.2-29.8 months) for the whole group, 38 months (95% CI, 22.9-53.1 months) in the low-risk, 31 months (95% CI, 26.1-35.9 months) in the intermediate-risk, and 16 months (95% CI, 12.6-19.4 months) in the high-risk group (log rank $P < .001$). Comparing the intermediate-risk group with the low-risk group, we obtained an HR of 1.36 and a 95% CI of 1.04 to 1.77 ($P = .023$), and comparing the high-risk group with the low-risk group, we obtained an HR of 2.62 and a 95% CI of 2.06 to 3.32 ($P < .001$) (Figure 1).

Intrinsic Subtypes

We further evaluated the relation between B^2 risk groups and intrinsic subtypes and the corresponding OS. Patients with luminal A tumors were mainly classified as low risk (63.1%) or intermediate risk (27.3%), but nevertheless, 9.6% of those patients were classified as high risk. Patients with MBC with luminal A in the low-risk group had a 5-year survival rate of 48.3%, in the intermediate-risk group of 29.6%, and in the high-risk group of 15.5%, showing that the B^2PS is still valid for patients with luminal A disease. The HR between intermediate-risk and low-risk luminal A patients was 1.49 (95% CI, 1.01-2.21; $P = .046$), and between high-risk and low-risk patients with luminal A disease, the HR was 2.11 (95% CI, 1.18-3.80; $P = .012$). About 70% of the patients with non-luminal A tumors were classified either as high risk (46.7%) or intermediate risk (24.2%). Patients with MBC with non-luminal A tumors in the low-risk group had a 5-year survival rate of 32.1%, in the intermediate-risk group of 24.7%, and in the high-risk group of 9.8%.

Patients with HER2 overexpressing or triple-negative advanced breast cancer were mainly classified as high risk (84.3%) or intermediate risk (15.7%), whereas not a single patient with HER2 overexpression was classified being at low risk. Conversely, patients with luminal B/HER2$^-$ or luminal B/HER2$^+$ disease were classified as low risk in 48.9%, as intermediate risk in 30.0%, and as high risk in 21.0% (Figure 2).

Figure 1 Overall Survival of Patients With Metastatic Breast Cancer Stratified by B^2-Score. For the Statistical Analysis, Data of the Intermediate-risk (Yellow) and High-risk (Red) Groups Were Compared With the Low-risk Group



Abbreviations: CI = confidence interval; HR = hazard ratio; OAS = overall survival.

For patients with luminal B advanced breast cancer, we obtained the following results: Intermediate risk compared with low risk: HR, 1.21; 95% CI, 0.83 to 1.77; $P = .320$ and high risk compared with low risk: HR, 1.61; 95% CI, 1.07 to 2.43; $P = .024$. Survival rates for patients with HER2 overexpressing or triple-negative advanced breast cancer in the high-risk group were also significantly impaired in comparison with those in the intermediate-risk group (HR, 2.46; 95% CI, 1.28-4.71; $P = .007$) (Figures 3-5).

B^2PS and Adjuvant Guideline Adherence

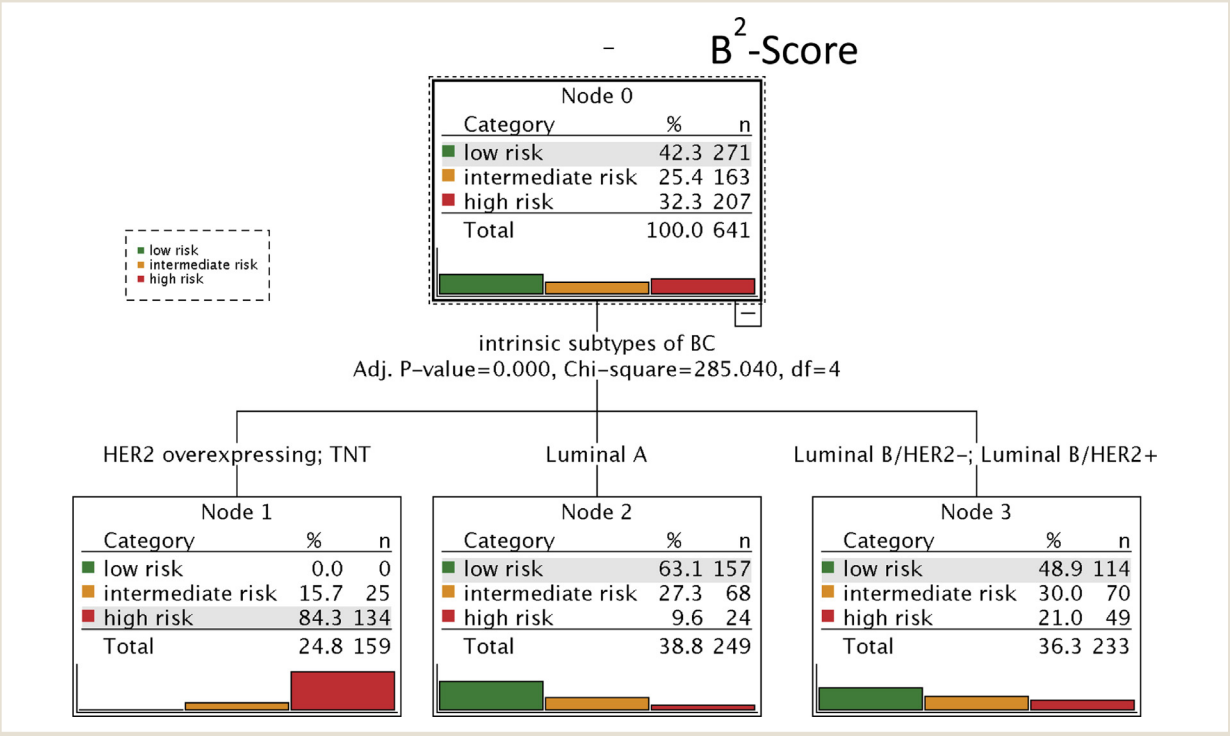
Of the patients with MBC (adjuvant M0) in this study, 68.2% received guideline−non-adherent adjuvant treatments. There was no significant difference between guideline non-adherence and the B^2 risk groups (low risk, 69.3%; intermediate risk, 63.8%; and high risk, 70.2%; $P = .423$). On the other side, we found a highly significant ($P < .001$) difference between chemotherapy non-adherence and B^2 risk groups (guideline non-adherent chemotherapy: low risk, 30.2%; intermediate risk, 36.6%; and high risk, 53.0%).

Discussion

The 2 major findings of the present study are: (1) the OS of patients with MBC is significantly associated with the B^2 risk score in the BRENDA collective, another external validation of this score; and (2) the B^2 risk classification is independent of the classification of intrinsic subtypes (ie, the B^2 risk score refines the classification based on intrinsic subtypes by subdividing each subtype into different risk groups).

The B^2 score is based on routine clinical parameters, including HR status in the adjuvant setting, the specific site of metastasis, and MFI integrated in a prognostic index formula, which can be used easily in daily clinical practice to stratify patients with MBC

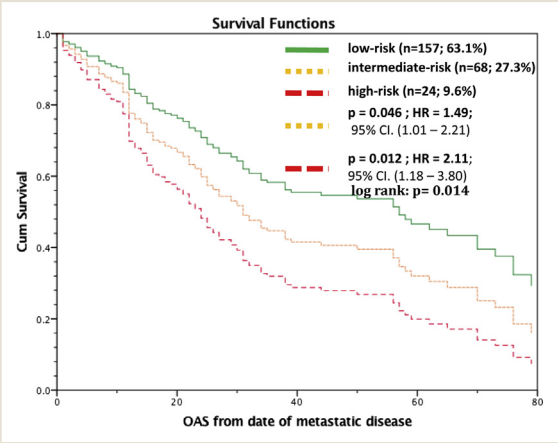
Figure 2 Cross-tabulation of Intrinsic Subtypes



Abbreviations: BC = breast cancer; HER2 = human epidermal growth factor receptor 2; TNT = triple-negative type.

into prognostic groups. This score for survival prognosis is in addition to intrinsic subtypes, comorbidity, and patients' wish for a helpful tool to personalize the decision between the various applicable treatment options. Initially, we thought to integrate the intrinsic subtypes characterized by their featured classical immunohistochemistry status into a new B^2 plus score for further enhancement. After discussion on daily clinical routines, we decided not to integrate the intrinsic subtypes into the B^2 score in order to retrieve the prognostic as well as the predictive part of this information separately. The identification of relevant prognostic factors as well as the evaluation of scoring systems in order to predict the prognosis in MBC has been described earlier,[20-23] all of which state that MFI, HR status, and the site of metastasis are independent factors. In comparison with those other evaluations on scoring systems, we are the first to present a prognostic scoring system that is feasible and independent of the intrinsic subtype classification.

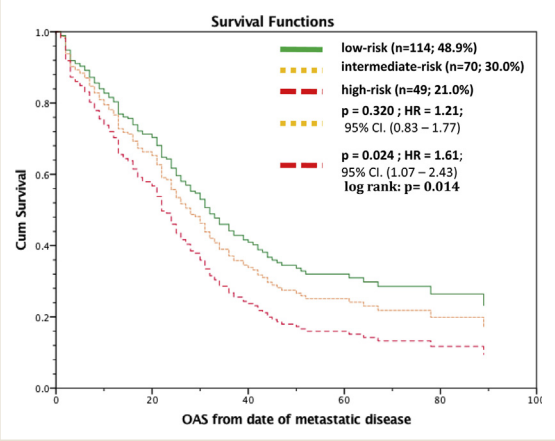
Figure 3 Overall Survival of Patients With Luminal A Metastatic Breast Cancer Stratified by B^2-Score. For the Statistical Analysis, Data of the Intermediate-risk (Yellow) and High-risk (Red) Group Were Compared With the Low-risk Group



Abbreviations: CI = confidence interval; HR = hazard ratio; OAS = overall survival.

The intrinsic subtypes can be distributed into 3 major classes (ie, luminal, HER2 overexpression, and triple-negative phenotypic tumors).[24] Triple-negative tumors mostly pertain to the basal type.[25] The 3 luminal subtypes (luminal A, luminal B/HER$^-$, and luminal B/HER$^+$) were associated with low-, intermediate-, and high-risk patients, whereas HER2 over-expressive or triple-negative metastatic breast tumors were associated with intermediate- or high-risk patients. None of these patients were classified as low risk. This confirms previous results on these subtypes. In each of these major subtypes, there were significant differences in OS. For example, patients with luminal A MBC with low risk had a 5-year OS rate of 48%; with intermediate risk, 30%; and with high risk, 16%. The 5-year OS rate of B^2 high-risk patients with triple-negative tumors or HER2 overexpression was only 6%.

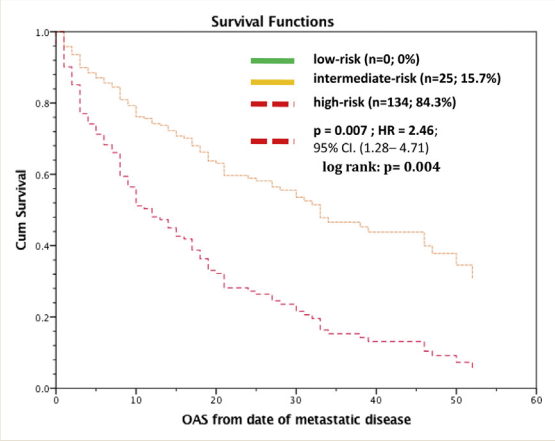
Figure 4 Overall Survival of Patients With Luminal B Metastatic Breast Cancer Stratified by B^2- Score. For the Statistical Analysis, Data of the Intermediate-risk (Yellow) and High-risk (Red) Groups Were Compared With the Low-risk Group



Abbreviations: CI = confidence interval; HR = hazard ratio; OAS = overall survival.

The limitations of the presented data comprise the time period of data collection. Certainly, there are several new targeting agents such as T-DM1, pertuzumab, or CDK4/6 inhibitors that are a therapeutic standard in the treatment of patients with MBC. Those agents might improve patients' outcome, especially for those with HER2 overexpressing or of HR^+ MBC with bone metastases only. Nevertheless, it is not clear if these targeting agents change the risk ranking (ie, the patients remain in their risk groups, but the survival curves might shift relative to each other).

Figure 5 Overall Survival of Patients With Triple-negative or HER2-overexpressing Metastatic Breast Cancer Stratified by B^2-Score. For the Statistical Analysis, Data of the High-risk (Red) Group Were Compared With the Intermediate-risk Group



Abbreviations: CI = confidence interval; HR = hazard ratio; OAS = overall survival.

Another limiting aspect is the occurrence of receptor changes throughout different treatment regimens in heavily pretreated patients, which has been evaluated in multiple studies. Around 12% of patients with estrogen receptor-positive breast cancer develop estrogen receptor loss, whereas about 22% are diagnosed with a change to progesterone receptor-negative recurrent disease. One of 10 patients with recurrent disease show a change in HER2 receptor expression.[26] Based on this fact, it is now common to revalidate the receptor status by histologic examination of biopsies in metastatic sites. As a limitation of this retrospective study, we did not include standardized biopsies when MBC was diagnosed and thus did not confirm the tumor biology and intrinsic subtype. Moreover, it is remarkable that about 68% of the patients with MBC included in this study did not receive 100% guideline-adherent adjuvant treatment.

The median MFI was 15 months in the whole collective, and the number of women with short MFI is significantly higher in the high-risk group when compared with the low-risk group. The association between MFI and survival for patients with MBC was seen in several publications and was irrespective of the use of (neo-) adjuvant systemic therapy.[27] Overall, patients with a more aggressive tumor biology at primary diagnosis were associated with a higher risk score in the metastatic situation.

Conclusion

In conclusion, this study shows that the distribution of the B^2 risk groups are similar in an independent series of MBC, and we can conclude that determination using the B^2 risk marker methodology is robust between patient series.

Clinical Practice Points

- The B^2PS is a clinical decision-making tool in MBC that provides risk classification based on routine parameters. This study validates the B^2PS in an independent series of MBC for the whole study group and especially for each intrinsic subtype. According to our analyses, intermediate- and high-risk patients had a statistically significant decreased OS compared with B^2PS low-risk patients. The distribution of B^2 risk groups varied significantly within the intrinsic subtypes, and the B^2PS gives an additional risk classification for each intrinsic subtype.
- This study demonstrates the reproducibility of the B^2PS based on routinely assessable parameters and confirms its prognostic value in an independent entire cohort of MBC as well as in the separate intrinsic subtypes. It therefore can help in counseling and individualizing the therapeutic regimens of those patients.

Disclosure

T.N.S. received fees from Roche Pharma, Pfizer, and Gedeon Richter; A.W. received fees from Novartis, Teva, Tesoro, Amgen, Pfizer, Celgene, Roche, Riemser, Aurikamed, and Hexal as indicated in the disclosure form. The remaining authors have stated that they have no conflicts of interest.

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