Prognostic Nomogram and Risk Stratification System for Breast Cancer Bone Metastasis: A SEER-Based Population Study

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Abstract

Purpose To construct and validate a nomogram and risk stratification model for predicting overall survival (OS) of patients with breast cancer bone metastasis (BCBM).

Methods We collected data on BCBM patients between 2010 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database. Patients were excluded if the data on the follow-up time or clinicopathological information were incomplete. The patients were randomly divided into the training set and validation set. Univariate and multivariate Cox proportional hazard regression models were performed. By integrating these variables, a predictive nomogram and risk stratification model were constructed and assessed using C-indexes and calibration curves.

Results Multivariate analysis showed that age, race, marital status, tumor subtype, grade, T classification, surgery, chemotherapy, brain metastasis, liver metastasis, and lung metastasis were independent prognostic indicators of BCBM. These results were reproducible when nomograms were applied to the testing cohort for external validation. The C-index of the nomogram to predict OS was 0.704, which was higher than that of the seventh edition American Joint Committee on Cancer TNM staging system (0.564; $P<0.001$). A risk stratification model was further generated to accurately differentiate patients into two prognostic groups. The survival rates predicted by the nomogram showed significant distinctions between the Kaplan–Meier curves in the entire cohort and each tumor subtype.

Conclusion The nomogram and risk stratification system predicting 1-, 3-, and 5-year OS for patients with newly diagnosed BCBM with satisfactory performance were constructed to help physicians in evaluating the mortality risk in patients with BCBM.

Introduction

Breast cancer (BC) is the most frequently diagnosed female cancer and the second leading cause of cancer death[1, 2].BC cells most frequently metastasize to bone, with up to 75% of stage IV BC patients developing bone metastases[3]. Multiple systemic organ metastases are common in BC, and in 17–37% of patients, the disease is limited to the skeleton. Patients with bone-only first metastasis tend to experience a better prognosis than those with other-only first metastasis. Patients in whom the disease remains confined to the bone have longer survival than those with subsequent visceral involvement. Bone metastasis can result in poor survival, considerable morbidity, intractable pain, and decreased quality of life[4].

The 3- and 5-year survival rates of BC patients with bone metastasis are 25% and 13%, respectively[5, 6]. Additionally, surgery or radiotherapy for patients with bone metastasis can provide effective local control and improve quality of life, especially for patients with pathologic fractures.To our knowledge, the risk factors and their effects on prognosis of patients with BC and bone metastasis have rarely been explored. Zhaoming Ye et al. reported that tumor grade, histologic type, primary tumor size, tumor subtype, surgery,

chemotherapy, and number of metastatic organs except bone were significant independent variables of both overall survival (OS) and cancer-specific survival (CSS)[7].

In recent years, nomograms have gained increasing attention as strong prognostic statistical models with intuitive graphs to quantify risk by incorporating important factors for oncology prognostics[8]. They are a useful and convenient tool to quantify and predict risk and prognosis in cancer patients. However, no systematic attempts have ever been made to develop prognostic nomograms for BCBM patients. Therefore, in the present research, we intended to establish and validate a nomogram for those patients and assist clinicians to accurately predict patients' survival.

Material And Methods

Study Design and Patients Selection

By using SEER*stat version 8.3.5, we selected eligible patients with breast cancer between 2010 and 2015. The inclusion criteria were histologically confirmed breast cancer, age at diagnosis (codes: ≥ 18), primary tumor site (breast), and initial bone metastasis. We excluded patients with unknown follow-up information and missing information on tumor stage, histologic grade, tumor size, therapy, or marital status. The selection flow chart is shown in Fig. 1. Finally, 3885 eligible patients were enrolled into the study and randomly divided into the training cohort (70%, n = 2721) and internal validation cohort (30%, n = 1164). For this type of retrospective study, there was no need for formal consent.

Statistical Methods

The chi-square test was used to compare the rates. Univariate comparisons of survival data were performed using the Kaplan–Meier method and Cox univariate analysis. Based on the results of the univariate analysis and combined with clinically important factors, further multivariate analysis using the Cox risk regression model with backward elimination was performed. Following the multivariate analysis, variables with a $P < 0.05$ were selected for developing the nomogram.

We used 1-, 3-, and 5-years OS for the analysis in the nomogram. One thousand bootstrap resamples were used to calculate C-indexes and generate calibration plots, which assessed the predictive accuracy of the nomogram. Furthermore, a risk stratification model was developed on the basis of each patient's total scores in the nomogram to divide all of the cases into two prognostic groups according to its median value.

All of the analyses were performed using R (http://www.r-project.org) and Empower (R) (www.empowerstats.com, XY Solutions, inc. Boston MA). Statistical significance was reached when P-value was lower than 0.05 in a two-tailed test.

Results

Patient characteristics

A total of 3885 eligible female patients with BCBM from 2010 to 2015 were retrieved from the SEER database (2721 patients for the training cohort and 1164 patients for the testing cohort). The sociodemographic and clinicopathologic characteristics of the three cohorts are summarized in Table 1. The major tumor subtype for the training and testing cohorts was luminal A. In the training cohort, 458 of 2721 patients (16.8%) were diagnosed with the luminal B subtype, whereas 158 patients (5.8%) were diagnosed with the HER2-enriched subtype. Most of the patients were White (76.0%) and the median age was 59 years. Survival analysis was conducted on the selected group of patients based on different clinical characteristics. The median OS for the training and testing cohorts was 24 months.

Survival Analysis

The Kaplan–Meier analysis determined the impact of variables on survival. The results generated by the log-rank test are listed in Table 2. We found that patients with bone metastasis had poorer survival than those without distant metastasis of breast cancer ($P < 0.0001$) (Fig. 2A). In the training cohort, bone combined with other-site metastasis was associated with worse prognosis ($P < 0.0001$) (Fig. 2B). Among all of the tumor subtypes, the luminal B subtype had the most favorable survival, whereas triple negative breast cancer(TNBC) was associated with the worst prognosis ($P < 0.0001$) (Fig. 2C). Married patients had better prognosis than unmarried BCBM patients ($P < 0.0001$) (Fig. 2D). Black patients had a relatively worse prognosis than White and other races ($P < 0.0001$) (Fig. 2E). With respect to the factors associated with treatments, we found that patients who had undergone chemotherapy (yes vs. no/unknown) experienced prolonged survival (Fig. 2F).

Independent prognostic factors in the training cohort

The univariate Cox regression analysis demonstrated that age, race, marital status, tumor size, tumor subtype, grade, T classification, surgery, radiotherapy, chemotherapy, brain metastasis, liver metastasis, and lung metastasis were associated with OS. All of these factors were entered into the multivariate Cox regression analysis; age, race, marital status, tumor subtype, grade, T classification, surgery, chemotherapy, brain metastasis, liver metastasis, and lung metastasis were found to be independent prognostic factors after multivariate analysis (Table 2).

Constructing and Validating of Nomogram

For predicting the overall survival of patients, these six significant independent factors were incorporated to construct a nomogram (Fig. 3). The score of each category was given on the point scale axis (Table 2). A total score was easily calculated by adding each single score; by projecting the total score to the bottom scale, we were able to estimate the probabilities of 1-, 3-, and 5-year OS for individual patients.

The C-index of the nomogram was larger than that of the seventh version AJCC-TNM staging system (0.704 vs 0.564, $P < 0.001$), suggesting that this model had an acceptable predictive accuracy. In addition, calibration plots of the nomogram were also developed (Fig. 4); they demonstrated that the predicted OS

agreed well with the actual observations. In addition, decision curve analysis is a net benefit analysis that compares the true-positive to the weighted false-positive rates across different risk thresholds that a clinician/patient might want to accept; this analysis was performed evaluating 3-year OS of BCBM patients. As shown in Fig. 5, all of the models had a better net benefit compared with the “treat all” strategy. The net benefit of the nomogram was higher than that of the TNM stage model across most of the modeled decision threshold probabilities.

Risk stratification system

These results proved the nomogram’s efficacy in predicting survival. Thus, we calculated total points according to the nomogram-predicted score. Patients were classified into two risk groups according to the median points as follows: low risk (total score < 3094.04) and high risk (total score ≥ 3094.04). In addition, we stratified the entire cohort according to the tumor subtype. Within each subtype, the survival rates predicted by the nomogram showed significant distinctions between the Kaplan–Meier curves (Fig. 6).

Discussion

The AJCC-TNM staging classification is the most widely used system for predicting survival and selecting clinical strategies for patients with cancers[9, 10]. However, this classical system cannot always accurately predict the difference in survival between different stages[11]. Furthermore, survival of patients with the same stage varies widely. An important reason may be that we ignore many of the factors that have been confirmed to be highly associated with survival. To solve this problem, we developed a nomogram, a more comprehensive, accurate, and useful prognostic model.

As few studies have established nomograms for predicting the survival of patients with BCBM; their sample size was small and the prognostic factors were limited. Thus, we developed a clinical nomogram to predict the survival based on the SEER database. The SEER registry is the largest population-based database of cancer patients in the United States, covering approximately 26% of patients diagnosed with cancer[12]. We reviewed patients’ data from the latest version of the SEER as released in 2015 (covering 18 registries, 1973–2015) by using SEER*Stat version 8.3.5, and we also set a strict inclusion and exclusion criteria.

In this study, we identified 11 independent prognostic predictors of BC with bone metastasis. Tumor subtype was a significant factor of OS, which is in accordance with the previous studies[13]. It has also been reported that TNBC subtype, an aggressive form, shows the worst prognosis in BC patients with brain metastasis, which is consistent with our results[14]. Marital status was found to be an independent predictor of survival among BC patients with bone metastasis. Patients in the married group had better survival compared with those in the unmarried group. Tumor grade is usually recognized as an important factor of survival among BC patients[15, 16]. Our multivariate analysis also revealed that well-

differentiated tumor was significantly associated with increased survival. Moreover, patients with bone-only metastasis had better survival than those with additional distant metastases.

For metastatic BC, chemotherapy is recommended as it can prolong survival, decrease cancer-related complications, and improve quality of life[17, 18]. Our research also revealed that BCBM patients who had received chemotherapy achieved survival benefits. It is generally accepted that radiotherapy has the potential to alleviate pain and achieve good local control. Some studies reported that breast radiotherapy is associated with improved survival in patients with metastatic disease.[19] However, our multivariate analysis failed to identify radiotherapy as a significant predictor of OS. Nava et al. also supported this finding and showed no effect of breast radiotherapy on survival in patients with metastatic disease[19].

For validation of the nomogram, to guarantee that the model could be generally applied and to avoid overfitting, it is necessary to evaluate the discrimination and calibration. Discrimination has usually been evaluated with the C-index, and calibration is assessed by comparing the agreement between the predicted and the actual survival of patients[20]. The results indicated that our nomogram had a better discriminating and predicting ability than the traditional staging system. Beyond that, we also performed the decision curves analysis to study the clinical net benefit of the nomogram for BCBM patients' prognosis [21, 22]. The results showed that this model improved the clinical net benefit across all the threshold probabilities.

In addition, we constructed a system to classify patients to two risk subgroups based on predicting the total scores. When the risk stratification system was applied in patients with the different tumor subtype, it discriminated OS well in each subtype (Fig. 6). Thus, the results confirmed that this risk stratification system based on the nomogram was an accurate and reliable prognostic model. It could help clinicians to identify the patients with high risk and to perform individualized adjuvant treatment, which might also be helpful in this highly selective cohort.

Nevertheless, the present study had several limitations. First and foremost, this was a retrospective analysis, which is inherent for the SEER database. Although we performed multivariate analysis to minimize confounders associated with the heterogeneities, the retrospective nature of this study must be considered when interpreting the results. Second, the SEER database does not contain data about recurrence or specific treatment, which may affect the clinical outcome. The third limitation was that other important factors, such as specific site of bone metastasis or treatment for bone metastasis, were not included in the database.

Conclusion

The current study comprehensively analyzed the prognosis of patients with newly diagnosed BCBM based on the SEER population-level data; we developed a tool for assessing the individualized survival estimates in patients with BCBM. The developed nomogram can provide more accurate survival

information for clinicians and help them to provide appropriate treatment measures for metastatic lesions. More external validations are recommended to further refine our conclusions.

Declarations

Acknowledgments

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Author Contributions: Hai Lu and Qianjun Chen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Qianjun Chen

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Hai Lu and Qianjun Chen

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Jinqun Jiang and Yihao Wang

Obtained funding: Qianjun Chen

Administrative, technical, or material support: Rui Xu and Liping Ren

Supervision:Hai Lu and Qianjun Chen

Disclosure

The authors report no conflicts of interest in this work

References

1. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, Ruddy K, Tsang J, Cardoso F (2019) Breast cancer. NAT REV DIS PRIMERS 5(1):66
2. Tray N, Taff J, Adams S (2019) Therapeutic landscape of metaplastic breast cancer. CANCER TREAT REV 79:101888

3. Croset M, Pantano F, Kan C, Bonnelye E, Descotes F, Alix-Panabieres C, Lecellier CH, Bachelier R, Allioli N, Hong SS et al (2018) miRNA-30 Family Members Inhibit Breast Cancer Invasion, Osteomimicry, and Bone Destruction by Directly Targeting Multiple Bone Metastasis-Associated Genes. CANCER RES 78(18):5259–5273
4. Brook N, Brook E, Dharmarajan A, Dass CR, Chan A (2018) Breast cancer bone metastases: pathogenesis and therapeutic targets. Int J Biochem Cell Biol 96:63–78
5. Yousefi M, Nosrati R, Salmaninejad A, Dehghani S, Shahryari A, Saberi A (2018) Organ-specific metastasis of breast cancer: molecular and cellular mechanisms underlying lung metastasis. Cell Oncol (Dordr) 41(2):123–140
6. Yang M, Liu C, Yu X (2019) Skeletal-related adverse events during bone metastasis of breast cancer: current status. DISCOV MED 27(149):211–220
7. Wang Z, Cheng Y, Chen S, Shao H, Chen X, Wang Z, Wang Y, Zhou H, Chen T, Lin N et al (2020) Novel prognostic nomograms for female patients with breast cancer and bone metastasis at presentation. Ann Transl Med 8(5):197
8. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP: **Nomograms in oncology**: **more than meets the eye**. *LANCET ONCOL* 2015, **16**(4):e173-e180
9. Scandura G, Wagner T, Beltran L, Alifrangis C, Shamash J, Berney DM (2019) Pathological risk factors for metastatic disease at presentation in testicular seminomas with focus on the recent pT changes in AJCC TNM eighth edition. HUM PATHOL 94:16–22
10. Escrig SJ, Gomez QL, Maiocchi K (2019) The 8th edition of the AJCC-TNM classification: New contributions to the staging of esophagogastric junction cancer. Cir Esp 97(8):432–437
11. Yu C, Zhang Y (2019) Development and validation of prognostic nomogram for young patients with gastric cancer. Ann Transl Med 7(22):641
12. Doll KM, Rademaker A, Sosa JA (2018) Practical Guide to Surgical Data Sets: Surveillance, Epidemiology, and End Results (SEER) Database. JAMA SURG 153(6):588–589
13. Chen QF, Huang T, Shen L, Wu P, Huang ZL, Li W (2019) Prognostic factors and survival according to tumor subtype in newly diagnosed breast cancer with liver metastases: A competing risk analysis. Mol Clin Oncol 11(3):259–269
14. Li Y, Su P, Wang Y, Zhang H, Liang Y, Zhang N, Song X, Li X, Li J, Yang Q (2020) Impact of histotypes on preferential organ-specific metastasis in triple-negative breast cancer. Cancer Med 9(3):872–881
15. Wu SG, Zhang WW, Wang J, Lian CL, Sun JY, Chen YX, He ZY (2019) Progesterone receptor status and tumor grade predict the 21-gene recurrence score of invasive lobular breast cancer. BIOMARK MED 13(12):1005–1012
16. Whelan TJ, Julian JA, Berrang TS, Kim DH, Germain I, Nichol AM, Akra M, Lavertu S, Germain F, Fyles A et al (2019) External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. LANCET 394(10215):2165–2172

17. O'Halloran N, Lowery A, Curran C, McLaughlin R, Malone C, Sweeney K, Keane M, Kerin M (2019) A Review of the Impact of Neoadjuvant Chemotherapy on Breast Surgery Practice and Outcomes. CLIN BREAST CANCER 19(5):377–382
18. Abdel-Qadir H, Thavendiranathan P, Fung K, Amir E, Austin PC, Anderson GS, Lee DS (2019) Association of Early-Stage Breast Cancer and Subsequent Chemotherapy With Risk of Atrial Fibrillation. JAMA Netw Open 2(9):e1911838
19. Nava MB, Benson JR, Audretsch W, Blondeel P, Catanuto G, Clemens MW, Cordeiro PG, De Vita R, Hammond DC, Jassem J et al (2019) International multidisciplinary expert panel consensus on breast reconstruction and radiotherapy. Br J Surg 106(10):1327–1340
20. Luo WQ, Huang QX, Huang XW, Hu HT, Zeng FQ, Wang W (2019) Predicting Breast Cancer in Breast Imaging Reporting and Data System (BI-RADS) Ultrasound Category 4 or 5 Lesions: A Nomogram Combining Radiomics and BI-RADS. Sci Rep 9(1):11921
21. Lu YG, Pan ZY, Zhang S, Lu YF, Zhang W, Wang L, Meng XY, Yu WF: **Living Donor Liver Transplantation in Children**: **Perioperative Risk Factors and a Nomogram for Prediction of Survival**. *TRANSPLANTATION* 2019
22. Hou X, Wang D, Zuo J, Li J, Wang T, Guo C, Peng F, Su D, Zhao L, Ye Z et al (2019) Development and validation of a prognostic nomogram for HIV/AIDS patients who underwent antiretroviral therapy: Data from a China population-based cohort. EBIOMEDICINE 48:414–424

Tables

Table 1. Patients Demographics and Clinicopathological Characteristics.

Factors	Entire cohort (n=3885)		Training cohort (n=2721)		Validation cohort (n=1164)	
	N	%	N	%	N	%
Age at diagnosis, years						
Median	59		59		60	
Range	22-103		22-103		23-96	
Race						
White	2938	75.6	2069	76.0	869	74.7
Black	553	14.2	381	14.0	172	14.8
Other	394	10.1	271	10.0	123	10.6
Marital status						
Married	1851	47.6	1277	46.9	574	49.3
Unmarried[a]	2034	52.4	1444	53.1	590	50.7
YOD						
2010-2012	1987	51.2	1393	51.2	594	51.0
2013-2015	1898	48.8	1328	48.8	570	49.0
Laterality						
Left	1988	51.2	1388	51.0	600	51.5
Right	1897	48.8	1333	49.0	564	48.5
Tumor size, diameter, cm						
≤1	2552	65.7	1793	65.9	759	65.2
1	1333	34.3	928	34.1	405	34.8
Subtype						
Luminal A	2630	67.7	1849	68.0	781	67.1
Luminal B	640	16.5	458	16.8	182	15.6
HER2 enriched	238	6.1	158	5.8	80	6.9
Triple negative	377	9.7	256	9.4	121	10.4
Histologic grade						

Well	391	10.1	274	10.1	117	10.1
Moderately	1838	47.3	1307	48.0	531	45.6
Poorly	1656	42.6	1140	41.9	516	44.3
T						
T1	563	14.5	396	14.5	167	14.3
T2	1349	34.7	952	35.0	397	34.1
T3	703	18.1	487	17.9	216	18.6
T4	1270	32.7	886	32.6	384	33.0
N						
N0	974	25.1	696	25.6	278	23.9
N1	1841	47.4	1293	47.5	548	47.1
N2	493	12.7	336	12.4	157	13.5
N3	577	14.9	396	14.6	181	15.5
Surgery						
None	2515	64.7	1767	64.9	748	64.3
Yes	1370	35.3	954	35.1	416	35.7
Radiotherapy						
None	3031	78.0	2119	77.9	912	78.4
Yes	854	22.0	602	22.1	252	21.6
Chemotherapy						
None	1755	45.2	1227	45.1	528	45.4
Yes	2130	54.8	1494	54.9	636	54.6
Brain metastasis						
None	3636	92.6	2544	93.5	1092	93.8
Yes	249	6.4	177	6.5	72	6.2
Liver metastasis						
None	3036	78.2	2133	78.4	903	77.6

Yes	849	21.8	588	21.6	261	22.4
Lung metastasis						
None	2909	74.9	2041	75.0	868	74.6
Yes	976	25.1	680	25.0	296	25.4
Follow-up, months						
Median	24		24		24	

Note: YOD, year of diagnosis.

Table 2. Univariate and multivariate analysis for the training cohort

Factors	Univariate analysis			Multivariate analysis			Score
	HR	95% CI	*p**	HR	95% CI	*p***	
Age at diagnosis, years							
≤59	1			1			0
59	1.6	1.4, 1.7	<0.001	1.5	1.4,1.7	**<0.001**	50
Race							
White	1						0
Black	1.5	1.3, 1.7	<0.001	1.3	1.1,1.5	**<0.001**	3
Other	1.0	0.8,1.2	0.967	0.9	1.8,1.1	0.296	6
Marital status							
Married	1			1			0
Unarried	1.4	1.3,1.5	<0.001	1.2	1.1,1.4	**<0.001**	22
YOD							
2010-2012	1						
2013-2015	1.0	0.9,1.1	0.778				
Laterality							
Left	1						
Right	1.0	0.9,1.2	0.387				
Tumor size, diameter, cm							
≤1	1			1			
1	0.6	0.5,0.6	<0.001	0.9	0.7,1.2	0.453	
Subtype							
Luminal A	1			1			0
Luminal B	0.8	0.7,0.9	<0.001	0.7	0.6,0.8	**<0.001**	33
HER2 enriched	1.1	0.9,1.4	0.435	0.9	0.7,1.1	0.376	67
Triple negative	3.0	2.6,3.5	<0.001	2.9	2.4,3.4	**<0.001**	100
Histologic grade							
Well	1			1			0
Moderately	1.3	1.1,1.6	0.004	1.4	1.1,1.7	**0.001**	24

Poorly	1.8	1.5,2.2	<0.001	1.8	1.5,2.2	**<0.001**	49
T							
T1	1			1			0
T2	1.0	0.8,1.1	0.538	1.0	0.8,1.1	0.613	10
T3	1.1	0.9,1.4	0.189	1.1	0.9,1.4	0.178	20
T4	1.5	1.3,1.8	<0.001	1.2	1.0,1.4	**0.022**	30
N							
N0	1						
N1	1.0	0.9,1.1	0.859				
N2	0.9	0.8,1.1	0.301				
N3	1.1	1.0,1.3	0.137				
Surgery							
None	1			1			58
Yes	0.5	0.5,0.6	<0.001	0.7	0.5,0.9	**0.012**	0
Radiotherapy							
None	1			1			
Yes	0.6	0.6,0.7	<0.001	0.9	0.8,1.0	0.143	
Chemotherapy							
None	1			1			51
Yes	0.8	0.7,0.9	<0.001	0.7	0.6,0.8	**<0.001**	0
Brain metastasis							
None	1			1			0
Yes	2.5	2.1,2.9	<0.001	2.1	1.7,2.5	**<0.001**	77
Liver metastasis							
None	1			1			0
Yes	1.9	1.7,2.1	<0.001	1.8	1.5,2.0	**<0.001**	50
Lung metastasis							
None	1			1			0
Yes	1.6	1.4,1.8	<0.001	1.2	1.0,1.3	**0.011**	19

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; YOD, year of diagnosis.

*p<0.1 was considered significant in univariate Cox-Regression analysis.

** p<0.05 was considered significant in multivariate Cox-Regression analysis.

Figures

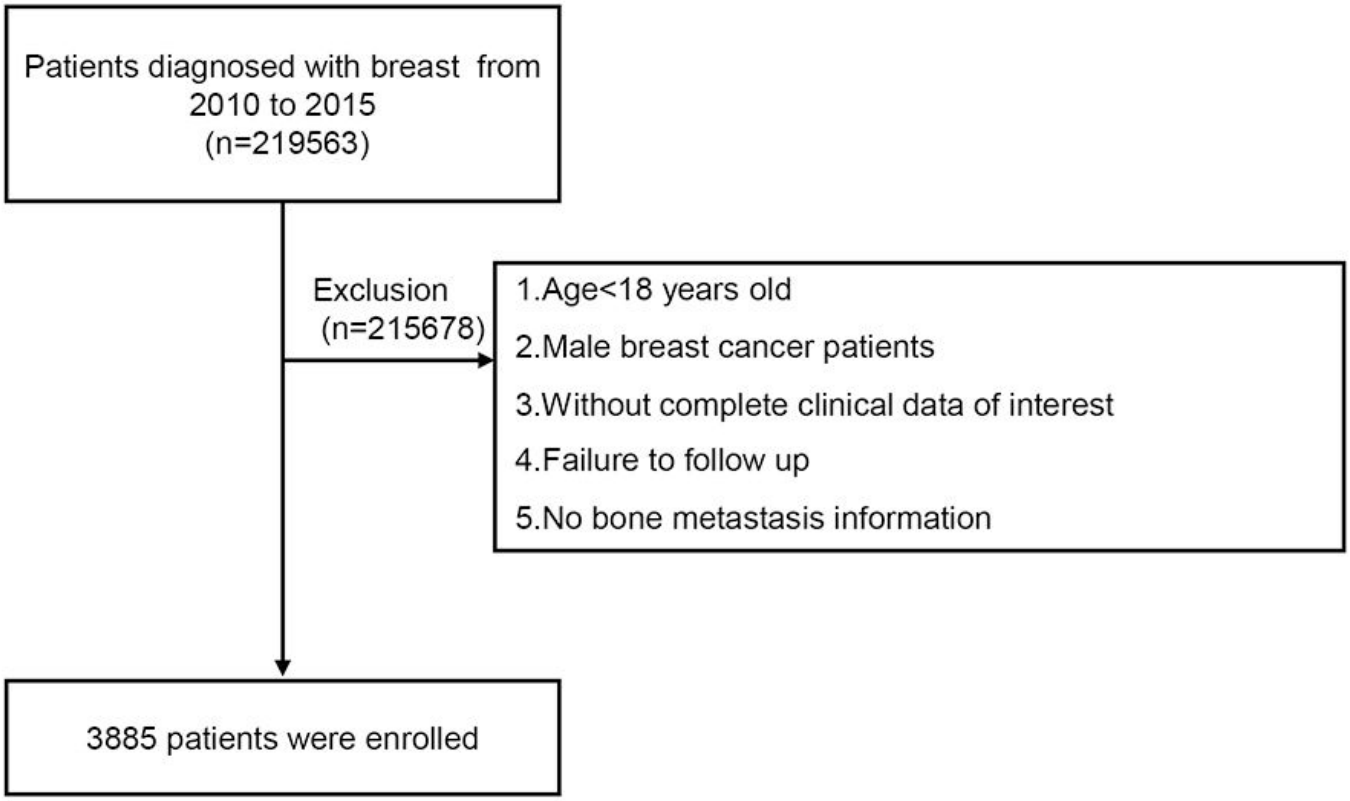

Figure 1

Flow chart of the selection of the study population.

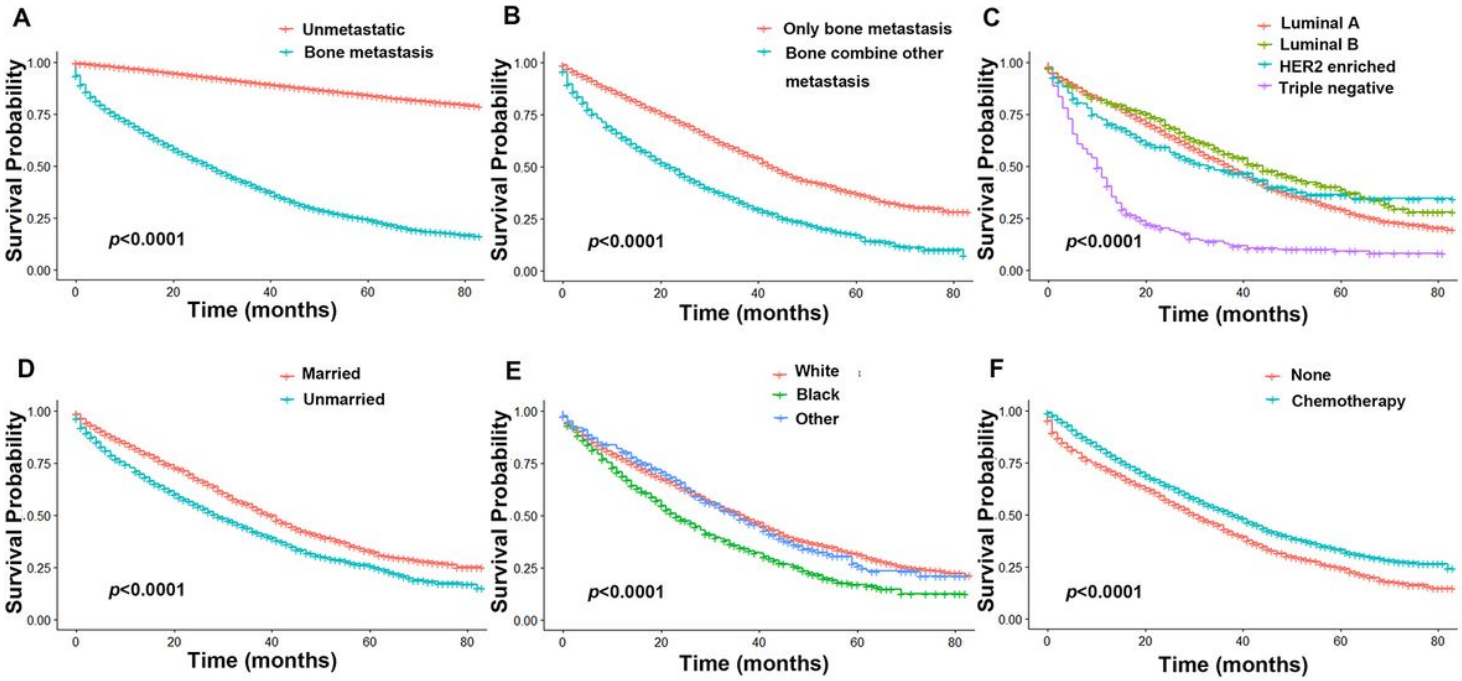

Figure 2

Overall survival (OS) among patients with newly diagnosed breast cancer bone metastasis (BCBM). Survival curves for patients with BCBM and non-metastatic breast cancer (A). Overall survival for patients with BCBM stratified by other metastasis site except bone (B), tumor subtypes (C), marital status (D), race (E), and chemotherapy (F).

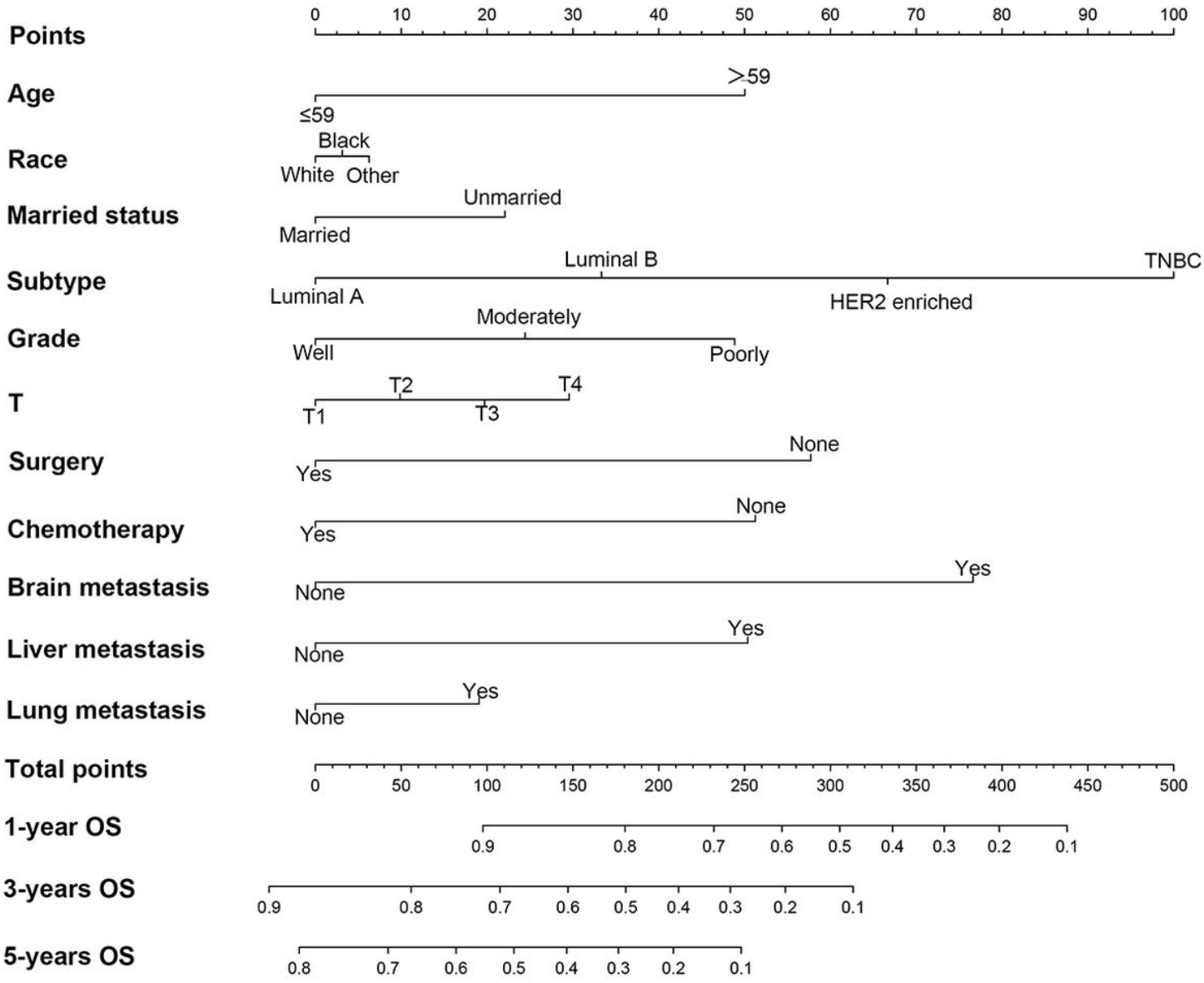

Figure 3

Nomogram predicting 1-, 3-, and 5-year overall survival in BCBM patients.

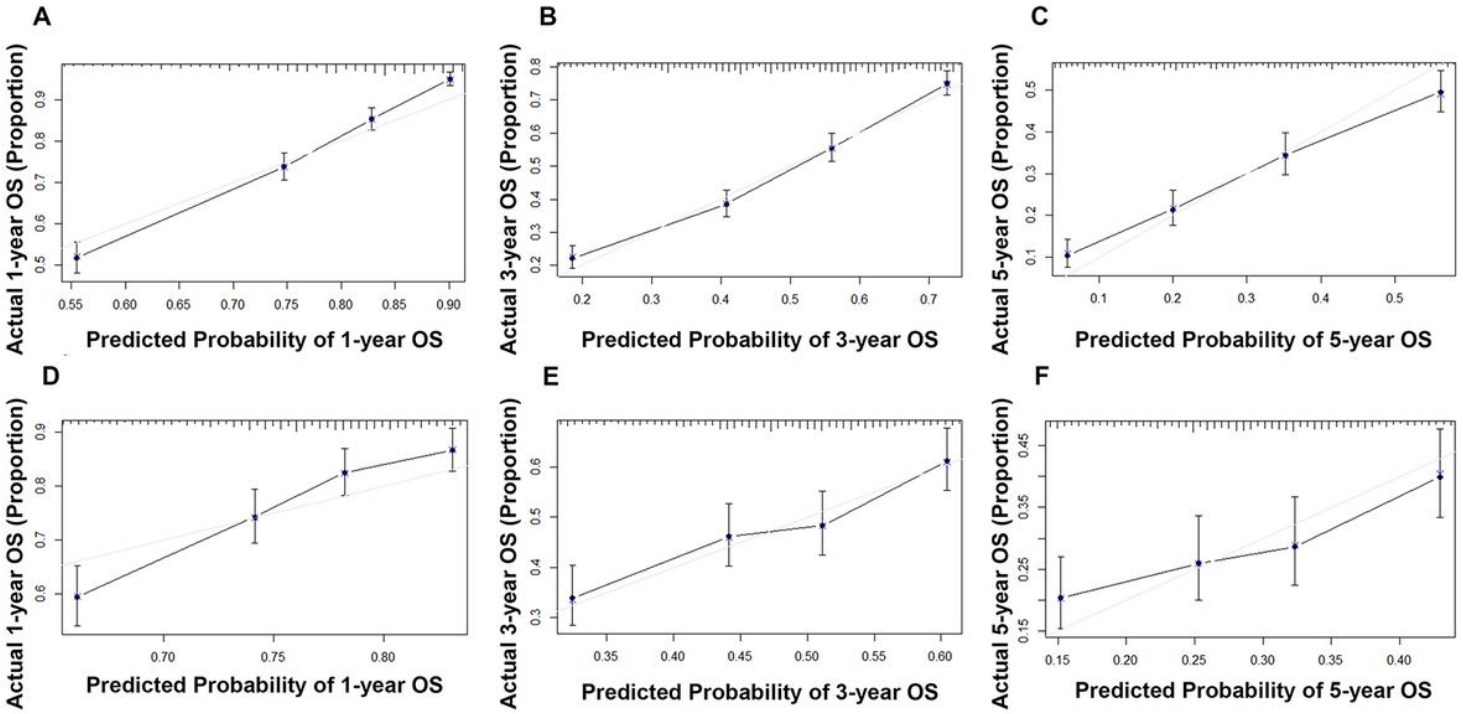

Figure 4

The calibration curves predicting 1-, 3-, and 5-year overall survival in the training cohort (A, B, C) and validation cohort (D, E, F).

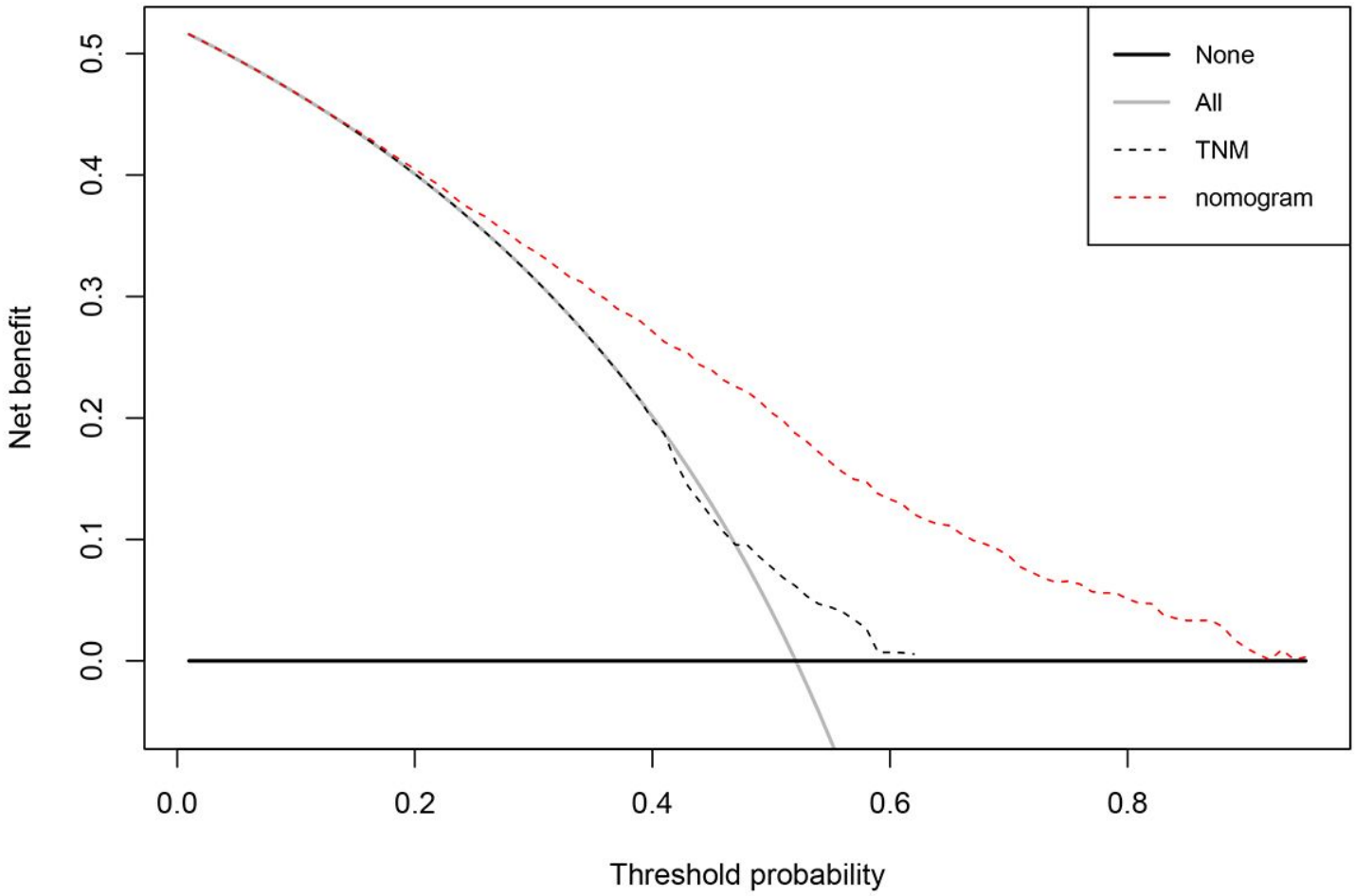

Figure 5

Decision curve analysis to show the comparison of performance. The horizontal black solid line represents the assumption that no patient should take the necessary measures, while the grey solid line represents the assumption that all patients should take the necessary measures. The y-axis represents the net benefit, which was calculated by adding points associated with benefits and subtracting those associated with harms. Based on the threshold probabilities obtained, our findings indicated that the nomogram model (grey dotted line) provided a greater net benefit than the clinical model (red dotted line) and TNM staging model (grey dotted line).

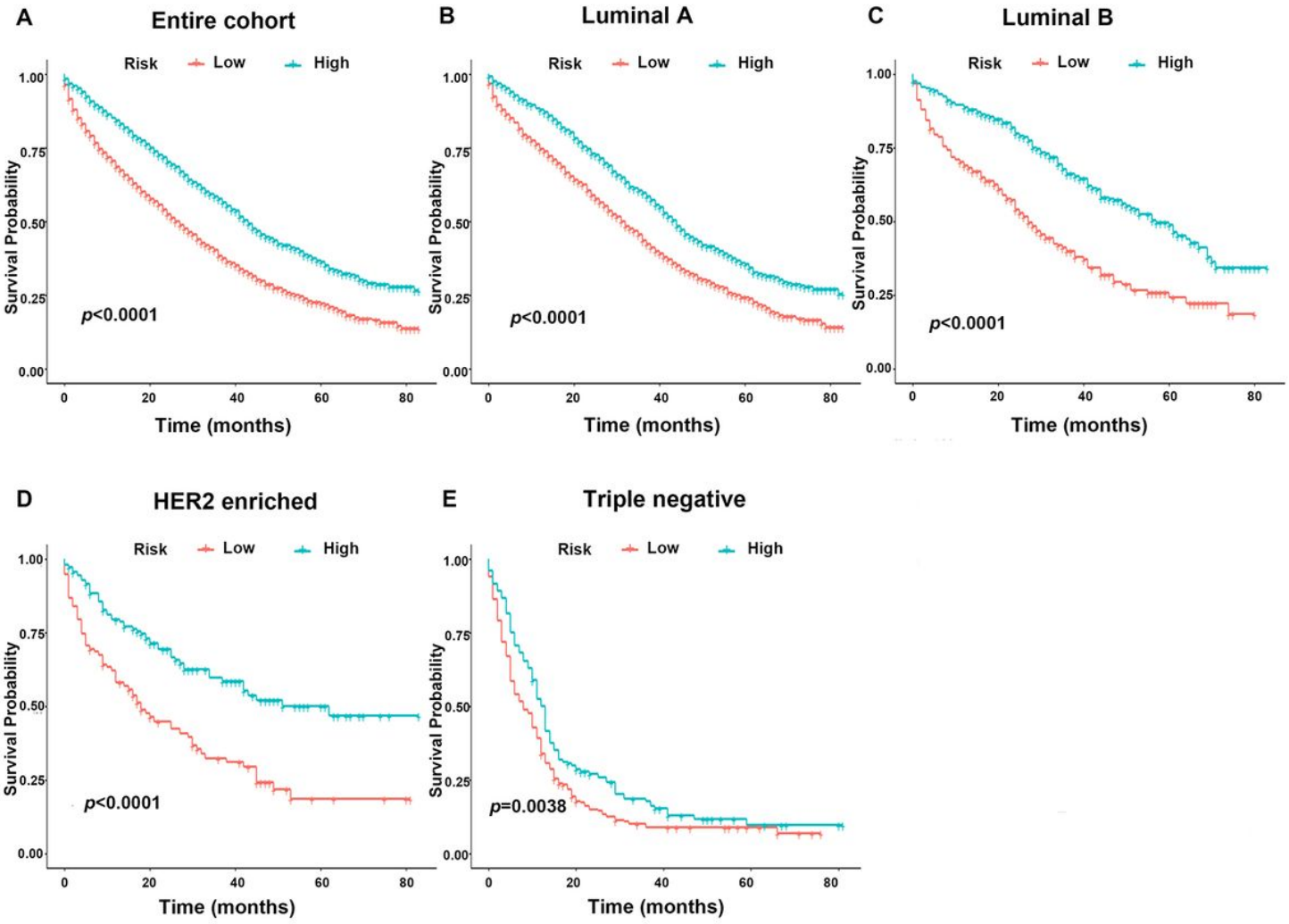

Figure 6

Risk stratification of the nomogram. The Kaplan–Meier curve for OS in the entire cohort (A), Luminal A (B), Luminal B (C), and triple-negative breast cancer (D) patients.