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ORIGINAL RESEARCH ARTICLE

Risk factor analysis for human epidermal growth factor receptor 2-positive breast cancer patients with brain metastasis: A risk prediction model based on the Surveillance, Epidemiology, and End Results database

Xulong Zhu[1,2†], Xinmiao Liu[1†], Ziyu Luo[1], Shuhan Wu[1], Hengtao Song[1], Ke Yan[1], Yue Wang[1], Liping Yang[1], Wenjun Shu[1], Kenian Pan[2], and Jianhui Li[1,2*]

[1]Department of Surgical Oncology, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, China

[2]Department of First Clinical Medicine, Faculty of Surgery Teaching and Research, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, China

Abstract

Introduction: Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is characterized by increased cell proliferation and a high potential for metastasis, resulting in a poorer prognosis–especially when brain metastases occur. At present, no definitive clinical factors or predictive models exist to guide prognosis in this patient group.

Objective: This study aims to identify prognostic factors affecting survival in HER-2 breast cancer patients with brain metastases and to construct a model to assess prognosis based on clinical characteristics.

Methods: Data from female patients diagnosed with breast cancer brain metastases between 2011 and 2020 were extracted from the Surveillance, Epidemiology, and End Results database. Seventeen clinical factors were evaluated for their association with brain metastasis in HER2-positive breast cancer. Univariate and multivariate Cox proportional hazard regression analyses were performed, and Kaplan-Meier survival curves were plotted based on independent risk factors. A nomogram model was then developed to predict survival rates at different time intervals. Model performance was evaluated using calibration curves and the concordance index. Receiver operating characteristic analysis and decision curve analysis (DCA) were also conducted to evaluate predictive accuracy and clinical utility.

Results: Cox regression analyses identified nine clinical characteristics significantly associated with overall survival (OS) and seven factors influencing breast cancer-specific survival: molecular subtype, age, node stage, liver and lung metastases, and estrogen receptor and progesterone receptor status. The models achieved concordance indices of 0.680 (OS) and 0.663 (breast cancer-specific survival). The nomogram demonstrated strong predictive power, with area under the curve values of 0.767 and 0.700, respectively. DCA showed that the model curve significantly outperformed the two extreme curves.

Conclusion: This study identified key prognostic factors and developed a nomogram-based model with strong predictive value for HER2-positive breast cancer patients with brain metastases.

Keywords: Brain metastasis; Human epidermal growth factor receptor 2; Risk prediction model; Surveillance, Epidemiology, and End Results database; Survival rate

[†]These authors contributed equally to this work.

***Corresponding author:**
Jianhui Li
(lijianhuimd@163.com)

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1. Introduction

According to statistics from the International Agency for Research on Cancer, 2.3 million new cases of breast adenocarcinoma were reported globally in 2022, making breast cancer the second most common cancer worldwide, following lung cancer.[1] It remains the most frequently diagnosed cancer among women, accounting for nearly 25% of all cancer cases and one-sixth of cancer-related deaths in the female population. As such, breast cancer continues to represent a major threat to women's health.[1]

Approximately 20–40% of breast cancer patients develop brain metastases during disease progression.[2] Among these, brain metastasis is particularly prevalent in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, with central nervous system involvement occurring in 30–55% of cases.[3] A retrospective study involving 1,256 patients with breast cancer brain metastases reported overall survival (OS) of 8.7 months, with a relatively high proportion of HER2-positive cases. Notably, HER2-positive patients who received targeted therapy–regardless of estrogen receptor (ER) and progesterone receptor (PR) expression–exhibited longer survival following the development of brain metastases compared to HER2-negative patients.[4]

Among all cases of breast cancer metastasis, nearly 15% of patients develop brain metastases. This suggests that breast cancer is one of the most likely tumors to metastasize to the brain, with the incidence of brain metastases second only to lung cancer.[5] With advancements in breast cancer treatment, the survival rate of HER2-positive patients has significantly improved.[6-8] However, due to the protective nature of the blood–brain barrier, drug penetration into the brain is limited, reducing the efficacy of treatments targeting tumor cells that have metastasized to the brain. As a result, the current therapies remain inadequate, and effective clinical strategies to eliminate tumor cells in breast cancer patients with brain metastases are still lacking.[9]

At present, the general treatment approach for patients with brain metastases from breast cancer involves prioritizing surgical or radiotherapy interventions–such as stereotactic radiosurgery and whole-brain radiotherapy–while incorporating appropriate systemic treatments based on a comprehensive clinical evaluation. The aim is to control brain metastases, alleviate patient symptoms, improve quality of life, and extend survival through a multidisciplinary collaborative model. However, beyond therapeutic strategies, the clinical characteristics that influence survival in patients with breast cancer brain metastases have not been clearly established. Furthermore, there remains a lack of reliable clinical prognostic models capable of accurately predicting outcomes in this patient population.[10]

Previous studies on risk factors for brain metastasis in breast cancer have identified HER2 positivity as one of the main contributors to the development of brain metastases.[11] However, the prognostic risk factors specific to patients with HER2-positive breast cancer and brain metastases remain insufficiently explored. Therefore, this study aims to analyze clinical data of female patients with HER2-positive breast cancer brain metastases from the Surveillance, Epidemiology, and End Results (SEER) database. The objective is to identify factors associated with prognosis and survival in this patient population and to construct a predictive model based on these clinical characteristics to assess the prognosis of female patients with HER2-positive breast cancer brain metastases.

2. Materials and methods

2.1. Data resource

In this study, data from female patients diagnosed with breast cancer and brain metastases between 2011 and 2020 were extracted from the SEER database, supported by the National Cancer Institute, United States.

2.2. Inclusion and exclusion criteria

The inclusion criteria for this study were as follows:

(i) Female patients diagnosed with breast cancer and brain metastasis between 2011 and 2020, with HER2-positive and either hormone receptor-negative (HER2+/HR−) or hormone receptor-positive (HER2+/HR+) subtypes,
(ii) Histologically confirmed breast cancer as the only primary tumor,
(iii) Availability of complete clinical and follow-up data.

Patients with a survival time of <1 month were excluded from this study. A total of 576 patients who met the inclusion criteria were selected, comprising 325 in the HER2+/HR+ group and 253 in the HER2+/HR− group. The study included 17 independent variables as research variables: molecular subtype, age, presence of bone metastasis, presence of liver metastasis, presence of lung metastasis, ER status, PR status, whether surgical treatment was received, laterality, tumor grade, pathological classification, number of metastases excluding the brain (e.g., bone, liver, and lung), sequence of surgery and radiotherapy, sequence of systemic treatment and surgery, and tumor (T) and node (N) stage based on the 7th edition of the American Joint Committee on Cancer.

2.3. Statistics

Baseline patient data were analyzed using R software version 4.2.1 (R Core Team). Univariate and multivariate Cox regression analyses were performed using the survival

and rms packages to identify clinical characteristics associated with OS and breast cancer-specific survival (BCSS). Kaplan-Meier survival curves for each independent risk factor influencing OS and BCSS were generated using the survival and survminer packages, with visualization carried out using ggplot2. The proportional hazard assumption was tested using the survival package, and cumulative risk Kaplan-Meier curves were also fitted and visualized using survminer and ggplot2.

Significant variables identified through Cox regression analysis were subsequently used to construct a nomogram model for predicting 1-, 3-, and 5-year OS and BCSS in HER2-positive breast cancer patients with brain metastases, using the rms package. Calibration curves were plotted to evaluate the predictive performance of the nomogram, and the consistency index (C-index) was calculated to assess its predictive ability. Decision curve analysis (DCA) was conducted using the stdca.R package. Receiver operating characteristic (ROC) curves were generated using the pROC package to evaluate the model's accuracy, with all visualizations performed using ggplot2. A $p<0.05$ was considered statistically significant.

3. Results

3.1. Patients' clinical feature

In this study, data from 576 female patients diagnosed with HER2-positive breast cancer brain metastasis were extracted from the SEER database between 2011 and 2020, comprising 323 patients in the HER2+/HR+ group and 253 in the HER2+/HR− group. The inclusion and screening process is illustrated in Figure 1. Statistical analysis reveals significant differences between the two groups in terms of tumor grade, pathological type, presence of liver metastasis, number of metastases excluding the brain, and ER and PR status ($p<0.05$). No statistically significant differences are observed in molecular subtype, age, T stage, N stage, presence of lung or bone metastases, whether surgery was performed, laterality, the sequence of surgery

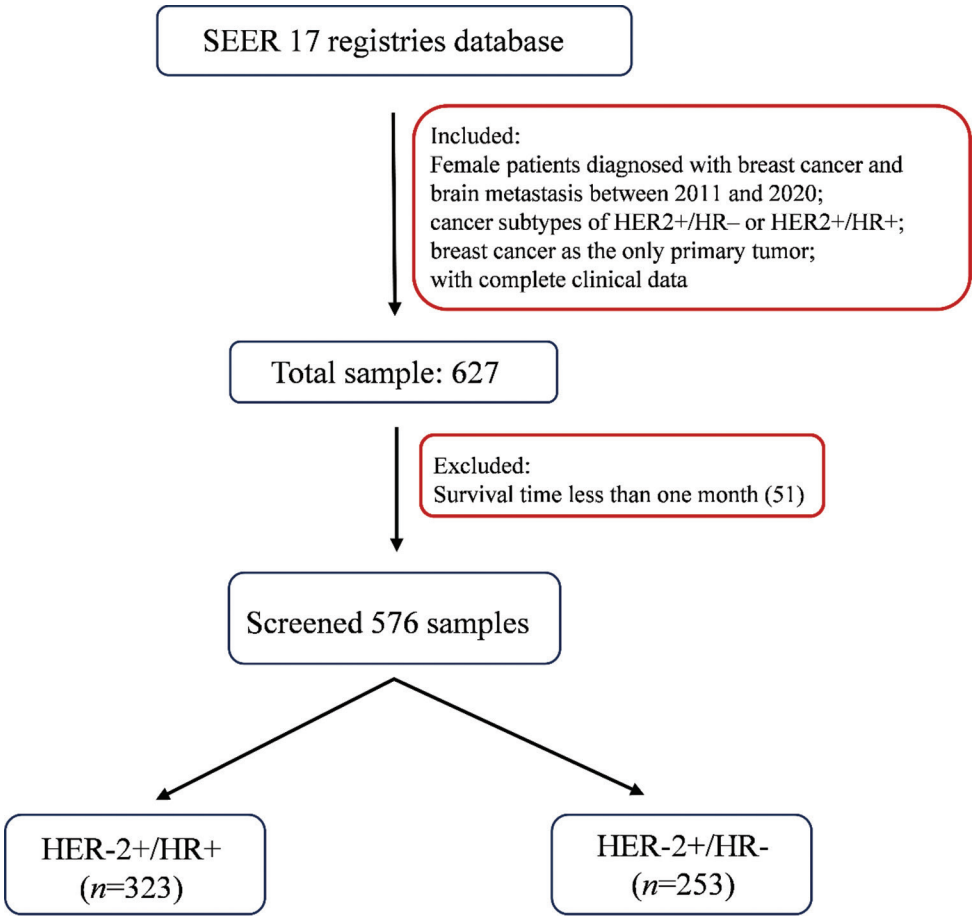

Figure 1. Clinical data selection procedure
Abbreviations: HER2+/HR+: Human epidermal growth factor receptor 2-positive and hormone receptor-positive; HER2+/HR−: Human epidermal growth factor receptor 2-positive and hormone receptor-negative; SEER: Surveillance, Epidemiology, and End Results.

and radiotherapy, or the sequence of systemic treatment and surgery (p>0.05).

In terms of tumor grade, the HER2+/HR+ group included 2.6% grade I, 14.4% grade II, 24.7% grade III, and 14.4% unknown. The HER2+/HR− group included 0.2% grade I, 7.6% grade II, 23.4% grade III/IV, and 12.7% unknown, suggesting a slightly better degree of differentiation in the HER2+/HR+ group.

For pathological type, infiltrating duct carcinoma, lobular carcinoma, and other types accounted for 42.9%, 3.1%, and 10.1% of cases in the HER2+/HR+ group and 10.8%, 32.3%, and 0.9%, respectively, in the HER2+/HR− group.

Liver metastasis was present in 22.7% of the HER2+/HR− group and 21.7% of the HER2+/HR+ group. In the HER2+/HR+ group, 53.1% of patients were ER-positive, and 34.4% were PR-positive. In contrast, 43.9% of HER2+/HR− patients were both ER- and PR-negative. The median number of metastatic organs, excluding the brain, is 2 in the HER2+/HR− and 1 in the HER2+/HR+ group (Table S1).

3.2. Identification of prognosis-related characteristics in patients

Univariate Cox regression analysis was conducted on 16 independent variables, including molecular subtype, age, presence of liver metastasis, presence of lung metastasis, ER status, PR status, whether surgical treatment was received, presence of bone metastasis, laterality, tumor grade, pathological classification, number of metastases excluding the brain, sequence of surgery and radiotherapy, sequence of systemic treatment and surgery, and T and N staging based on the 7th edition of the American Joint Committee on Cancer.

To minimize statistical bias caused by insufficient sample size in certain categories (n < 3), several variables were excluded from the analysis, including unknown race, PR status, surgery both before and after radiation, radiation both before and after surgery, and intraoperative radiation. Variables with statistical significance (p<0.05) in the univariate analysis were subsequently selected for multivariate Cox regression analysis.

Cox regression analysis reveals that molecular subtype, age, race, T stage, N stage, presence of lung metastasis, ER status, and PR status serve as independent risk factors affecting OS in patients (p<0.05). Among these, HER2+/HR−, other races (excluding Black and White), N1, N2, N3, unknown N stage (NX), ER positivity, and PR positivity act as protective factors (hazard ratio [HR] < 1). In contrast, older age, T2, T3, T4, unknown T stage (TX), and the presence of lung metastasis are identified as risk factors (HR > 1). Detailed results are shown in Table S2 and Figure 2.

In addition, BCSS analysis demonstrates that molecular subtype, age, race, T stage, presence of lung metastasis, ER status, and PR status are also independent risk factors affecting BCSS in patients (p<0.05). HER2+/HR−, other races (excluding Black and White), ER positivity, and PR positivity are protective factors (HR < 1), whereas age, presence of lung metastasis, T4 stage, and TX stage increase the risk of mortality (HR > 1) (Table S3 and Figure 3).

3.3. Cumulative risk analysis of different risk stratification samples

Multivariate Cox regression analysis was employed to identify independent risk factors associated with OS and BCSS and to quantify the risk value for each patient. Based on the median risk score, all cases were classified into high-risk and low-risk groups. The cumulative risk differences between the groups are illustrated using Kaplan–Meier survival curves. As shown in Figure 4, the cumulative risk of the low-risk group for both OS and BCSS is significantly lower than that of the high-risk group, indicating that the model effectively distinguishes patient risk levels.

3.4. Construction of independent risk factor-related survival curves

Kaplan-Meier survival curves for OS were constructed based on variables such as molecular subtype, age, T stage, N stage, presence of lung metastasis, presence of liver metastasis, ER status, PR status, whether surgical treatment was received, the sequence of surgery and radiation, and the sequence of systemic therapy and surgery.

For OS, Kaplan–Meier survival curves were constructed using molecular subtype, age, T stage, presence of lung metastasis, ER status, PR status, the sequence of surgery and radiation, whether surgical treatment was received, and the sequence of systemic therapy and surgery as independent variables (Figure 5).

Since the Kaplan–Meier method only supports a maximum of four groups for data analysis, the "T stage" categories were combined into "T0" and "others," while the "NX" group in the "N stage" was excluded because its p-value in the multivariate Cox analysis was >0.05.

Kaplan–Meier survival curve results indicate that patients who were younger, ER-positive, PR-positive, had no lung or liver metastases, were classified as N2, had a molecular subtype of HER2+/HR+, were in T4 stage, underwent surgical treatment, received radiation therapy after surgery, and received systemic therapy after surgery had a longer OS (p<0.05). In addition, patients who were

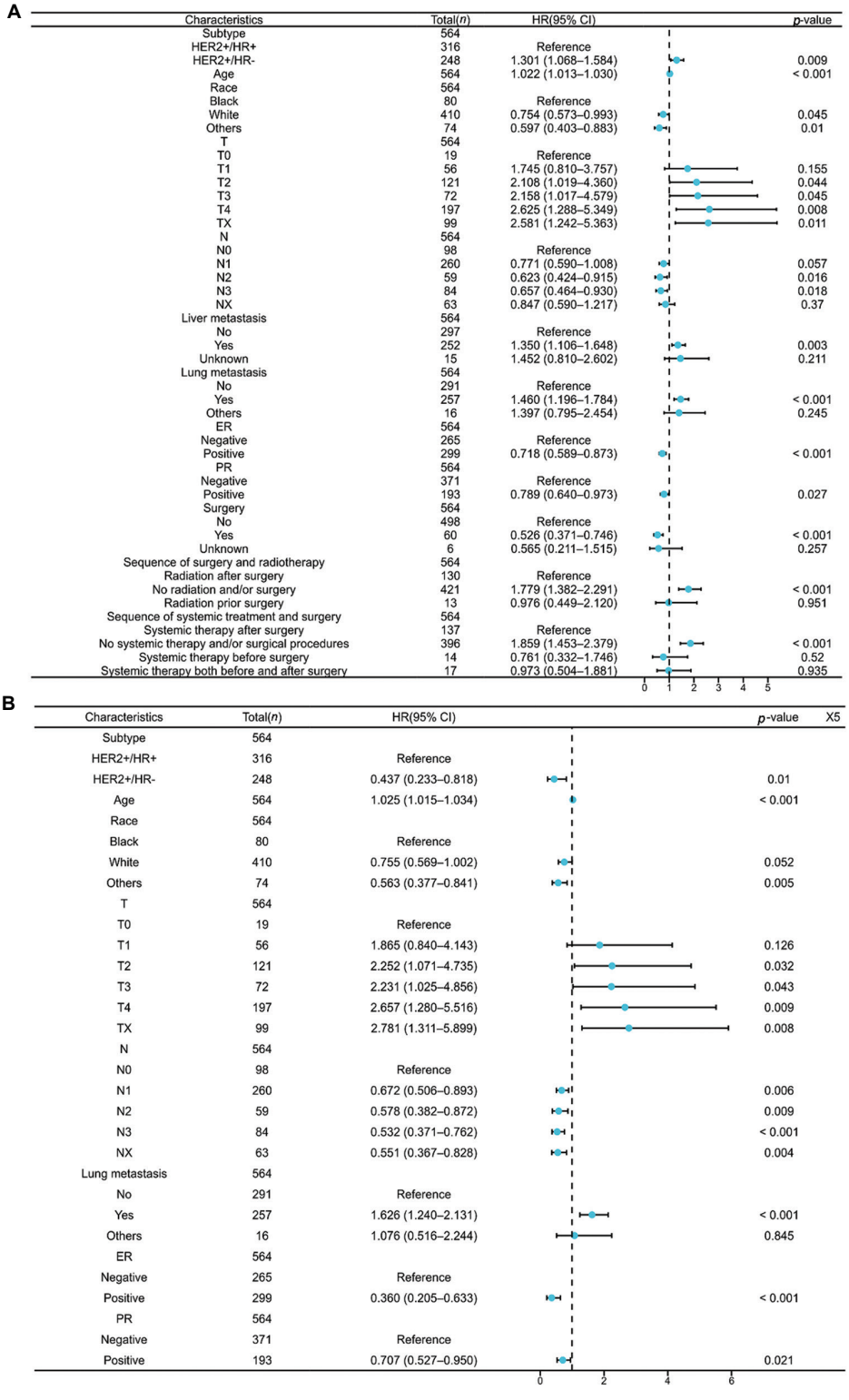

Figure 2. Forest plots of clinical characteristics associated with overall survival: (A) Forest plot of univariate Cox regression analysis; (B) forest plot of multivariate Cox regression analysis. "Reference" indicates the reference group for ordinal variables, with all other categories compared against it. Blue dots represent hazard ratio values, and horizontal lines indicate the 95% confidence intervals.

Abbreviations: CI: Confidence interval; ER: Estrogen receptor; HER2+/HR+: Human epidermal growth factor receptor 2-positive and hormone receptor-positive; HER2+/HR−: Human epidermal growth factor receptor 2-positive and hormone receptor-negative; HR: Hazard ratio; N: Node stage; NX: Unknown node stage; PR: Progesterone receptor; T: Tumor stage; TX: Unknown tumor stage.

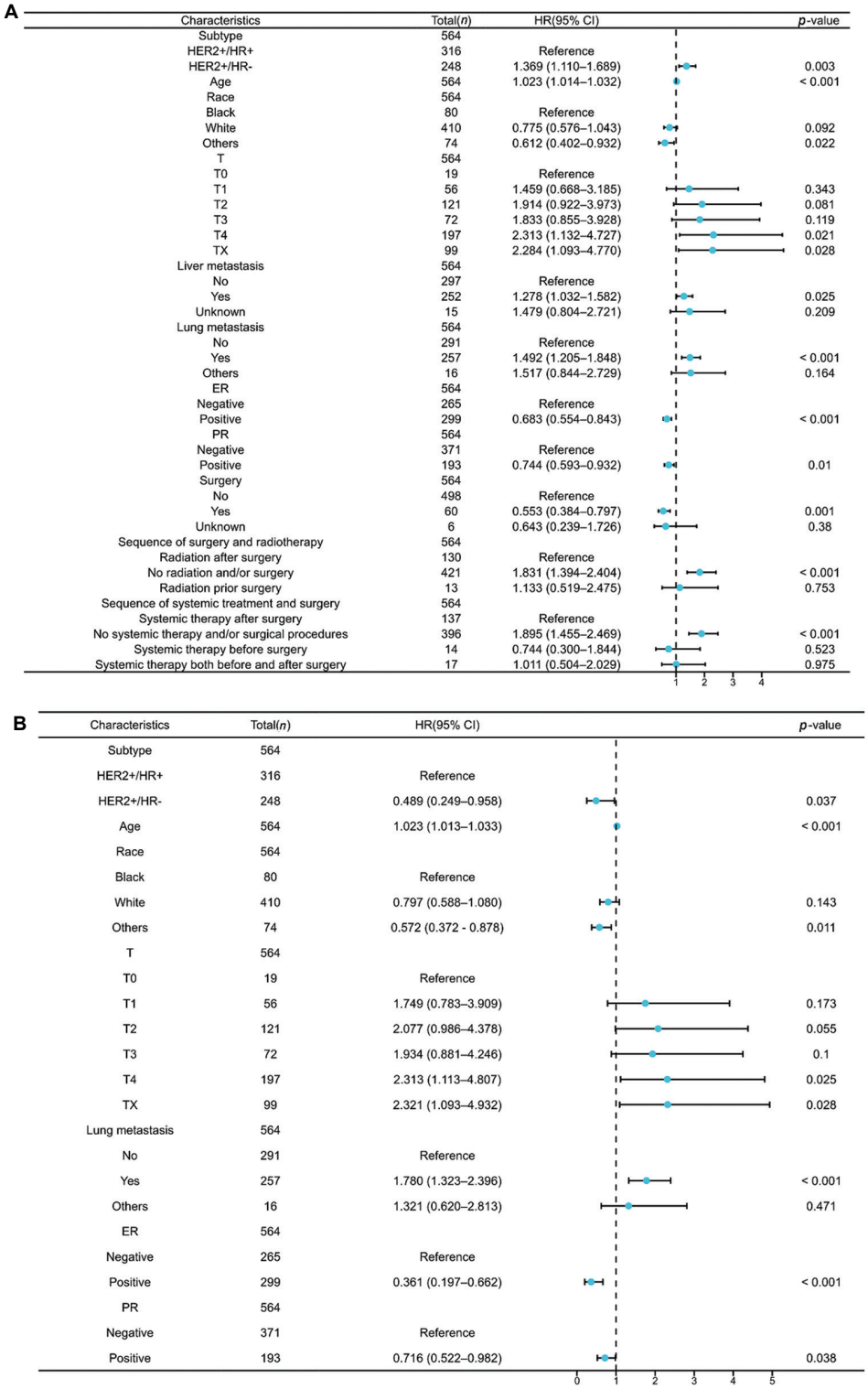

Figure 3. Forest plots of clinical characteristics associated with breast cancer-specific survival: (A) Forest plot of univariate Cox regression analysis; (B) forest plot of multivariate Cox regression analysis. "Reference" indicates the reference group for ordinal variables, with all other categories compared against it. Blue dots represent hazard ratio values, and horizontal lines indicate the 95% confidence intervals.

Abbreviations: CI: Confidence interval; ER: Estrogen receptor; HER2+/HR+: Human epidermal growth factor receptor 2-positive and hormone receptor-positive; HER2+/HR–: Human epidermal growth factor receptor 2-positive and hormone receptor-negative; HR: Hazard ratio; N: Node stage; NX: Unknown node stage; PR: Progesterone receptor; T: Tumor stage; TX: Unknown tumor stage.

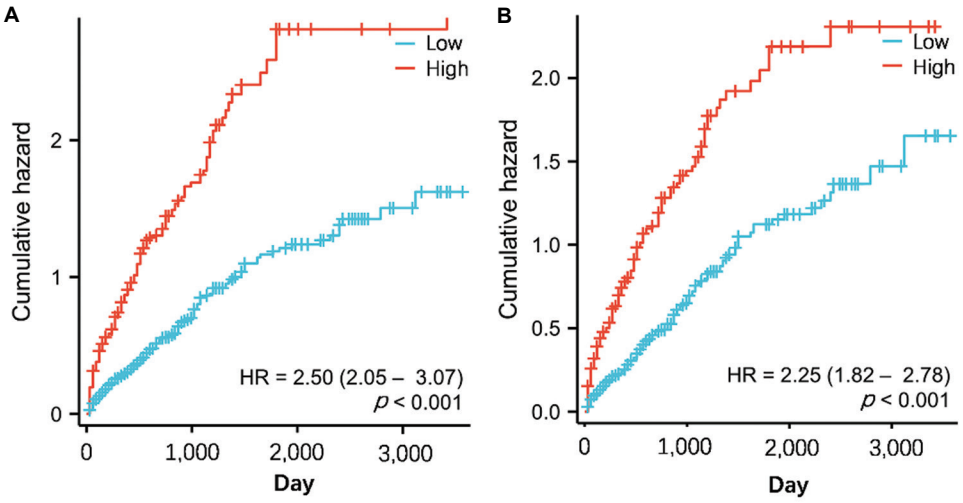

Figure 4. Cumulative risk-related survival analysis: (A) Overall survival curves for different cumulative risk groups; (B) Breast cancer-specific survival curves for different cumulative risk groups
Abbreviations: BCSS: Breast cancer-specific survival; HR: Hazard ratio; OS: Overall survival.

younger, ER-positive, PR-positive, had no lung or liver metastases, were classified as N2, were in T0 stage, had a molecular subtype of HER2+/HR+, underwent surgical treatment, received radiation therapy after surgery, and received systemic therapy after surgery had a longer BCSS (p<0.05) (Figure 6).

3.5. Construction of nomogram models for predicting OS and BCSS

Nomogram models for predicting 1-, 3-, and 5-year OS and BCSS were constructed based on statistically significant variables identified in the multivariate Cox regression analysis. Each prognostic factor was assigned a score according to its regression coefficient, reflecting its relative contribution to the risk of mortality. The total score, obtained by summing individual scores across all variables, corresponds to the predicted probability of OS or BCSS for each patient (Figure 7).

3.6. Calibration and validation of the nomogram risk prediction model

To assess the performance of the nomogram models, calibration curves were generated. As shown in Figure 8, the calibration curves for predicting 1-, 3-, and 5-year OS and BCSS closely align with the ideal reference line, indicating good agreement between predicted and actual outcomes. The C-index values for the OS and BCSS prediction models are 0.683 and 0.687, respectively, suggesting moderate predictive accuracy. Although the C-index values are not optimal, they still offer an initial estimation of the models' performance.

To further evaluate the predictive ability of the models, a time-dependent ROC curve analysis was performed. ROC curves, widely used in machine learning, are commonly applied for binary classification and evaluation of regression models through transformation methods. A common approach is to convert the predictions of the regression model into a binary classification problem.

In this study, patient outcomes were classified as binary (survival or death), making ROC analysis appropriate for assessing the performance of the multivariate Cox model. Time-dependent ROC curves represent a specialized application of ROC curves in survival data. By dividing groups based on various variable thresholds, the sensitivity and specificity at each threshold can be determined, allowing for the identification of optimal thresholds and evaluation of survival model performance.

The time-dependent ROC curves indicate that the nomogram models for predicting OS and BCSS in patients with HER2-positive breast cancer brain metastases exhibit high sensitivity, with areas under the curve of 0.731, 0.727, 0.791 for 1-, 3-, and 5-year OS, respectively, and 0.742, 0.719, 0.77 for 1-, 3-, and 5-year BCSS, respectively (Figure 9).

The clinical effectiveness of the predictive model was evaluated using DCA, which further assessed the clinical net benefit of the nomogram prediction model. The DCA curves for all positive and all negative represent the clinical net benefit under the assumptions of intervening in all patients or none, respectively. As shown in Figure 10, the model curves lie significantly above these two extremes,

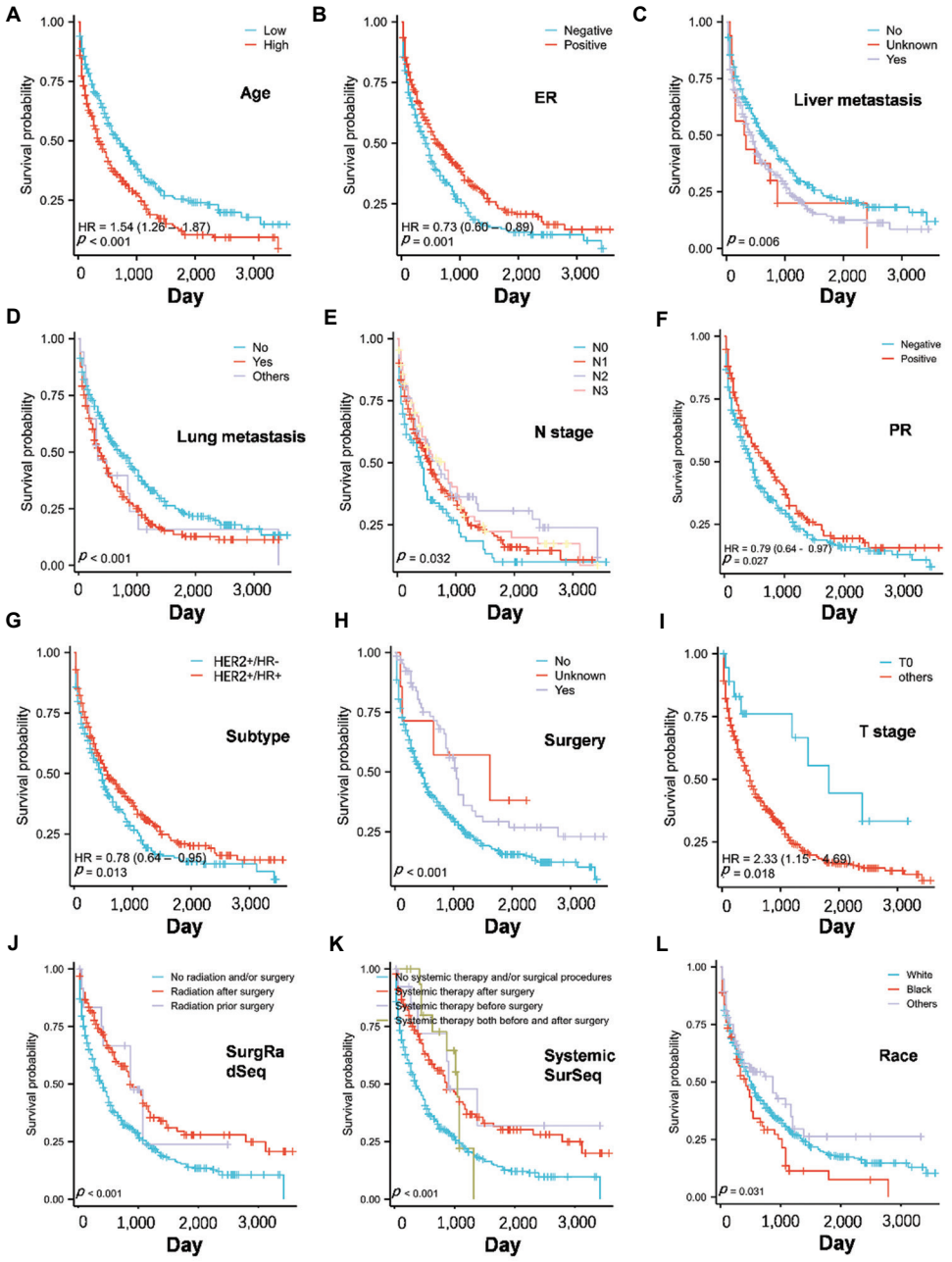

Figure 5. (A-L) Kaplan–Meier survival analysis of overall survival based on independent risk factors
Abbreviations: ER: Estrogen receptor; HER2+/HR+: Human epidermal growth factor receptor 2-positive and hormone receptor-positive; HER2+/HR−: Human epidermal growth factor receptor 2-positive and hormone receptor-negative; HR: Hazard ratio; N: Node; PR: Progesterone receptor; SurgRadSeq: Sequence of surgery and radiotherapy; SystemicSurSeq: Sequence of systemic treatment and surgery; T: Tumor.

indicating that the predictive model provides good clinical benefit.

4. Discussion

Patients with tumors–such as breast cancer–that metastasize to the brain typically have shorter life expectancy due to delayed detection and systemic treatment options, leading to a continuous increase in mortality rates.[12] Moreover, since routine brain imaging procedures–such as cranial magnetic resonance imaging–are not standard practice for breast cancer patients, the actual incidence of brain metastases may be underestimated.[13] Patients with stage III breast cancer are more likely to develop central nervous system metastases as the initial site of recurrence,

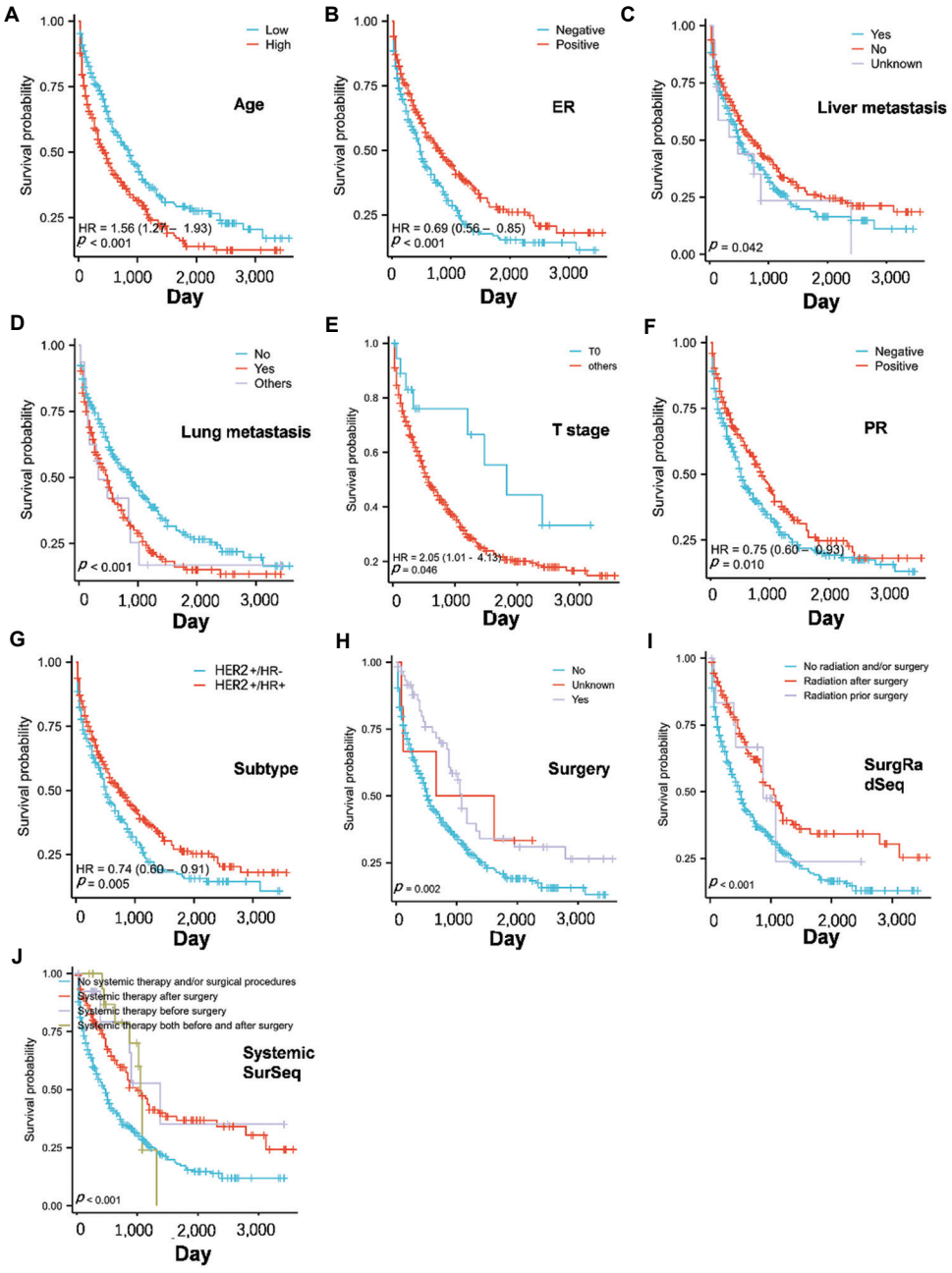

Figure 6. (A-J) Kaplan–Meier survival analysis of breast cancer-specific survival based on independent risk factors
Abbreviations: ER: Estrogen receptor; HER2+/HR+: Human epidermal growth factor receptor 2-positive and hormone receptor-positive; HER2+/HR–: Human epidermal growth factor receptor 2-positive and hormone receptor-negative; HR: Hazard ratio; N: Node; PR: Progesterone receptor; SurgRadSeq: Sequence of surgery and radiotherapy; SystemicSurSeq: Sequence of systemic treatment and surgery; T: Tumor.

while those with stage I or II breast cancer show relatively lower rates of brain metastasis.[14-18]

The SEER database, established by the American Cancer Society, provides publicly available tumor data and includes demographic and clinical pathological information representing nearly 30% of the United States population. In this study, the epidemiological status of the patient population was extracted from the SEER database. The median survival time for patients with breast cancer brain metastases ranges from 3.4 to 25.3 months, depending on prognostic factors such as molecular subtype and clinical symptoms. The median OS for HER2-positive breast

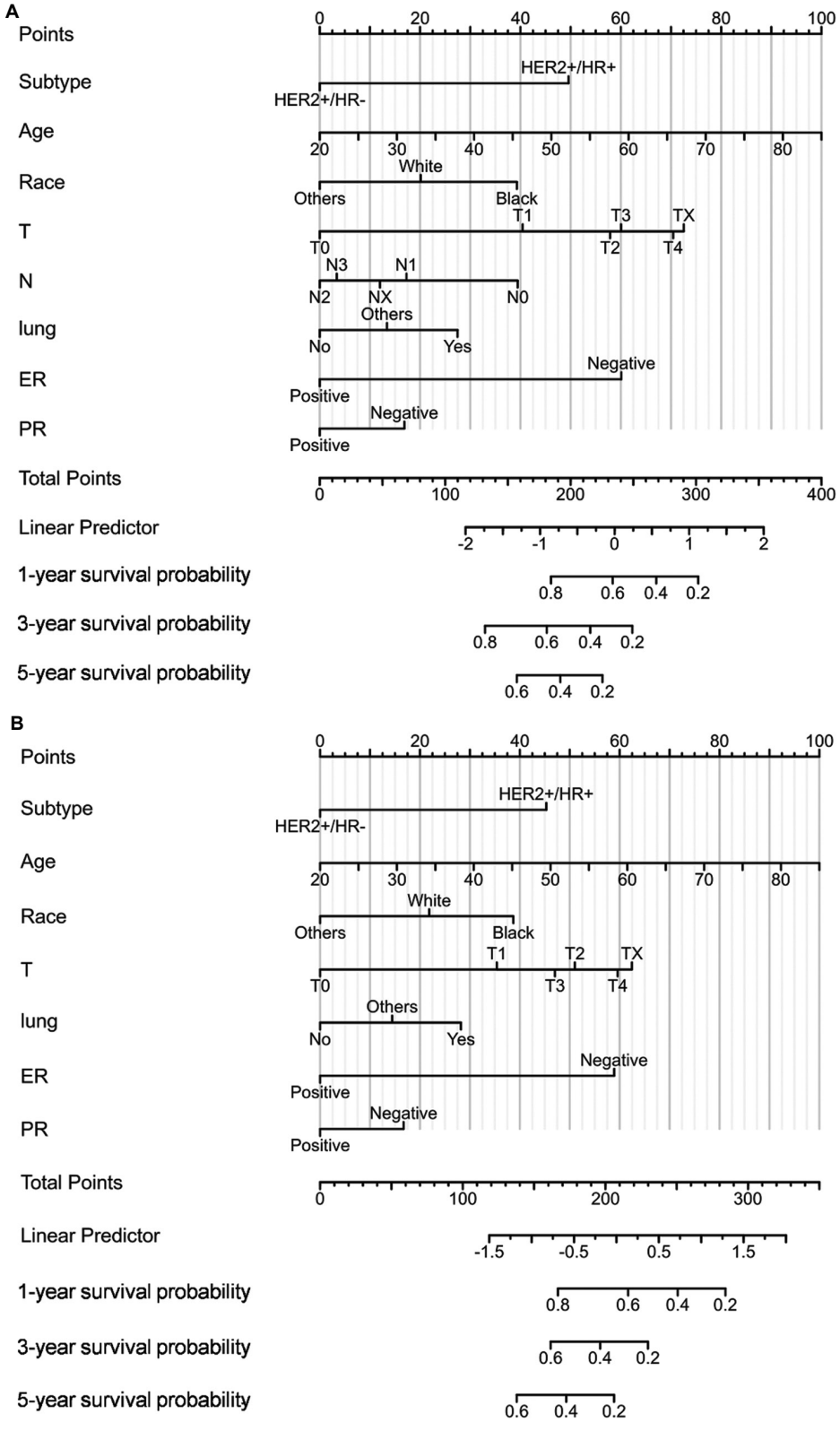

Figure 7. Nomogram prediction models for 1-, 3-, and 5-year outcomes: (A) Overall survival and (B) Breast cancer-specific survival
Abbreviations: ER: Estrogen receptor; HER2+/HR+: Human epidermal growth factor receptor 2-positive and hormone receptor-positive; HER2+/HR–: Human epidermal growth factor receptor 2-positive and hormone receptor-negative; HR: Hazard ratio; N: Node stage; NX: Unknown node stage; PR: Progesterone receptor; T: Tumor stage; TX: Unknown tumor stage.

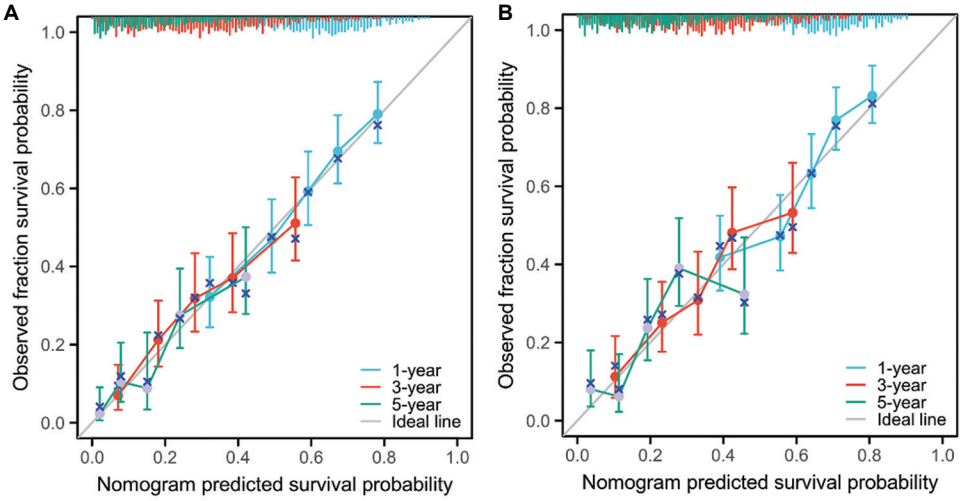

Figure 8. Calibration curves for the nomogram prediction model: (A) Overall survival, (B) Breast cancer-specific survival. The vertical lines at the top represent the survival probability corresponding to specific samples (i.e., the distribution of predicted survival rates).

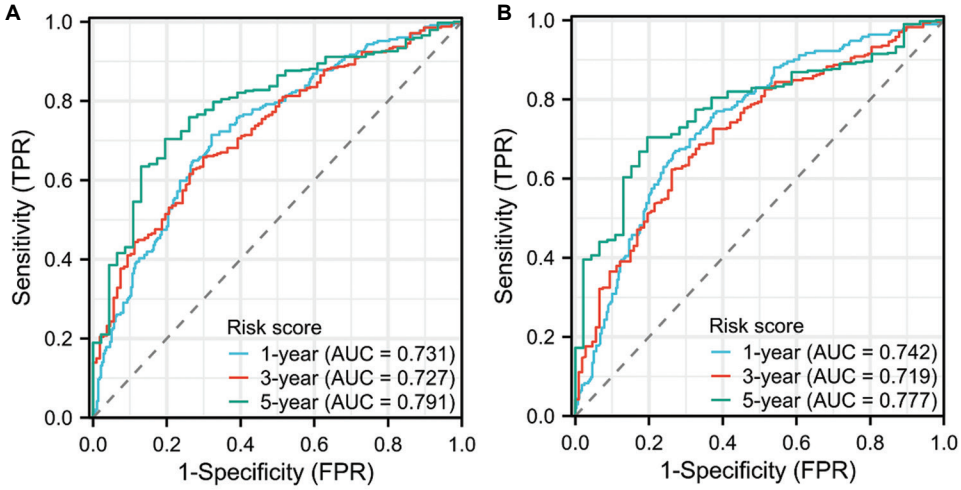

Figure 9. Time-dependent receiver operating characteristic analysis for the nomogram prediction model: (A) Overall survival, (B) Breast cancer-specific survival
Abbreviations: AUC: Area under the curve; FPR: False-positive rate; TPR: True-positive rate.

cancer patients with brain metastases is 10 months, which aligns with previously published research findings.[19-21]

Current targeted therapies for HER2-positive breast cancer mainly include trastuzumab, pertuzumab, lapatinib, and ado-trastuzumab emtansine, all of which demonstrate favorable efficacy and safety profiles.[22-25] However, trastuzumab is unable to cross the blood–brain barrier, resulting in an increased risk of recurrence within the central nervous system.[26-28]

This increased risk is not only due to therapeutic limitations but also linked to the inherent tendency of HER2-positive breast cancer to metastasize to the brain. This tendency may be associated with the upregulation of receptor tyrosine kinase HER2 in brain metastatic tumors and its role in facilitating the colonization of breast cancer cells within the brain microenvironment.[29] Regarding molecular subtypes, HER2-positive breast cancer is associated with the longest OS due to the availability of targeted therapies, whereas triple-negative breast cancer shows the shortest survival. ER-positive breast cancer presents an intermediate prognosis between the two.[29]

Notably, several studies have examined survival rates in relation to prognostic variables–such as tumor subtype,[30,31] age,[32] systemic chemotherapy status,[32] radiotherapy,[33] surgical status,[34] the time interval from initial cancer diagnosis to brain metastasis,[35] and primary tumor

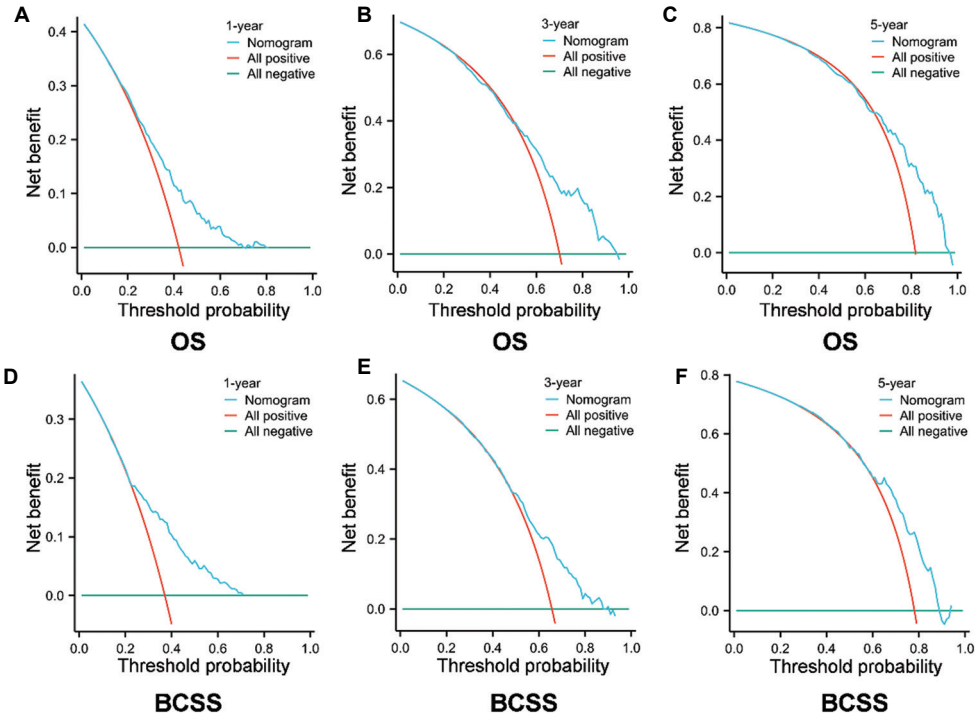

Figure 10. Decision curve analysis for the nomogram prediction model: (A-C) 1-, 3-, and 5-year overall survival; (D-F) 1-, 3-, and 5-year breast cancer-specific survival
Abbreviations: BCSS: Breast cancer-specific survival; OS: Overall survival.

size[35]–and have identified independent factors influencing survival in breast cancer patients with brain metastases, including estrogen and PRs, as well as the presence of extracranial metastases.

It is therefore evident that the prognosis of breast cancer patients with brain metastases exhibits significant heterogeneity. Previous studies confirmed that younger age, high tumor grade, multiple metastatic sites, lung or liver involvement, and negative hormone receptor status could indicate a higher risk of brain metastases in patients with breast cancer.[35]

In this study, factors associated with the prognosis of HER2-positive breast cancer patients with brain metastases are identified. The results show that both median OS and BCSS are significantly higher in patients who underwent surgery at the primary tumor site. Younger patients tend to have a higher risk of developing brain metastases and a poorer prognosis.

The findings indicate that brain metastases in HER2-positive breast cancer patients are significantly associated with lung metastases. Lung metastasis is confirmed to be an independent prognostic factor for brain metastases in breast cancer. This may be related to the expression of neuronal adhesion molecule integrin α6 and glial cell-derived neurotrophic factor in both the brain and lungs, which promotes the extravasation of breast cancer cells into the lungs and their eventual colonization in the brain.[36,37] However, further research is needed to fully elucidate this mechanism.

In addition, whole-brain radiation therapy–one of the primary treatment options during the brain metastasis stage of breast cancer–has shown the greatest OS benefit for patients with brain metastases. Furthermore, incorporating targeted therapy into systemic treatment across all subgroups further enhances OS benefits. Previous studies also suggest that treating only brain metastases, without addressing the primary breast cancer, may lead to reduced OS. This indicates that the effectiveness of treatment targeting the primary breast cancer lesion is a key predictor of OS, while the management of brain metastases may play more of a palliative role.[38]

However, the lack of specific data on surgery and radiotherapy in the SEER database limits the ability to evaluate their effects on HER2-positive breast cancer patients with brain metastases. Based on the findings of this study, receiving radiation therapy before surgery may act as a protective factor for OS but not for BCSS. Preoperative radiation may reduce the risk of non-cancer-related deaths, thereby improving OS, while its effect on BCSS may be diminished by other contributing factors.

Moreover, BCSS typically requires a longer follow-up period to observe disease-specific mortality, whereas OS includes all causes of death and may reveal differences earlier. If follow-up time is insufficient, the statistical power to detect BCSS differences may be limited. In addition, lymph node metastasis might serve as a protective factor for OS. This could be explained by better responsiveness to targeted or endocrine therapies in patients with lymph node involvement, and earlier detection of metastasis at diagnosis, which facilitates timely initiation of systemic treatment and improves disease control.

The nomogram prediction model was constructed based on the Cox proportional hazards model to analyze survival rates, evaluate its performance through calibration and validation, and further assess its clinical net benefit through DCA. Instead of examining only the direct associations between individual risk factors and patient survival, this study incorporated multiple potential predictors to improve the model's accuracy and applicability.[39] Notably, compared to previous studies, this is the first to explore the prognostic impact of treatment sequencing in patients with HER2-positive breast cancer brain metastases. The model was constructed using data from a large-scale, long-term cohort and integrates a broader range of clinicopathological features, including TX and NX stages. These additions expand upon and complement the findings of Chen *et al.*[40] and Lin *et al.*[40,41]

However, several limitations remain in this study. The SEER database lacks data on recurrence and subsequent metastatic sites for HER2-positive breast cancer, limiting the ability to evaluate patients who develop brain metastases at later stages of the disease. Although the SEER database provides a large sample size and high reliability compared to smaller, single-center studies on brain metastases in breast cancer, it does not provide information on several potentially important risk factors. These include the presence of vascular tumor thrombus, nerve invasion, lymph node positivity rate, Ki67 index, detailed surgical procedures, and specific types and dosages of chemotherapy or radiotherapy. Future updates to the SEER database that include such variables, along with external validation studies, would help improve the accuracy and clinical relevance of the predictive model.

5. Conclusion

This study provides a comprehensive analysis of prognostic factors in patients with HER2-positive breast cancer brain metastases. The findings highlight age, disease stage, liver metastasis, lung metastasis, and ER and PR status as significant independent prognostic indicators. Furthermore, a nomogram-based predictive model was developed to estimate individualized survival outcomes, offering potential clinical value for guiding treatment decisions.

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Conflict of interest

The authors declare that they do not have any competing interests.

Author contributions

Conceptualization: Xulong Zhu, Jianhui Li
Formal analysis: Shuhan Wu, Hengtao Song
Funding acquisition: Jianhui Li
Investigation: Yue Wang, Liping Yang
Methodology: Ziyu Luo, Wenjun Shu
Writing–original draft: Xinmiao Liu, Xulong Zhu
Writing–review & editing: *Ke Yan, Kenian Pan*

Ethics approval and consent to participate

The SEER database is a public database collected and collected by the National Cancer Institute of the United States, and the data have been removed from the information that can identify the patient, which is de-identified data. According to Article 32 of the Declaration of Helsinki, anonymized data research is exempt from ethical scrutiny. The SEER database meets this requirement, so studies based on it generally do not require informed consent from the patient.

Consent for publication

Not applicable.

Availability of data

All original data can be acquired from the Surveillance, Epidemiology, and End Results database (https://seer.cancer.gov/data-software/).

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