

# A nomogram for predicting survival in patients with breast cancer brain metastasis

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**Abstract.** Brain metastasis (BM) is common in patients with breast cancer. Predicting patient survival is critical for the clinical management of breast cancer brain metastasis (BCBM). The present study was designed to develop and evaluate a prognostic model for patients with newly diagnosed BCBM. Based on the clinical data of patients with BCBM treated in the Affiliated Hospital of Academy of Military Medical Sciences (Beijing, China) between 2002 and 2014, a nomogram was developed to predict survival using proportional hazards regression analysis. The model was validated internally by bootstrapping, and the concordance index (c-index) was calculated. A calibration curve and c-index were used to evaluate discriminatory and predictive ability, in order to compare the nomogram with widely used models, including recursive partitioning analysis (RPA), graded prognostic assessment (GPA) and breast-graded prognostic assessment (Breast-GPA). A total of 411 patients with BCBM were included in the development of this predictive model. The median overall survival time was 14.1 months. Statistically significant predictors for patient survival included biological subtype, Karnofsky performance score, leptomeningeal metastasis, extracranial metastasis, the number of brain metastases and disease-free survival. A nomogram for predicting 1- and 2-year overall survival rates was constructed, which exhibited good accuracy in predicting overall survival with a concordance index of 0.735. This model outperformed RPA, GPA and Breast-GPA, based on the comparisons of the c-indexes. The nomogram

constructed based on a multiple factor analysis was able to more accurately predict the individual survival probability of patients with BCBM, compared with existing models.

## Introduction

Breast cancer is the leading cancer in women worldwide, in terms of incidence and cancer-associated mortality (1). The brain is one of the most common sites for breast cancer metastasis, with a rate of brain metastasis of 10-15% in patients with advanced breast cancer (2) and a rate of 30-55% in patients with HER-2 overexpression (3). The median survival time for patients with breast cancer brain metastasis (BCBM) ranges between 4 and 14 months (4-6).

In the era of personalized medicine, the use of the same treatments for all BCBM patients is no longer appropriate. The choice of treatment for a given patient depends upon numerous factors, including age, performance status and tumor characteristics such as breast biological subtypes, tumor site, number of brain metastases and extracranial metastasis. Considering that patients with BCBM are a heterogeneous group, it is necessary to introduce a simple breast cancer-specific prognostic index that may aid clinicians in selecting the appropriate treatment. Several prognostic models for patients with cancer have been developed and widely used in clinical oncology practice (7-9). For example, the Radiation Therapy Oncology Group established recursive partitioning analysis (RPA) in 1997 (7). The graded prognostic assessment (GPA) was constructed in 2008 and has been regarded as more accurate than RPA (8). Although RPA and GPA are widely used in the clinic, these were constructed on the basis of several different histological types of cancer and have limited use in breast cancer. In 2012, the Breast-GPA was developed based on analysis of the clinical features of 400 cases of BCBM (9).

Considering the limitations of RPA, GPA and Breast-GPA, there is a requirement for developing a novel prognostic model. A nomogram is a visual predictive tool based on statistical regression models, which measures the impact of various factors on the possibility of an event (10). This tool may aid clinicians in assessing patient risk of recurrence and prognosis, and in selecting appropriate patients for clinical trials. It has

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been demonstrated that a nomogram may improve predictive accuracy for clinical outcomes, compared with traditional prognostic models (11-17). The present study was designed to construct a novel prognostic model for BCBM using a nomogram approach. Furthermore, the present study also compared the novel model with existing PRA, GPA and Breast-GPA models, with the aim that the newly developed model would be useful in the treatment of patients with BCBM.

## Materials and methods

**Patients and treatment.** The medical records of patients with BCBM, who had been admitted to the Affiliated Hospital of Academy of Military Medical Sciences (Beijing, China) between January 2002 and December 2014, were retrospectively analyzed. The diagnosis of breast cancer was pathologically confirmed, and brain metastasis was diagnosed by imaging or pathology. Patients who had more than one histological tumor type or missing data on key medical information were excluded from the present study. A total of 411 female patients with a median age of 47.6 years (range, 25.3-80.0 years) at brain metastases were finally included in present study. Based on the number and dimensions of brain metastases (BMs), these patients underwent local treatments, including surgical resection, whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS). The most common regimen of WBRT was 40 Gy in 20 fractions and the most common regimen of SRS was 17 Gy in 1 fraction. Among the 411 patients with BCBM, 265 (64.5%) were treated with WBRT with or without SRS, 188 (45.7%) received SRS or surgical resection with or without WBRT, 154 (37.5%) received WBRT only, and 69 (16.9%) did not receive local treatment. For patients with fewer than three BMs, SRS was initially performed and WBRT was administered when the BM progressed or additional BMs developed.

**Variables.** In the present study, possible factors that affect BM prognosis were selected based on review of current literature (9,18-21), including age, clinical stage, biological subtype, disease-free survival (DFS), occurrence time of BM, duration between diagnosis and BM, Karnofsky performance score (KPS) (22), extracranial metastasis, meningeal metastasis, symptoms of BM, and the number and size of BM lesions. The classification of biological subtypes was based on the 2011 St. Gallen International Expert Consensus (23). The response to treatment was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (24).

**Data analysis, model construction and statistical analysis.** Brain metastasis overall survival (BMOS) was defined as the duration between the diagnosis of BM and mortality or the end of follow-up. DFS was defined as the duration between surgery and the first recurrent metastasis. The database was closed on May 15, 2016. Univariate analysis and a multivariate Cox proportional hazards model were used to analyze the association between risk factors and survival. Variables that were significant in the univariate analysis were incorporated into the Cox proportional hazards model, and variable-independent prognostic factors were selected through backward stepwise analysis.  $P < 0.05$  was considered to indicate a statistically significant difference.

The nomogram model was constructed on the foundation of the Cox proportional hazards model, and its performance was evaluated by internal validation with Bootstrap resampling (1,000 times), in order to minimize biases in the performance of the model (10,25). Discrimination and calibration were used to assess nomogram performance. The discrimination ability (how well a model is able to distinguish between patients who succumbed to mortality and patients who survived.) of the nomogram was quantified by using the Harrell C-index (25). The c-index was similar to the area under the receiver operating characteristic (ROC) curve, with an index of 0.5 and 1 indicating the lack of concordance and perfect concordance, respectively (26). Calibration was obtained by plotting the calibrated curve of the association between the observed incidence and the predicted probabilities (27). The c-index was also used for the comparison of different models. The Kaplan-Meier method was used to plot the survival curves according to RPA, GPA and Breast-GPA prognosis models. The RPA model divides the patients into three different prognostic groups: group I (patients  $< 65$  years, KPS  $\geq 70$ , controlled primary tumor, and no extracranial metastasis), group II (all other patients not included in group I or III), and group III (KPS  $< 70$ ). The GPA model divides the patients into four prognostic groups, according to the sum scores (GPA score 0-1, 1.5-2.5, 3.0 and 3.5-4) of four factors, including age, KPS, number of brain metastases, and extracranial metastasis. Furthermore, the Breast-GPA model also divides the patients into four prognostic groups, according to the sum scores (Breast-GPA score 0-1, 1.5-2.0, 2.5-3.0 and 3.5-4.0) of three prognostic factors: age, KPS and biological subtype. Statistical analyses were performed using SPSS 18.0 (SPSS, Inc., Chicago, IL, USA) and R software version 3.2.2 (<http://www.r-project.org>).

## Results

**Clinical features and survival.** The characteristics of the selected patients are presented in Table I. The median follow-up time was 48.2 months. Cases of mortality, survival and loss to follow-up were 322 (78.3%), 50 (12.2%) and 39 (9.5%), respectively. The median overall survival (OS) time following diagnosis of breast cancer was 68.2 months, while the median BMOS time was 14.1 months (range, 0.1-100.3 months), with 1-, 2- and 3-year survival rates of 55.9, 29.6 and 16.2%, respectively. Furthermore, the median DFS time was 23.9 months (range, 0-232.3 months), the median duration between diagnosis of breast cancer and BM was 43.3 months (range, 0-353.2 months), and the median volume of brain metastases was 4.8 cm<sup>3</sup> (range, 0.1-139.7 cm<sup>3</sup>).

### Nomogram model construction and validation

**Model construction.** Univariate analysis results indicated that several factors, including molecular subtype, DFS, KPS, symptoms of BM, extracranial metastasis control, leptomeningeal metastasis and the number of BM lesions were associated with the survival of patients with BCBM (Table I). Furthermore, multivariate analysis results indicated that molecular type, KPS score, leptomeningeal metastasis, extracranial metastasis control, the number of BM lesions and DFS were independent factors that influenced the survival of patients with BCBM

Table I. Patient characteristics.

| Characteristics                     | Number (%) | Median survival, months | P-value |
|-------------------------------------|------------|-------------------------|---------|
| Age at BM, years                    |            |                         | 0.318   |
| ≤40                                 | 105 (25.5) | 11.1                    |         |
| 40-60                               | 259 (63.0) | 14.7                    |         |
| >60                                 | 47 (11.5)  | 16.1                    |         |
| Clinical stage                      |            |                         | 0.828   |
| I and II                            | 306 (74.5) | 15.0                    |         |
| III and IV                          | 105 (25.5) | 12.3                    |         |
| Biological subtype                  |            |                         | <0.001  |
| Luminal A                           | 140 (34.0) | 14.7                    |         |
| Luminal B                           | 87 (21.2)  | 20.2                    |         |
| HER-2 Positive                      | 86 (20.9)  | 14.0                    |         |
| Triple Negative                     | 94 (22.9)  | 8.7                     |         |
| Unknown                             | 4 (1.0)    | -                       |         |
| DFS, months                         |            |                         | 0.012   |
| >36                                 | 125 (30.4) | 17.1                    |         |
| ≤36                                 | 276 (67.2) | 12.1                    |         |
| Unknown                             | 10 (2.4)   | -                       |         |
| Diagnosis to BM, months             |            |                         | 0.072   |
| >44                                 | 208 (49.4) | 15.9                    |         |
| ≤44                                 | 203 (50.6) | 11.6                    |         |
| Symptoms of BM present              |            |                         | <0.001  |
| Yes                                 | 261 (63.6) | 10.3                    |         |
| No                                  | 111 (27.0) | 21.1                    |         |
| Unknown                             | 39 (9.5)   | -                       |         |
| KPS                                 |            |                         | <0.001  |
| ≥90                                 | 169 (41.1) | 19.3                    |         |
| 70-90                               | 149 (36.3) | 13.5                    |         |
| <70                                 | 74 (18.0)  | 2.8                     |         |
| Unknown                             | 19 (4.6)   | -                       |         |
| Extracranial metastasis control     |            |                         | <0.001  |
| Controlled (CR+PR+SD)               | 162 (39.4) | 18.5                    |         |
| Uncontrolled (PD)                   | 227 (55.2) | 9.8                     |         |
| Unknown                             | 22 (5.4)   | -                       |         |
| Leptomeningeal metastasis           |            |                         | <0.001  |
| Yes                                 | 69 (16.8)  | 6.9                     |         |
| No                                  | 336 (81.8) | 16.7                    |         |
| Unknown                             | 6 (1.5)    | -                       |         |
| Number of BM lesions                |            |                         | <0.001  |
| ≤3                                  | 148 (36.0) | 20.9                    |         |
| >3                                  | 223 (54.3) | 11.8                    |         |
| Unknown                             | 40 (9.7)   | -                       |         |
| Total tumor volume, cm <sup>3</sup> |            |                         | 0.782   |
| ≤4.8                                | 113 (27.5) | 16.1                    |         |
| >4.8                                | 113 (27.5) | 14.2                    |         |
| Unknown                             | 185 (45.0) | -                       |         |

BM, brain metastasis; DFS, disease-free survival; luminal A, ER/PR-positive and HER-2-negative; luminal B, ER/PR positive and HER-2-positive; HER-2, ER/PR-negative and HER-2-positive; Triple-negative ER/PR negative and HER-2-negative; KPS, Karnofsky performance score; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; -, unknown.

Table II. Multivariate analysis of prognostic factors.

| Factor   | b      | P-value | HR    | 95% CI |       |
|--|--------|---------|-------|--------|-------|
|  |        |         |       | Lower  | Upper |
| Biological subtype                               |        | <0.001  |       |        |       |
| Luminal B vs. A                                  | -0.612 | <0.001  | 0.542 | 0.385  | 0.764 |
| HER-2-positive vs. luminal A                     | -0.600 | 0.003   | 0.549 | 0.368  | 0.818 |
| Triple negative vs. luminal A                    | -0.690 | <0.001  | 0.502 | 0.346  | 0.728 |
| KPS  |        |         |       |        |       |
| 70-80 vs. <70                                    | 1.428  | <0.001  | 4.172 | 2.884  | 6.036 |
| 90-100 vs. <70                                   | 0.167  | 0.278   | 1.182 | 0.874  | 1.599 |
| Leptomeningeal metastasis                        | -0.596 | 0.003   | 0.551 | 0.370  | 0.821 |
| Extracranial metastasis control                  | 0.616  | <0.001  | 1.852 | 1.392  | 2.463 |
| Number of brain metastases ( $\leq 3$ vs. $>3$ ) | 0.571  | <0.001  | 1.770 | 1.338  | 2.343 |
| DFS ( $>36$ vs. $\leq 36$ )                      | -0.312 | 0.039   | 0.732 | 0.544  | 0.985 |

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance score; extracranial disease control,  $\geq$ SD (CR + PR + SD) of extracranial diseases at the time of diagnosis of BM; luminal A, ER/PR-positive and HER-2-negative; luminal B, ER/PR positive and HER-2-positive; HER-2, ER/PR-negative and HER-2-positive; DFS, disease-free survival.

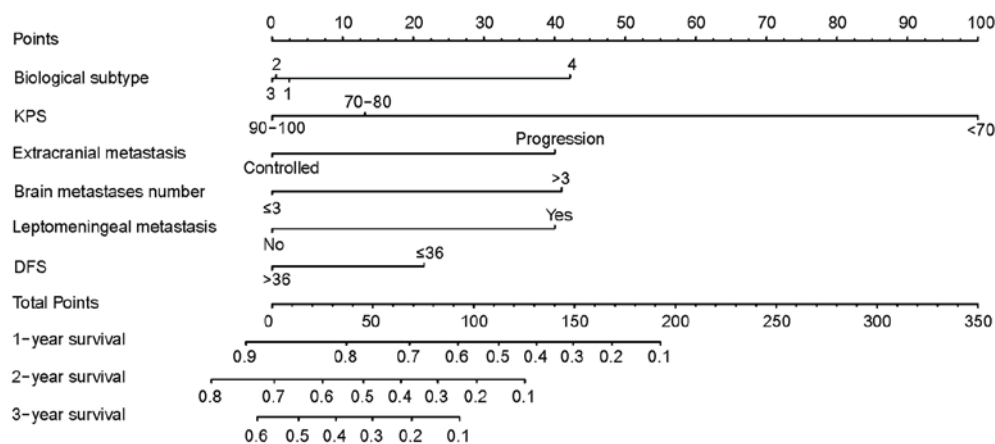


Figure 1. The nomogram for predicting overall survival was established for patients with breast cancer brain metastasis. The predictor points of each variable were observed on the upper-most point axis. There was a Total Points line at the bottom of the nomogram, and each variable score was summed to give the total points. A vertical line down to the 1-, 2- and 3-year survival lines allowed for the determination of probabilities for each individual. 1, luminal A; 2, luminal B; 3, HER-2 positive; 4, Triple negative; KPS, Karnofsky performance score (22); DFS, disease-free survival.

(Table II). The nomogram prognostic evaluation model was constructed based on the multivariate analysis (Fig. 1).

**Model validation.** The present study employed the bootstrap resampling method for the internal validation of the model to reduce the over-fitting of the model. The c-index was 0.73 (95% CI, 0.70-0.77), indicating a good discrimination. The calibration plot of 1- and 2-year OS rates revealed a good agreement between observed values and predicted values (Fig. 2).

As shown in Fig. 3, there was overlapping between groups I and II in the RPA model (Fig. 3A;  $P=0.091$ ). In addition, there was overlapping between groups II, III and IV in the using the GPA model (Fig. 3B;  $P=0.103$ ). Furthermore, the discrimination was not satisfactory between groups II and III

in Breast-GPA model (Fig. 3C;  $P=0.213$ ). Based on the results of the survival curves and P-values, it was concluded that the three aforementioned prognosis models were not satisfactory for differentiating patients with different survival times. The c-indexes were 0.73, 0.64, 0.61 and 0.63 for the nomogram, Breast-GPA, GPA and RPA, respectively (Table III).

## Discussion

Brain metastasis significantly impacts the prognosis and quality of life of patients with breast cancer. Precise prognostic predication contributes not only to the selection of a suitable therapeutic regimen, but also to the selection of appropriate patients for clinical trials. The present study developed a novel nomogram model for prognosis prediction through the

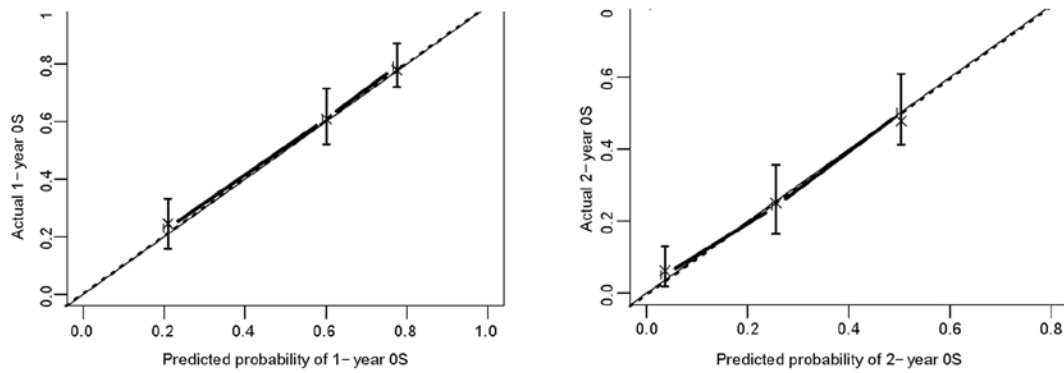


Figure 2. The calibration plots to predict the 1-year and 2-year OS rates for all patients. The x-axis represents the predicted OS and the y-axis represents the actual OS. The 45-degree line indicated an ideal reference line, which implies that the predicted OS rates were equal to the observed results. OS, overall survival.

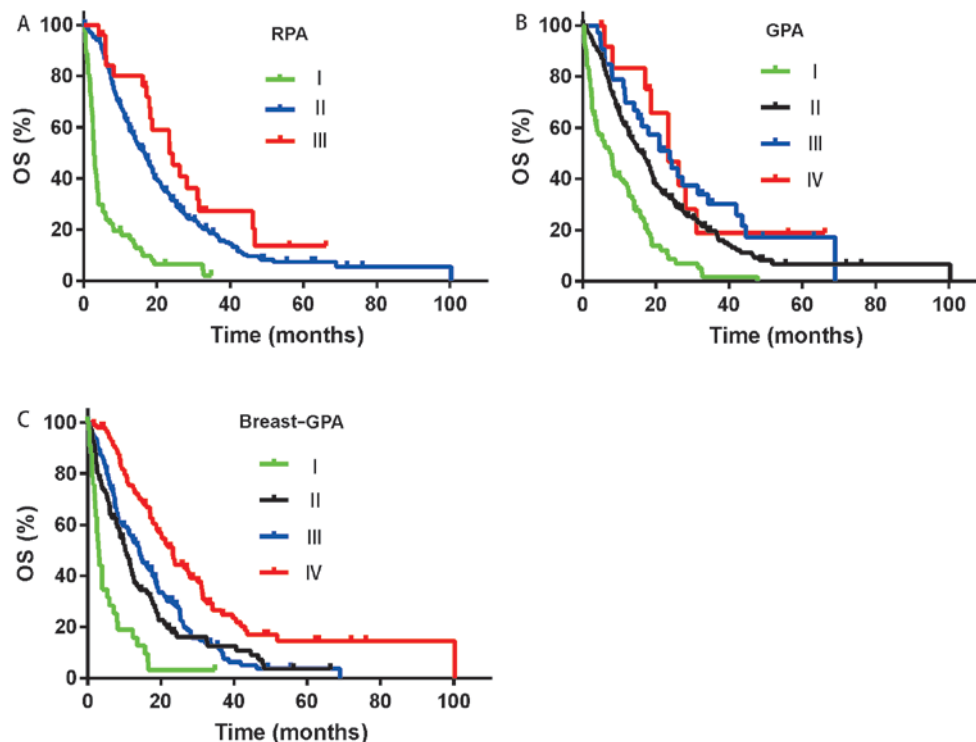


Figure 3. Overall survival of 411 patients according to the (A) RPA, (B) GPA and (C) Breast-GPA models. RPA, recursive partitioning analysis; GPA, graded prognostic assessment.

evaluation of several prognostic factors in a relatively large group of patients with BCBM.

The median survival of the patients with BCBM enrolled in the present study was 14.1 months, with a 1-year survival rate of 56.5%, which was slightly higher than that reported previously (9,28,29). This may be associated with the recent advances in the diagnosis and treatment of brain tumors, particularly in the application of targeted therapies in patients with BCBM. Targeted therapeutic agents, including trastuzumab, lapatinib and pertuzumab have become the standard treatment for patients with HER-2 overexpression. In the present study, up to 85.5% of patients with HER-2 overexpression received anti-HER-2 therapy, with a median survival time of 17.9 months, which was similar to that reported previously (range, 11.6-19.5 months) (30,31).

The primary purpose of developing a prognostic model is to guide clinical treatment. Therefore, it would be better to exclude therapeutic and subjective factors when selecting prognostic factors (32,33). Prognostic models used previously or currently in clinic often lack the evaluation of tumor biology factors, including tumor volume, meningeal metastases, molecular types and symptoms of BM (7-9), which are the influencing factors of prognosis (34,35). Therefore, these models failed to accurately predict patient survival. In order to overcome the weaknesses of these models, the present study used univariate and multivariate analyses to identify factors that influence patient survival. It was revealed that molecular subtypes, KPS, extracranial control, leptomeningeal metastasis, number of BM lesions and DFS were independent



Table III. Comparison of the nomogram with different predictive models.

| Method     | C-index | 95% CI |       |
|------------|---------|--------|-------|
|            |         | Lower  | Upper |
| Nomogram   | 0.735   | 0.703  | 0.767 |
| RPA        | 0.633   | 0.603  | 0.662 |
| GPA        | 0.614   | 0.583  | 0.646 |
| Breast-GPA | 0.640   | 0.609  | 0.671 |

CI, confidence interval; RPA, recursive partitioning analysis; GPA, graded prognostic assessment.

factors for the prognosis of patients with BCBM. Patients with leptomeningeal metastasis were generally excluded in published studies. However, literature and clinical experience indicated that meningeal metastasis is one of the major factors of poor prognosis in patients with BCBM (36). Therefore, the present study included the clinical conditions of patients in the development of the model; and multivariate analysis results revealed that meningeal metastasis was an independent factor for patient prognosis. There were 69 (16.8%) cases of meningeal metastases among the patients enrolled in the present study, which was slightly more than the numbers reported in previous studies (37,38). This may be associated with the extended survival of patients, as well as the wide application of magnetic resonance imaging in the diagnosis of brain tumors.

A nomogram is able to assess patient survival time, which is beneficial for individualized therapy. The existing RPA, GPA and Breast-GPA models simply divide these patients into several subgroups, with great difference existing within the same subgroups (39). The present study compared different models using the c-index and survival curves, and demonstrated that the novel nomogram was superior to existing prognostic models (RPA, GPA and Breast-GPA). Furthermore, a crossover of survival curves among different groups in the RPA, GPA and Breast-GPA models was observed, which may be associated with the lack of molecular indices of breast cancer, inconsistent pathological types, differences in patient grouping, the selection of different prognostic factors, as well as defects in the modeling methods of RPA and GPA. Although the RPA model was constructed based on the results of 1,200 cases of BM, there were only 137 (12%) cases of breast cancer (7). The GPA model was based on the analysis of 1,960 cases, but only 222 (11%) cases of breast cancer were included (8).

Among the 411 patients included in the present study, 74.5% would be diagnosed with grade II disease based on the RPA model, and the median survival time of patients with grade II disease was 16.7 months (range, 0.2-100.3 months). This indicated the significantly different survival times within the same group. This discrepancy may result in administering palliative treatment to patients who should receive active treatment.

Although the nomogram model developed in the present study exhibited a good predictive ability, certain shortcomings remained. For example, as is often the case with retrospective studies, certain patient information was not available and

therefore, bias was inevitable. Although the sample size was relatively large, the study population was selected from one hospital. Furthermore, it requires validation in other research institutions.

In conclusion, the present study developed and validated a nomogram prognosis evaluation model for patients with BCBM, which was demonstrated to be improved compared with the presently used RPA, GPA and Breast-GPA models. This model may be used to guide individual treatments and in selecting an appropriate patient population for clinical trials.

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### Availability of data and materials

All data are fully available upon request.

### Author's contributions

Conception and design were undertaken by SKW. Collection of patient information and drafting of the article was undertaken by ZH. Data interpretation was performed by BS and ZH. XYM, YC, GS and STS participated in patient treatment, and helped revising the manuscript. All authors read and approved the final manuscript.

### Ethical approval and consent to participate

All procedures involving human participants were performed in accordance with the ethical standards of the Affiliated Hospital of Academy of Military Medical Sciences and China Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants included in the present study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that there are no competing interests.

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