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*Original Article*

# Incidence, prognosis and nomograms of breast cancer with bone metastases at initial diagnosis: a large population-based study

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**Abstract:** Background: Bone is the most common metastatic site for breast cancer, and patients' condition will deteriorate when it occurs. Methods: We performed a retrospective analysis on 6482 breast cancer patients with bone metastases (BCBM), who were selected from the Surveillance, Epidemiology, and End Result (SEER) 18 registry database. The optimal age cut-points were generated by using the X-tile software. By using Cox regression, we selected independent prognostic factors from 21 variables, and plotted a visual nomogram to predict the probability of surviving to the median survival time. We also diagrammed a competing risk nomogram on the basis of competitive risk model. Results: Compared with other three common metastatic sites, the incidence of bone metastasis was the highest for patients with breast cancer. The incidence of BCBM peaked around the age of 60, and a large majority of patients were between the ages of 50 and 70. The survival rate decreased with age, and the median survival time was about 19 months. Factors of age, race, marital status, grade, human epidermal growth factor receptor-2 (HER2) receptor, hormone receptor, concurrent brain metastasis, concurrent liver metastasis, concurrent lung metastasis, surgery and chemotherapy are strongly related to the prognosis of patients with BCBM. It was revealed that the C-index of the nomogram was 0.72 and the calibration curves showed good agreement between the nomogram prediction and actual observation. Conclusion: Our practical nomograms provide a visual and user-friendly tool in the risk evaluation and prognostic prediction for breast cancer patients with bone metastases.

**Keywords:** Breast cancer, bone metastasis, surveillance, epidemiology, and end result (SEER), prognosis, nomograms

## Introduction

Nowadays, breast cancer is one of the biggest threats to women's health. According to the global cancer statistics in 2018, breast cancer is the second most common malignant tumor worldwide, accounting for 11.6% of all cases and 6.6% of all death [1]. As for the United States, there were 279,100 new cases in 2020, and 42,690 people died of breast cancer. For female, breast cancer is the most commonly diagnosed cancer (30% of female cases), and the second leading cause of death (15% of female cancer deaths), according to the statistics provided by *Cancer Statistics, 2020* [2].

Breast cancer metastases accounts for the majority of deaths from breast cancer, while bone is the most common site of metastases. Spine, ribs, pelvis, and long bones are sites that most commonly develop metastases in patients with breast cancer. Previous studies demonstrated that the median survival time of patients with breast cancer is about 24-55 months after detection of bone metastases [3-5]. The clinical course of breast cancer with bone metastasis (BCBM) is relatively long, with patients suffering from bone pain, fractures, hypercalcemia or spinal cord compression over a period of several years, which has a significantly negative impact on patients' survival and quality of life [6-9].

The systematic therapy has been widely applied to breast cancer, which includes radiotherapy, neoadjuvant chemotherapy, endocrine therapy and surgery for primary/metastatic sites. Especially, the development of targeted drugs, like Trastuzumab and Pyrotinib, improves the quality of life and prolongs survival of patients significantly.

Despite some studies of BCBM have done before [10, 11], the features and epidemiology of BCBM is still not completely clear. Thus, the aim of our study was to figure out the characteristics and possible prognostic factors of patients with BCBM as comprehensive as we can and analyze their connections with patients' prognosis. Based on the Surveillance, Epidemiology, and End Result (SEER) database, the prognostic factors of patients' information, characteristics of tumors and therapy record were all dug out and put into our analyses.

## Materials and methods

### *Data source and study population*

Our study was based on the SEER Program, which is one of the most representative large cancer registry databases in the United States, supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS). Including criteria: breast cancer patients with bone metastasis at initial diagnosis of all ages and races between January 1, 2010 and December 31, 2016. Patients whose detailed information was unknown or unspecified, or whose survival time was equal to zero were excluded. Cases with the other three main metastases from breast cancer were dealt with in the same way in order to compare with each other.

### *Data components*

As is exhibited in **Table 1**, we selected 21 prognostic variables in this study, which could be roughly separated into three parts. The first part is demographic information including age at diagnosis, gender, race and marital status. It should be clearly noted that we categorized marital status into three groups. "Unmarried" included unmarried and single ones and "Other" included widowed, divorced and separated ones. Then, the next section contained some characteristics related to the tumor, like the total number of in situ/malignant tumors, primary site, histological type and the next eleven variables. In addition, histological types were sorted according to the International Classification of Diseases for Oncology, 3rd Edition (IDO-0-3) codes: "8500. Intraductal carcinoma", which accounted for three-quarters of the total, and the rest was defined as "Other" for the reasonableness of analysis. In terms of the 8$^{th}$ edition of the TNM staging guideline released by the Union for International Cancer Control (UICC), we stratified tumor sizes into three levels, and removed cases with tumor size appearing as zero or "990-999". What is more, for the accuracy of the study, patients with ambiguous or not applicable details were excluded as well. The last section was treatments: surgery, radiotherapy and chemotherapy, which were known as the major methods of cancer treatment.

We accessed all the primary research data through the SEER*Stat client-server system after we signed the Research Data Agreement on SEER website (http://seer.cancer.gov/data) and got an account.

### *Statistical analysis*

Age is a continuous variable. So, in order to show the association between OS and different ages more obviously, we stratified patients' ages with the X-tile software [12], which was developed to provide the optimal cut-points and illustrate the robustness of the relationship between a biomarker and outcome. Based on Kaplan-Meier method, the optimal cutoff points of ages were confirmed as 55 and 80 years (**Figure 1A** and **1B**), and the survival curve for age subgroups (**Figure 1C**) was also plotted according to overall survival (OS).

The incidence of cases with four main metastases diagnosed from 2010 to 2016 was illustrated by a broken-line graph (**Figure 2A**) to visualize the trend of disease. The relative survival rates of patients with different metastatic sites and non-metastatic individuals were displayed through a survival curve by using Kaplan-Meier method for OS (**Figure 2B**). And survival curves for race, marital status, grade, HER2, ER, PR, concurrent brain metastasis, concurrent liver metastasis, concurrent lung metastasis, surgery and chemotherapy were created in the same way (**Figure 3**). The

**Table 1.** Characteristics of patients with metastatic breast cancer to bones

| Characteristics | Total (n=6482) | | Population (n=74448) | |
|---|---|---|---|---|
| | N | Percent | N | Percent |
| Age, years | | | | |
| 0-54 | 2350 | 36.3 | 25726 | 34.6 |
| 55-79 | 3573 | 55.1 | 42021 | 56.4 |
| 80+ | 559 | 8.6 | 6701 | 9.0 |
| Gender | | | | |
| Female | 6390 | 98.6 | 73891 | 99.3 |
| Male | 92 | 1.4 | 557 | 0.7 |
| Race | | | | |
| White | 4987 | 76.9 | 57106 | 76.7 |
| Black | 994 | 15.3 | 7418 | 10.0 |
| Other | 501 | 7.7 | 9924 | 13.3 |
| Marital status | | | | |
| Married | 3146 | 48.5 | 42906 | 57.6 |
| Unmarried | 1539 | 23.7 | 12694 | 17.1 |
| Other | 1797 | 27.7 | 18848 | 25.3 |
| Total number of in situ/malignant tumors for patient | | | | |
| N=1 | 5920 | 91.3 | 68496 | 92.0 |
| N>1 | 562 | 8.7 | 5952 | 8.0 |
| Primary site | | | | |
| Nipple | 30 | 0.5 | 268 | 0.4 |
| Central portion | 503 | 7.8 | 3850 | 5.2 |
| Upper-inner quadrant | 471 | 7.3 | 9105 | 12.2 |
| Lower-inner quadrant | 273 | 4.2 | 4113 | 5.5 |
| Upper-outer quadrant | 1794 | 27.7 | 25906 | 34.8 |
| Lower-outer quadrant | 382 | 5.9 | 5615 | 7.5 |
| Axillary tail | 38 | 0.6 | 304 | 0.4 |
| Overlapping lesion | 1431 | 22.1 | 17266 | 23.2 |
| Breast, NOS | 1560 | 24.1 | 8021 | 10.8 |
| Histologic type | | | | |
| Intraductal carcinoma | 4926 | 76.0 | 56214 | 75.5 |
| Other | 1556 | 24.0 | 18234 | 24.5 |
| Grade | | | | |
| Grade I | 581 | 9.0 | 17572 | 23.6 |
| Grade II | 3049 | 47.0 | 32606 | 43.8 |
| Grade III | 2829 | 43.6 | 24125 | 32.4 |
| Grade IV | 23 | 0.4 | 145 | 0.2 |
| Laterality | | | | |
| Left-origin of primary | 3337 | 51.5 | 37545 | 50.4 |
| Right-origin of primary | 3137 | 48.4 | 36888 | 49.5 |
| Bilateral | 8 | 0.1 | 15 | 0.1 |
| Tumor size | | | | |
| [0, 2] | 991 | 15.3 | 41518 | 55.8 |
| [2, 5] | 3079 | 47.5 | 24926 | 33.5 |
| >5 | 2412 | 37.2 | 8004 | 10.8 |
| HER2 | | | | |
| Negative | 4940 | 76.2 | 62654 | 84.2 |
| Positive | 1542 | 23.8 | 11794 | 15.8 |

| | | | | |
|---|---|---|---|---|
| ER | | | | |
| Negative | 1094 | 16.9 | 12477 | 16.8 |
| Positive | 5388 | 83.1 | 61971 | 83.2 |
| PR | | | | |
| Negative | 1994 | 30.8 | 20365 | 27.4 |
| Positive | 4488 | 69.2 | 54083 | 72.6 |
| T | | | | |
| T1 | 819 | 12.6 | 41183 | 55.3 |
| T2 | 2414 | 37.2 | 23324 | 31.3 |
| T3 | 1283 | 19.8 | 5661 | 7.6 |
| T4 | 1966 | 30.3 | 4280 | 5.7 |
| N | | | | |
| N0 | 1399 | 21.6 | 48234 | 64.8 |
| N1 | 3144 | 48.5 | 18853 | 25.3 |
| N2 | 890 | 13.7 | 4299 | 5.8 |
| N3 | 1049 | 16.2 | 3062 | 4.1 |
| Concurrent brain metastasis | | | | |
| No/Unknown | 6107 | 94.2 | - | - |
| Yes | 375 | 5.8 | - | - |
| Concurrent liver metastasis | | | | |
| No/Unknown | 5068 | 78.2 | - | - |
| Yes | 1414 | 21.8 | - | - |
| Concurrent lung metastasis | | | | |
| No/Unknown | 4957 | 76.5 | - | - |
| Yes | 1525 | 23.5 | - | - |
| Surgery | | | | |
| No/Unknown | 4189 | 64.6 | 7572 | 10.2 |
| Yes | 2293 | 35.4 | 66876 | 89.8 |
| Radiation | | | | |
| No/Unknown | 3874 | 59.8 | 31509 | 42.3 |
| Yes | 2608 | 40.2 | 42939 | 57.7 |
| Chemotherapy | | | | |
| No/Unknown | 2651 | 40.9 | 42128 | 56.6 |
| Yes | 3831 | 59.1 | 32320 | 43.4 |
| Survival months (median [IQR]) | 19.00 [8.00, 36.00] | | 33.00 [16.00, 55.00] | |

differences among subgroups were tested by log-rank test. What is more, a density curve for patients with BCBM (**Figure 2C**) was performed to reveal the distribution of bone metastasis by age.

*Prognostic nomogram for OS*

We analyzed the relationship between OS and all the 21 prognostic factors by using Cox proportional hazard regression. Univariate and multivariate Cox proportional hazard regressions were performed in sequence, calculating hazard ratios (HR) and their 95% confidence intervals (CI), to select independent prognostic factors for OS (**Table 2**). The results were illustrated by a forest plot (**Figure 4**). After that, an exquisite nomogram (**Figure 5A**) was developed and tested by C-index and calibration curve (**Figure 5B-D**). Furthermore, on the basis of previous research, we established a competitive risk model and another nomogram (**Figure 6**) to evaluate the outcome after eliminating the effects of competing risk events. *P* values less than 0.05 were considered significant.

All statistical analyses were completed using the R software with relative R packages and

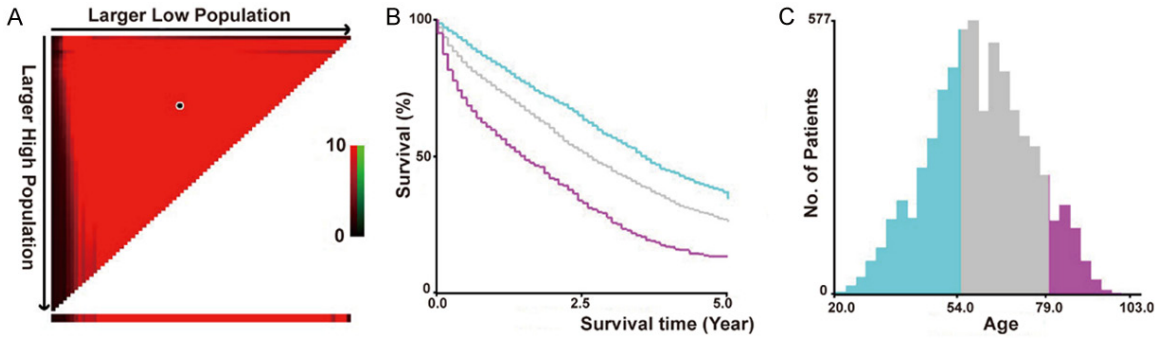


**Figure 1.** It shows patient age divided at the optimal cut-points.

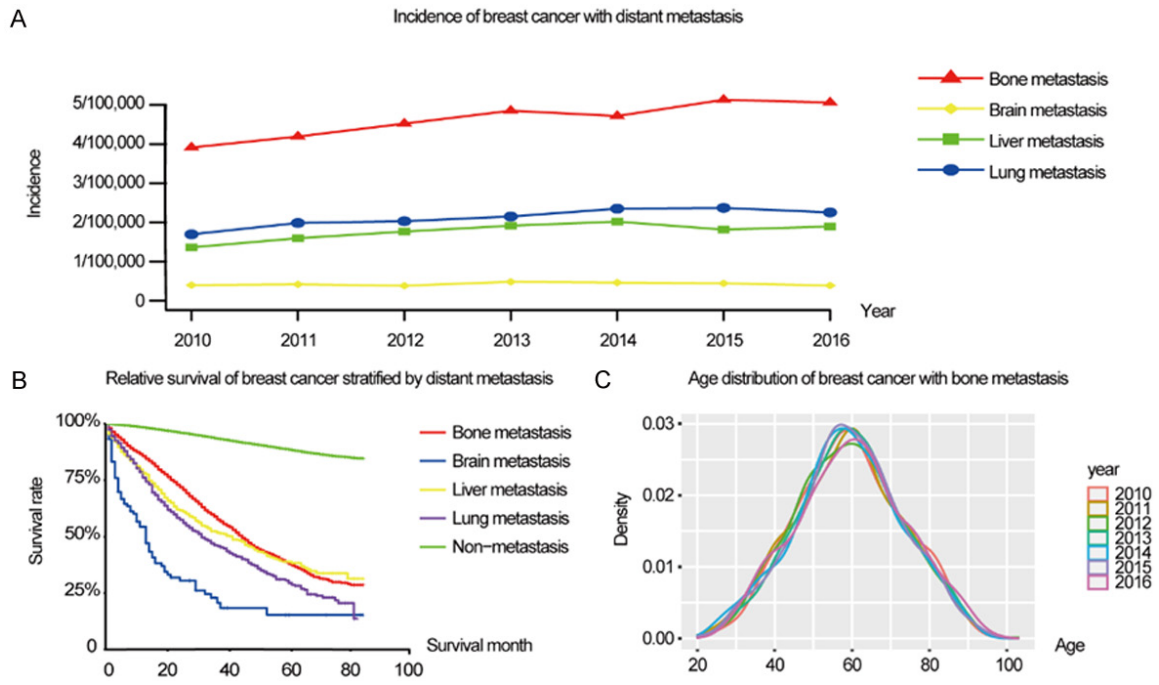


**Figure 2.** A. Incidence of breast cancer with distant metastasis; B. Relative survival of breast cancer stratified by distant metastasis; C. Age distribution of breast cancer with bone metastasis.

functions such as survival, rms, ggplot2 packages and so on (version 4.0.2; http://www.r-projecct.org/).

## Results

### *Patient characteristics*

There were 74,448 cases diagnosed with breast cancer in the United States between 2010 and 2016, whose information was complete on our 21 variables. And a total of 6,482 patients with bone metastasis were included in our research after excluding unspecified or not applicable data.

The demographic details, characteristics of tumors and therapy information are displayed in **Table 1**. According to the optimal cut-off points provided by X-tile program, we divided ages into three groups: 0-54 years (36.3%), 55-79 years (55.1%) and 80+ years (8.6%). Female (98.6%) made up the majority of the population. More than three quarters of the total were white patients (76.9%), along with 15.3% of black patients and 7.7% of other race patients (included American Indian/Alaska Native and Asian/Pacific Islander). As for marital status, 3146 (48.5%) patients were married, 1539 (23.7%) patients were unmarried (included unmarried or single ones), and 1797 (27.7%)

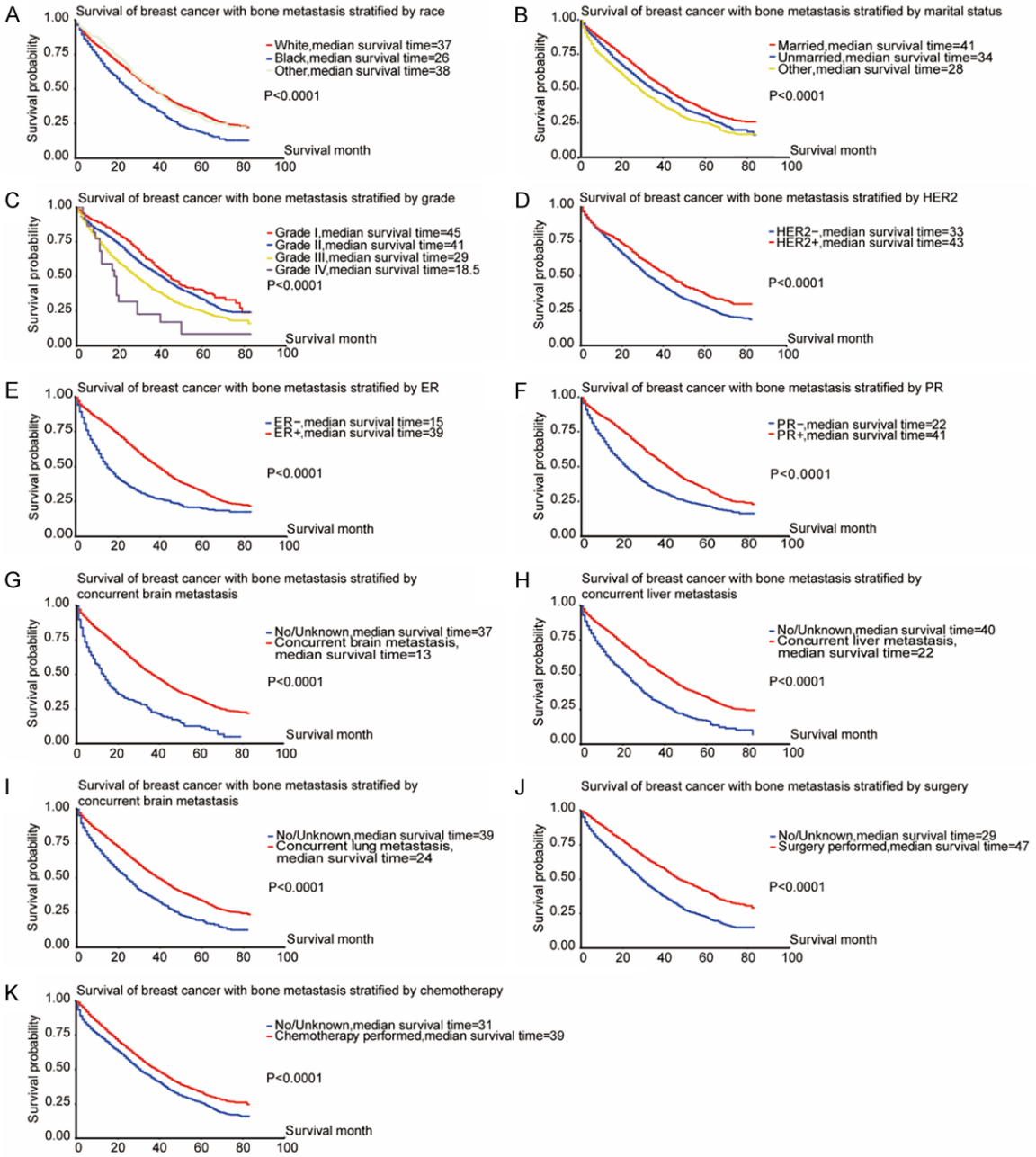


**Figure 3.** A. Survival of breast cancer with bone metastasis stratified by race; B. Survival of breast cancer with bone metastasis stratified by marital status; C. Survival of breast cancer with bone metastasis stratified by grade; D. Survival of breast cancer with bone metastasis stratified by HER2; E. Survival of breast cancer with bone metastasis stratified by ER; F. Survival of breast cancer with bone metastasis stratified by PR; G. Survival of breast cancer with bone metastasis stratified by concurrent brain metastasis; H. Survival of breast cancer with bone metastasis stratified by concurrent liver metastasis; I. Survival of breast cancer with bone metastasis stratified by concurrent lung metastasis; J. Survival of breast cancer with bone metastasis stratified by surgery; K. Survival of breast cancer with bone metastasis stratified by chemotherapy.

patients were widowed, divorced or separated, who had negative marital experience, classified as “Other”.

Most patients in our study had only one single tumor site (91.3%), while the rest were affected with multiple sites. Upper-outer quadrant (27.7%) was the most predilection site of breast cancer. In the light of the IDO-0-3 codes, histologic type was predominantly categorized as “Intraductal carcinoma” (76%), so, in order to ensure comparability, we classified the rest as

**Table 2.** Univariable and multivariable COX regression for patients of bone metastasis at diagnosis of breast cancer

| Characteristics | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Hazard ratios (95% CI) | P | Hazard ratios (95% CI) | P |
| Age, years | | | | |
| 0-54 | Reference | <0.001 | Reference | |
| 55-79 | 1.427 (1.319-1.543) | | 1.309 (1.205-1.421) | <0.001 |
| 80+ | 2.426 (2.152-2.736) | | 2.072 (1.809-2.373) | <0.001 |
| Gender | | | | |
| Female | Reference | 0.226 | - | |
| Male | 1.193 (0.897-1.586) | | - | |
| Race | | | | |
| White | Reference | <0.001 | Reference | |
| Black | 1.477 (1.350-1.617) | | 1.391 (1.266-1.529) | <0.001 |
| Other | 0.952 (0.829-1.094) | | 0.955 (0.831-1.099) | 0.523 |
| Marital status | | | | |
| Married | Reference | <0.001 | Reference | |
| Unmarried | 1.230 (1.125-1.344) | | 1.106 (1.009-1.212) | 0.031 |
| Other | 1.523 (1.404-1.652) | | 1.219 (1.118-1.328) | <0.001 |
| Total number of in situ/malignant tumors for patient | | | | |
| N=1 | Reference | 0.003 | Reference | |
| N>1 | 0.824 (0.725-0.936) | 8.7 | 0.895 (0.787-1.018) | 0.091 |
| Primary site | | | | |
| Nipple | Reference | 0.662 | - | |
| Central portion | 0.809 (0.488-1.343) | | - | |
| Upper-inner quadrant | 0.828 (0.498-1.376) | | - | |
| Lower-inner quadrant | 0.929 (0.554-1.558) | | - | |
| Upper-outer quadrant | 0.895 (0.546-1.468) | | - | |
| Lower-outer quadrant | 0.730 (0.436-1.221) | | - | |
| Axillary tail | 1.109 (0.589-2.088) | | - | |
| Overlapping lesion | 0.837 (0.510-1.375) | | - | |
| Breast, NOS | 1.045 (0.637-1.714) | | - | |
| Histologic type | | | | |
| Intraductal carcinoma | Reference | 0.167 | - | |
| Other | 1.059 (0.976-1.148) | | - | |
| Grade | | | | |
| Grade I | Reference | <0.001 | Reference | |
| Grade II | 1.234 (1.072-1.422) | | 1.261 (1.094-1.454) | 0.001 |
| Grade III | 1.723 (1.498-1.982) | | 1.680 (1.451-1.944) | <0.001 |
| Grade IV | 2.787 (1.745-4.453) | | 2.245 (1.398-3.606) | <0.001 |
| Laterality | | | | |
| Left-origin of primary | Reference | 0.061 | - | |
| Right-origin of primary | 1.043 (0.972-1.118) | | - | |
| Bilateral | 2.153 (0.966-4.801) | | - | |
| Tumor size | | | | |
| [0, 2] | Reference | <0.001 | Reference | |
| [2, 5] | 0.953 (0.858-1.059) | | 1.048 (0.828-1.326) | 0.696 |
| >5 | 1.244 (1.118-1.358) | | 1.222 (0.980-1.524) | 0.075 |
| HER2 | | | | |
| Negative | Reference | <0.001 | Reference | |

| | | | | |
|---|---|---|---|---|
| Positive | 0.781 (0.715-0.852) | | 0.535 (0.485-0.590) | <0.001 |
| ER | | | | |
| Negative | Reference | <0.001 | Reference | |
| Positive | 0.488 (0.448-0.531) | | 0.623 (0.554-0.700) | <0.001 |
| PR | | | | |
| Negative | Reference | <0.001 | Reference | |
| Positive | 0.553 (0.514-0.594) | | 0.646 (0.586-0.712) | <0.001 |
| T | | | | |
| T1 | Reference | <0.001 | Reference | |
| T2 | 0.940 (0.836-1.058) | | 0.917 (0.705-1.192) | 0.517 |
| T3 | 1.146 (1.008-1.303) | | 0.912 (0.709-1.174) | 0.474 |
| T4 | 1.382 (1.228-1.556) | | 1.023 (0.809-1.292) | 0.852 |
| N | | | | |
| N0 | Reference | 0.090 | - | |
| N1 | 0.942 (0.861-1.031) | | - | |
| N2 | 0.901 (0.799-1.016) | | - | |
| N3 | 0.958 (0.856-1.073) | | - | |
| Concurrent brain metastasis | | | | |
| No/Unknown | Reference | <0.001 | Reference | |
| Yes | 2.394 (2.111-2.716) | | 1.975 (1.728-2.257) | <0.001 |
| Concurrent liver metastasis | | | | |
| No/Unknown | Reference | <0.001 | Reference | |
| Yes | 1.915 (1.770-2.072) | | 1.795 (1.646-1.957) | <0.001 |
| Concurrent lung metastasis | | | | |
| No/Unknown | Reference | <0.001 | Reference | |
| Yes | 1.672 (1.548-1.806) | | 1.289 (1.189-1.398) | <0.001 |
| Surgery | | | | |
| No/Unknown | Reference | <0.001 | Reference | |
| Yes | 0.560 (0.519-0.604) | | 0.626 (0.578-0.679) | <0.001 |
| Radiation | | | | |
| No/Unknown | Reference | 0.025 | Reference | |
| Yes | 0.922 (0.859-0.990) | | 0.987 (0.916-1.063) | 0.729 |
| Chemotherapy | | | | |
| No/Unknown | Reference | <0.001 | Reference | |
| Yes | 0.746 (0.695-0.800) | | 0.698 (0.643-0.758) | <0.001 |

"Other". A large number of patients were identified as grade II (47.0%) and grade III (43.6%). There was a slight left breast predominance (51.5%) versus the right (48.4%). Patients with tumor size 2-5 cm occupied 47.5% of the population. The positive results of human epidermal growth factor receptor-2 (HER2), estrogen receptor (ER) and progesterone receptor (PR) accounted for 23.8%, 83.1% and 69.2% respectively. Among BCBM patients, 5.8% had concurrent brain metastasis, 21.8% had concurrent liver metastasis, and 23.5% had concurrent lung metastasis.

As for the treatment information, 35.4% of patients received surgery, 40.2% received radiotherapy, and 59.1% received chemotherapy.

*Incidence analysis*

We visualized the trend of incidence of four common metastases between 2010 and 2016 by a broken-line graph (**Figure 2A**). The incidence of bone metastasis took the first place in a large margin showing an up-trend year by year. In addition, a density curve (**Figure 2C**) was created to visualize the age distribution of

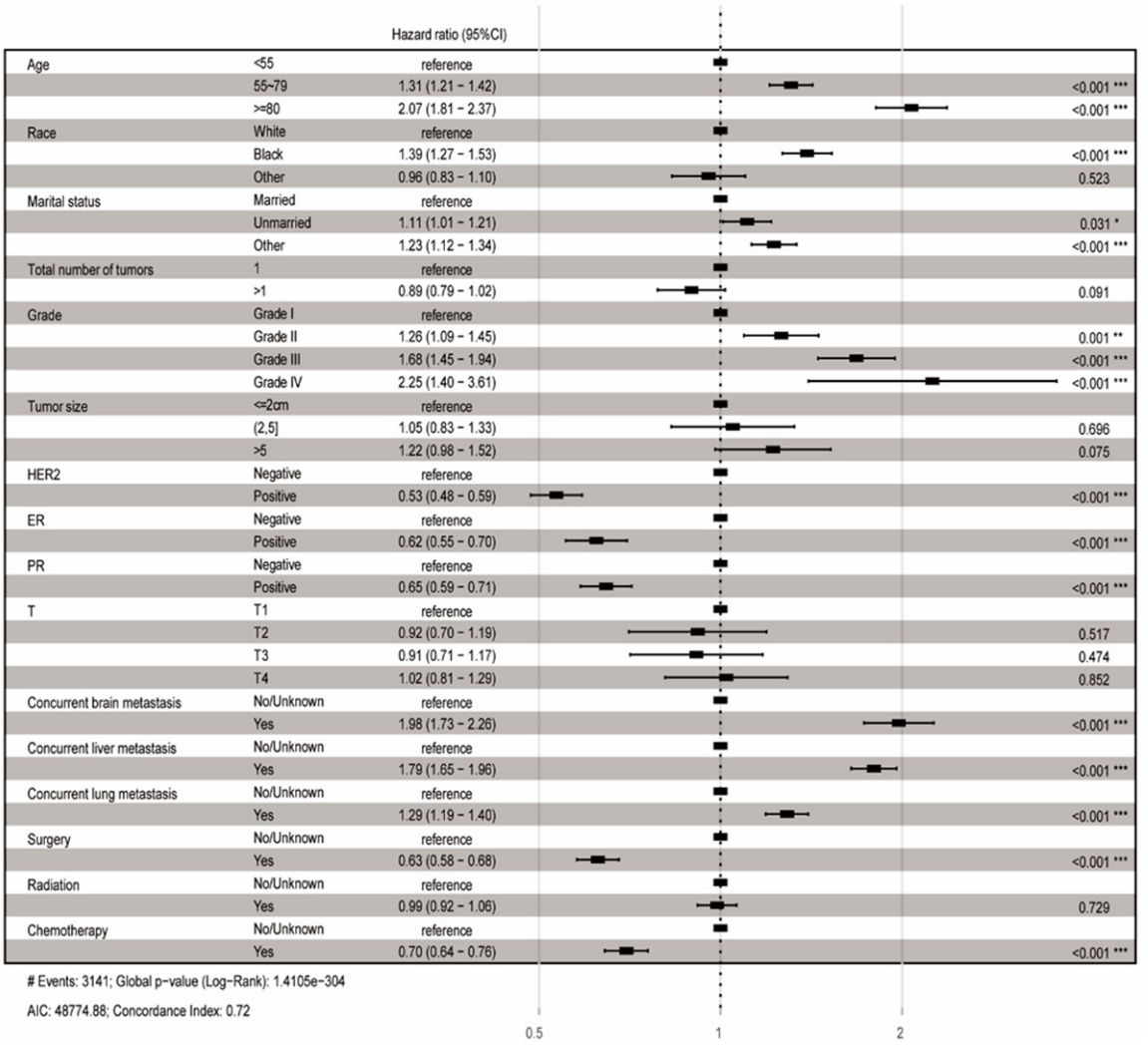


**Figure 4.** Forest plot depicting the effects of different prognosis factors.

patients with BCBM, which appeared to be a symmetrical, bell-shaped distribution. We can learn that the incidence of BCBM was normally distributed with age peaking around 60 and about 50% of patients were between 50 and 70 years old.

*Survival analysis*

We compared the OS of different metastases and non-metastasis of breast cancer (**Figure 2B**) by using Kaplan-Meier method. The prognosis of patients with distant metastases was not optimistic, among which the prognosis of brain metastasis was the worst.

Survival curves were also created in the same way to test the effect of prognostic factors, including race, marital status, grade, HER2, ER, PR, concurrent brain metastasis, concurrent liver metastasis, concurrent lung metastasis, surgery, and chemotherapy. The Log-rank tests were considered significant (P<0.05) for all survival curves. As shown in **Figure 3**, curves in each group are separated from each other, which means hazard ratios are consistent in the process of BCBM.

*Prognostic factors for OS*

All prognostic factors were screened by univariate and multivariate Cox regression in turn. It demonstrated that age (P<0.001), marital status (P<0.001), grade (P<0.001), HER2 (P<0.001), ER (P<0.001), PR (P<0.001), concurrent brain metastasis (P<0.001), concurrent

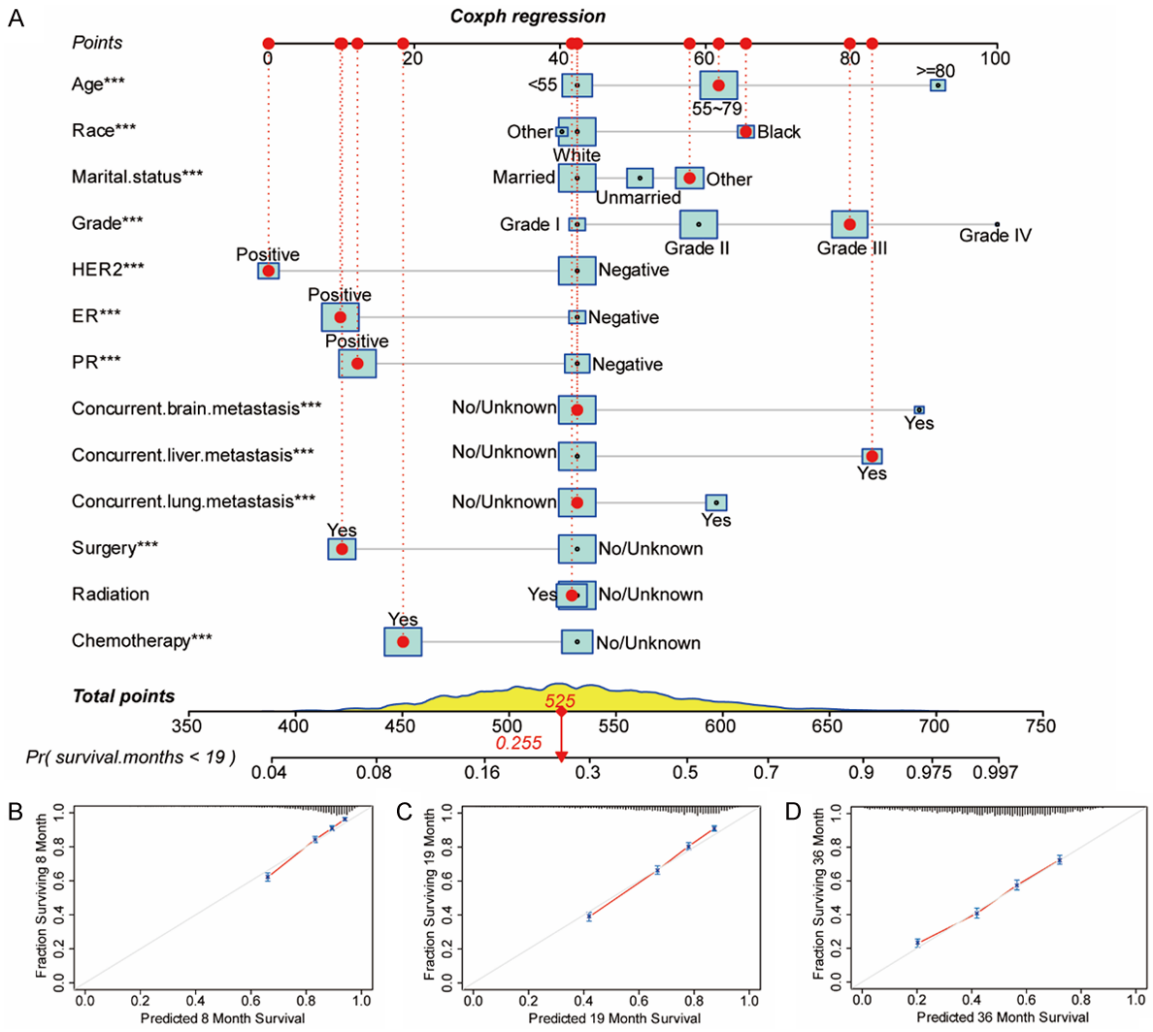


**Figure 5.** A. Overall survival nomogram for breast cancer with bone metastasis; B. Calibration curve for 8 months; C. Calibration curve for 19 months; D. Calibration curve for 36 months.

liver metastasis (P<0.001), concurrent lung metastasis (P<0.001), surgery (P<0.001) and chemotherapy (P<0.001) were independent prognostic factors. Factors with a *P* value more than 0.05 were sifted out at the same time. The result was illustrated by a forest plot (**Figure 4**).

*Nomograms*

According to the result of multivariate Cox regression, we developed a nomogram (**Figure 5A**) to predict the outcome of patients. There is a variable axis of each factor, and the score of each option is reflected by a point bar at the top. After matching a patient's information, the overall score will be read at the axis of total points with a red narrow showing the probability of median survival time (19 months). In our nomogram, the sizes of blue boxes and yellow area symbolize the population distribution reflecting the demographic characteristics of patients with BCBM. The C-index in the internal validation was 0.72 [95% CI, 0.714-0.726], and the calibration curves (**Figure 5B-D**) were plotted. Furthermore, according to previous analyses, another nomogram (**Figure 6**) was created based on the competitive risk model. We can calculate patients' survival probability after eliminating competing risk events by the latter.

For instance, there is a black woman with BCBM, 71 years old, separated, grade III, HR+/HER2+, concurrent liver metastasis, received surgery, radiotherapy and chemotherapy. In first nomogram, her total points are 525, and the odds of living less than 19 months (the

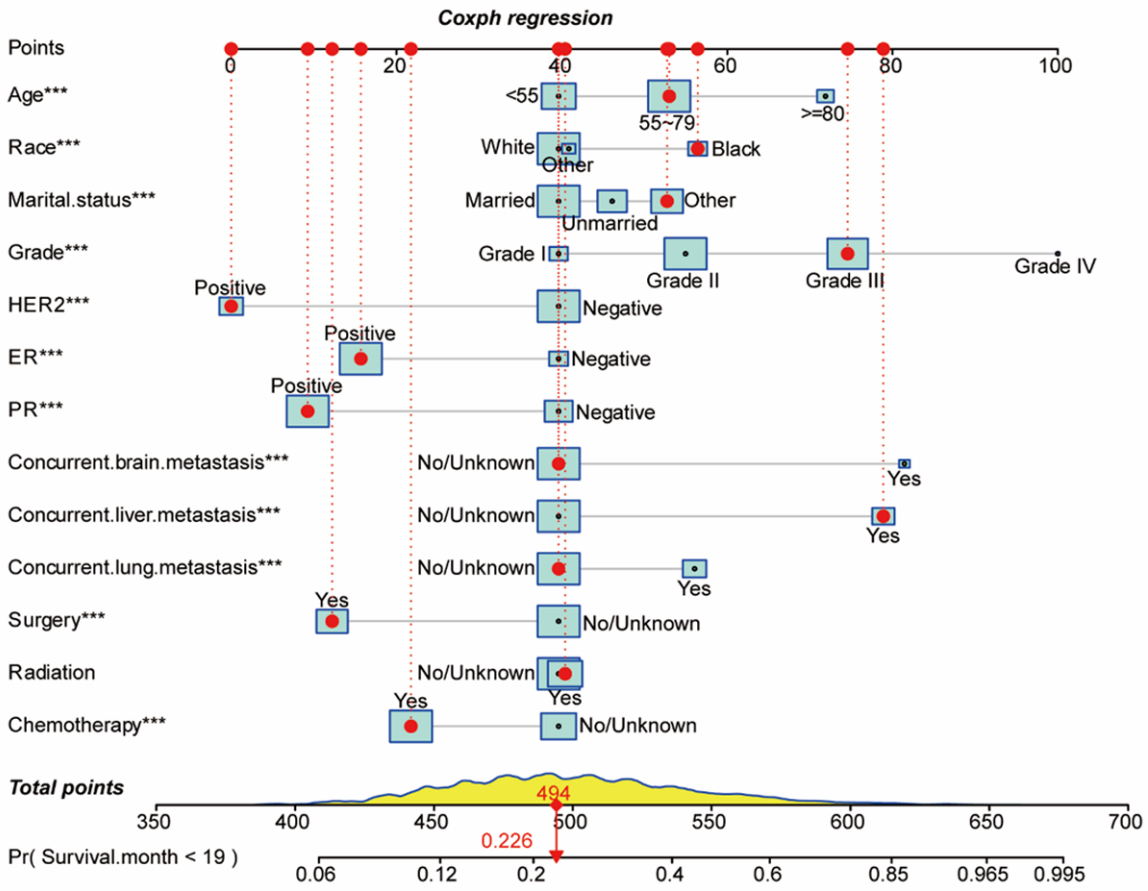


**Figure 6.** Competing risk nomogram for breast cancer with bone metastasis.

median survival time) is 0.255. However, in the second nomogram, the total points are 494 with the odds of 0.226. The result can be explained that patients' survival probability would increase slightly after eliminating the effect of competing risk events, like car accident, which probably could predict the outcomes more precisely.

## Discussion

Our research can be divided into following parts: First, according to the demographic data, we compared the incidence and survival rate of patients with/without different metastases. The age distribution of patients with BCBM, meanwhile, was visualized by a smooth curve. Second, by using Cox regression method, we selected the independent factors from total 21 variables, including patients' information, characteristics of tumors and treatment methods. Then those critical factors were reconfirmed by Log-rank test. Third, a practical and user-friendly nomogram was developed to predict the prognosis for individuals. In order to make outcome more precisely, we introduced the competitive risk model to eliminate the effects of other causes of death. Therefore, another nomogram was created. It is worth noting that the effect of radiotherapy is not significant. The dose of radiotherapy is always a controversial issue. According to the research of Wallace et al., the course of radiotherapy should be shortened for patients with poor prognosis, for the beneficial effect would be offset by long-term radiation [13].

Although there are a few previous studies on BCBM [4, 5, 10, 14-16], differences in median survival time do exist. It can be explained by some reasons, like different data sources, different inclusion criteria and different medical level in different area. For instance, in Canada, the median survival time for patients with BCBM without skeletal-related events (SREs) was 19.2 months, reported by Liede et al. [17].

In Denmark, Yong et al. reported that the median survival time for patients with BCBM without SREs was 16 months [18]. In Korea, as Ahn et al. reported, the median survival time for patients with bone metastases reached 55 months, a very impressive result [3]. Anyway, BCBM is still a big challenge to the world and its prognosis is still not optimistic. That is why we performed this research to screen out more independent and significant factors, which were integrated to create practical and user-friendly nomograms.

With the development of research, a large number of studies towards breast cancer were conducted in variable directions, including pathology [19-21], radiology [22-25], genetics [26] and therapy [27, 28]. Some studies focusing on some specific characteristics of breast cancer were performed to predict outcomes with nomograms [29, 30]. For example, Su et al. developed a 19-gene signature-based nomogram for patients with breast cancer [31]. Wang et al. figured out the relationship between immune scores and prognosis of breast cancer and developed a clinical nomogram to predict the outcomes [32]. Luo et al. reported a nomogram with the radiomics score (Rad-score) and Breast Imaging Reporting and Data System (BI-RADS) category incorporated, which revealed the association of prognosis with radiomics and imaging features [33]. Yue et al. reported that asynchronous transfer mode (ATM) gene was significantly associated with breast cancer and plotted a nomogram for prediction [34]. Besides, some studies focused on particular type of patients to make the prediction more accurate by narrowing the scope. For example, Zhao et al. performed a study on patients with T1 breast cancer and built a nomogram to predict the prognosis [35]. Another research was conducted by Shen et al., based on patients with bilateral primary breast cancer [36].

The commonality of all the studies above is to make prediction more precisely by narrowing the scope. However, the narrower the scope of research is, the narrower the scope of application will be. Thus, in order to accomplish the widest applicability under present conditions, we conducted this study to dig out as many of factors as we can and cover as much of the population as possible.

There are also some limitations in our study. First, for the lack of data from other databases, our models could not be externally validated, and only internal validation was done. Second, some critical indicators are not mentioned, like relative genes, radiation dose, specific chemotherapy regimens, specific surgical options, endocrine therapy, target therapy and immunotherapy, because of the lack of data support. As we known, for ER+ and/or PR+, HER2- BCBM patients, endocrine therapy (tamoxifen, an aromatase inhibitor or fulvestrant) is advised; for triple-negative BCBM patients, if patients have >1% PD-L1 immune cells, clinicians can choose nab-paclitaxel plus atezolizumab; for HER2+ BCBM patients, dual blockade (trastuzumab and pertuzumab) is an option. As we can see, the systemic therapies are rapidly evolving.

## Conclusions

Our study provides a perspective in the understanding of patients with BCBM. Our practical nomograms provide a visual and user-friendly tool in the risk evaluation and prognostic prediction for breast cancer patients with bone metastases, which are yet to be checked, modified and complemented by clinical practice. With our rigorous and meticulous analyses, we hope our predictive tools could help doctors to make clinical decisions before clinical management.

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## Disclosure of conflict of interest

None.

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