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# Prognostic nomograms for hormone receptor-positive breast cancer with lung metastasis: a SEER-based study with external validation

**Sihang Lin**
Tumor Hospital of Guangxi Medical University
**Lixia Liu**
Tumor Hospital of Guangxi Medical University
**Jiayu Guan**
ShenZhen People's Hospital
**Yanan Mo**
Tumor Hospital of Guangxi Medical University
**Jie Wang**
Tumor Hospital of Guangxi Medical University
**Siyu Luo**
Tumor Hospital of Guangxi Medical University
**Huawei Yang**
930060@sr.gxmu.edu.cn

Tumor Hospital of Guangxi Medical University

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## Abstract

# Background

Validated prognostic tools for breast cancer with lung metastasis (BCLM) are lacking, and most existing models have not been temporally validated for contemporary patients. Using large-scale data from the Surveillance, Epidemiology, and End Results (SEER) registry, this study developed a nomogram to predict survival in hormone receptor-positive (HR+) BCLM patients and validated it across multiple cohorts, including a temporal validation cohort of recently diagnosed patients.

# Methods

Among 8,850 HR+ BCLM records initially identified from the SEER database (2010–2021), 4,425 patients met the final eligibility criteria. Patients diagnosed from 2010 to 2017 (n = 2,706) were randomly divided into a training cohort (n = 1,894) and an internal validation cohort (n = 812) at a 7:3 ratio; patients diagnosed from 2018 to 2021 (n = 1,719) were assigned to a temporal validation cohort to assess model performance in contemporary practice. An external validation cohort (n = 374) was obtained from Guangxi Medical University Cancer Hospital to independently validate the models' generalizability. Independent predictors of overall survival (OS) and breast cancer-specific survival (BCSS) were identified using multivariate Cox regression analysis. Based on these predictors, two 3-year prognostic nomograms were constructed for OS and BCSS, and their predictive performance was evaluated at 1-, 2-, and 3-year time points. The models were evaluated using receiver operating characteristic (ROC) curves, calibration plots, Harrell's concordance index (C-index), and decision curve analysis (DCA).

# Results

Eleven clinicopathological variables were incorporated into the final multivariable models, with individual category-specific associations varying between OS and BCSS. In the training cohort, the C-index was 0.655 (95% CI: 0.637–0.673) for OS and 0.662 (95% CI: 0.644–0.680) for BCSS. In the internal validation cohort, the corresponding values were 0.648 (95% CI: 0.621–0.675) and 0.657 (95% CI: 0.630–0.684). The temporal validation cohort (2018–2021) showed numerically higher C-index values than the other cohorts: 0.681 (95% CI: 0.663–0.699) for OS and 0.686 (95% CI: 0.667–0.704) for BCSS, suggesting that the models maintains acceptable discriminative performance in contemporary patients. The external validation cohort produced C-index values of 0.657 (95% CI: 0.613–0.686) for OS and 0.652 (95% CI: 0.611–0.683) for BCSS. ROC curves, calibration plots, and DCA further supported the predictive performance and potential clinical utility of the nomograms across all cohorts.

# Conclusion

The validated nomograms demonstrated acceptable predictive performance for HR+ BCLM patients across temporal and external validation cohorts, supporting individualized prognostic assessment for patients with HR-positive breast cancer and lung metastasis.

# Introduction

Breast carcinoma remains the most frequently diagnosed malignancy and the leading cause of cancer-related death among women worldwide, with age-standardized incidence rates exceeding 85 per 100,000 women annually in high-income countries(1, 2). Metastatic spread in breast cancer commonly involves the bone (35–40%), lung (21–32%), brain (10–15%), and liver (8–12%), with lung metastases exhibiting a particularly high prevalence in hormone receptor-positive ($HR^+$) subtypes(3, 4). Breast cancer with lung metastasis (BCLM) is associated with poor survival outcomes; contemporary cohort studies report a median overall survival of 18–27 months despite the administration of multimodal therapies(5). Furthermore, more than 90% of breast cancer-related deaths are associated with metastatic disease. Lung metastasis is of particular concern because an estimated 60–70% of patients who die from breast cancer have pulmonary involvement(6). Nevertheless, the specific determinants influencing the incidence and prognosis of BCLM remain incompletely understood.

The American Joint Committee on Cancer (AJCC) staging system is widely used in clinical practice for breast cancer prognosis. However, all BCLM patients are uniformly classified as stage IV, and the AJCC criteria lack precision in predicting outcomes due to considerable heterogeneity within metastatic presentations(7). This limitation underscores the urgent need for validated prognostic stratification tools tailored specifically to this patient population.

Growing evidence indicates that molecular subtypes of breast cancer are associated with varying risks of pulmonary metastasis. In particular, early-stage $HR^+$/human epidermal growth factor receptor 2-positive ($HER2^+$) and triple-negative breast cancers show a higher propensity for lung metastasis compared to $HR^+/HER2^-$ tumors(8, 9). However, the effect of molecular subtype on survival following lung metastasis remains unclear, and previous prognostic models for BCLM have often overlooked molecular classification. Given that $HR^+$ breast cancer represents the most common subtype, prognostic studies focusing specifically on $HR^+$ BCLM patients are of considerable clinical relevance.

Nomograms provide a useful methodological framework for developing prognostic models in BCLM. By integrating clinicopathological variables and survival data, they facilitate comprehensive risk stratification and enable early identification of high-risk individuals, thereby guiding timely intervention to mitigate metastatic complications(10). However, most existing prognostic models for BCLM have been developed using historical data without temporal validation, leaving their applicability to contemporary patients uncertain. Furthermore, few studies have incorporated independent external validation to confirm model generalizability across diverse populations.

To address these gaps, this study aimed to develop and validate a prognostic nomogram for $HR^+$ BCLM using data from the Surveillance, Epidemiology, and End Results (SEER) database and an independent external cohort from Guangxi Medical University Cancer Hospital. The models was evaluated across multiple cohorts—training, internal validation, temporal validation (2018–2021), and external validation—to provide clinicians with a reliable tool for personalized prognostic assessment and treatment decision-making support.

# Methods

# Patients

This study was approved by the Research Ethics Committee of Guangxi Medical University Cancer Hospital (Approval No. KY2025677). Retrospective clinical data from patients treated at this institution were collected with informed consent. For the anonymized data obtained from the SEER database, additional informed consent was waived. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013 revision).

The SEER program provides a publicly accessible population-based cancer registry, available at: https://seer.cancer.gov/data/access.html. Upon obtaining official permission (Authorization Number: 264491-1vlCSnNcyF), we retrieved detailed clinical information of breast cancer patients using SEER*Stat software (version 8.4.4). Given that molecular subtype information for distant metastases has been consistently recorded since 2010, we selected cases of hormone receptor-positive breast cancer with lung metastasis (BCLM) initially diagnosed between 2010 and 2021. To ensure sufficient follow-up for survival analysis, patients diagnosed from 2010 to 2017 were used for model development and internal validation, while patients diagnosed from 2018 to 2021 served as a temporal validation cohort to evaluate the models' applicability to contemporary patients.

The inclusion criteria were: (1) adult female patients; (2) breast cancer as the primary and only malignant tumor; (3) pathologically confirmed diagnosis supported by immunohistochemistry; (4) presence of lung metastasis; (5) patients were newly diagnosed with de novo stage IV breast cancer; and (6) HR-positive status. We excluded patients lacking documented age, race, or marital status, as well as cases identified only through autopsy or death certificates. Additional exclusion criteria included unknown T or N stage and unknown metastasis status. Figure 1 illustrates the patient selection process for the SEER cohort.

Among 8,850 records initially identified from the SEER database, 4,425 patients met the final eligibility criteria. Patients diagnosed between 2010 and 2017 (n = 2,706) were randomly divided into a training set (n = 1,894, 70%) and an internal validation set (n = 812, 30%) in a 7:3 ratio. The training set was used to develop the prognostic model, while the internal validation set assessed the models' robustness in an internal hold-out cohort. Patients diagnosed between 2018 and 2021 (n = 1,719) were assigned to a temporal validation cohort to assess the models' performance in contemporary clinical practice.

To enhance the validity of our findings, an external validation cohort comprising 374 eligible patients from the Guangxi Medical University Cancer Hospital was also included. These patients were diagnosed between 2015 and 2021 and met the same inclusion criteria as the SEER cohort: (1) adult female; (2) primary breast cancer with pathologically confirmed lung metastasis; (3) $HR^+$ status; (4) de novo stage IV; (5) complete clinical and follow-up data. The external cohort met the same major eligibility criteria as the SEER cohort; patients with unknown surgery status were additionally excluded because complete treatment information was required for external model validation. This external cohort was used to independently evaluate the generalizability of the nomograms through ROC curves, calibration plots, DCA, and Kaplan-Meier survival analysis. Figure 1B illustrates the patient selection process for the external validation cohort. Baseline characteristics of the external validation cohort are presented in Supplementary Table S1.

## Variables

The analytical dataset included the following multidimensional epidemiological parameters: age at diagnosis; year of diagnosis; race; marital status; histological type; tumor grade; HER2 status; T and N categories were

extracted from SEER records and harmonized into common T1–T4 and N0–N3 categories across diagnosis years; sites of metastasis (brain, liver, bone); and treatment modalities (surgery, chemotherapy, radiotherapy).

Age was stratified into clinically relevant groups: <50 years, 50–69 years, and ≥ 70 years. Race was categorized as White, Black, or Other. Marital status was classified as married, unmarried, or other (including divorced, widowed, or separated). Histological subtypes were defined according to WHO classification (ICD-O-3 codes) as ductal carcinoma (8500), lobular carcinoma (8520), or other. HR-positive disease was defined as estrogen receptor-positive and/or progesterone receptor-positive disease according to SEER records. Tumor grade was categorized according to the standard Nottingham grading system as Grade I, II, or III; Grade IV cases (0.2% of the cohort, n = 11) were merged with Grade III due to the extremely small sample size, as is commonly done in SEER-based studies. HER2 status was categorized as positive or negative. Metastatic involvement and treatment modalities were recorded as Yes, No, or Unknown. For treatment-related variables (surgery and chemotherapy), patients with missing or unknown data were merged with the 'No' category for the primary analysis, as this approach is commonly adopted in SEER-based studies to preserve sample size. The potential impact of this grouping on the models performance is acknowledged in the limitations. The models coefficients, baseline survival estimates, and risk score cutoff are presented in Supplementary Table S2. For external validation, variables were coded according to the same definitions used in the training cohort. Since race categories specific to the Chinese cohort were not available, all external patients were uniformly coded as 'Other' for consistency with the SEER classification.

# Statistical Analysis

This study adopted two primary endpoints: all-cause mortality and breast cancer-specific mortality. Overall survival (OS) was defined as the time from initial diagnosis to death from any cause or last follow-up. Breast cancer-specific survival (BCSS) was defined as the time from diagnosis to death attributable to breast cancer. For the cause-specific Cox analysis of BCSS, deaths from causes other than breast cancer were treated as censored observations. Because SEER records survival time in completed months, a survival time of 0 months indicates death or last follow-up within the first month; these records were retained in the analysis.

Demographic and clinical characteristics were compared using contingency tables and $\chi^2$ tests in R (version 4.4.1; R Foundation). Univariate Cox proportional hazards models were first applied to identify potential prognostic factors in $HR^+$ BCLM patients. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for each variable. Variables with a p-value < 0.05 in univariate analysis were included in the multivariate Cox regression model to identify independent predictors of OS and BCSS. The proportional hazards assumption was assessed using Schoenfeld residuals and was not violated (global P > 0.05).

Predictors significantly associated with survival in the multivariate analysis were incorporated into nomograms to estimate 3-year (36-month) probabilities of OS and BCSS. The discriminatory ability of the models was assessed using time-dependent receiver operating characteristic (ROC) curves, quantified by the area under the curve (AUC), with values ranging from 0.5 (random prediction) to 1.0 (perfect discrimination) (11). Calibration in the training cohort was assessed using bootstrap optimism correction with 500 resamples(12). For the internal, temporal, and external validation cohorts, survival probabilities were generated using the fixed training-cohort coefficients and baseline survival function, and observed survival probabilities were estimated using the Kaplan–Meier method without model refitting. Decision curve analysis (DCA) was performed to assess the clinical net

benefit using 36-month mortality risk (1 − S(36)) as the input(13), with censoring handled via Kaplan-Meier estimation. Harrell's concordance index (C-index) was also calculated as a measure of model discrimination(11).

Based on the multivariate Cox regression, a risk score for each patient was calculated by multiplying the value of each variable by its corresponding regression coefficient (β) and summing the products. Patients were classified into high- and low-risk groups according to the median risk score. The median risk score derived from the training cohort was used as the fixed cutoff and applied unchanged to all validation cohorts. Kaplan–Meier survival curves were generated to compare survival between the risk groups, and the log-rank test was used to assess statistical significance.

The predictive performance of the models was evaluated across multiple cohorts: the training cohort (model development), internal validation cohort (internal hold-out validation), temporal validation cohort (2018–2021, to assess applicability to contemporary patients), and an independent external cohort from Guangxi Medical University Cancer Hospital (to assess generalizability to diverse populations). Calibration, discrimination, and clinical utility were assessed in all four cohorts. The regression coefficients and baseline survival functions estimated in the training cohort were fixed and applied without refitting to the internal, temporal, and external validation cohorts.

All statistical analyses were performed using R version 4.4.1 (R Foundation for Statistical Computing). The following R packages were used for model development and validation: survival (version 3.5-7) for Cox regression and KM curves; rms (version 6.8-0) for nomogram construction and bootstrap-corrected calibration plots; timeROC (version 0.4) for time-dependent ROC curves; ggscidca (version 0.1.0) for decision curve analysis; and ggplot2 and survminer for figure generation. Randomization of the training–validation split was performed using set.seed(123) in R. Continuous variables were not included in the final models; therefore, no nonlinear functional form was modeled using restricted cubic splines.

## Results

# Baseline Characteristics

A total of 4,425 eligible patients with hormone receptor-positive breast cancer and lung metastasis (BCLM) were identified from the SEER registry (2010–2021) and divided into three cohorts: a training cohort (n = 1,894, 2010–2017), an internal validation cohort (n = 812, 2010–2017), and a temporal validation cohort (n = 1,719, 2018–2021). An independent external validation cohort (n = 374) was obtained from Guangxi Medical University Cancer Hospital. The follow-up period for the SEER cohorts ranged from 0 to 166 months (median: 32 months). The training, internal validation, and temporal validation cohorts had median follow-up durations of 31, 34, and 33 months, respectively. In the training cohort, a total of 1,575 OS events (83.2%) and 1,416 BCSS events (74.8%) were recorded. In the internal validation cohort, 688 OS events (84.7%) and 600 BCSS events (73.9%) were recorded; in the temporal validation cohort, 973 OS events (56.6%) and 858 BCSS events (49.9%) were recorded; and in the external validation cohort, 262 OS events (70.1%) and 232 BCSS events (62.0%) were recorded, with a median follow-up of 34 months. Detailed demographic and clinical characteristics of the training, internal validation, and temporal validation cohorts are presented in Table 1.

Table 1
Baseline characteristics of HR+ breast cancer patients with lung metastasis in the training, internal validation, and temporal validation cohorts

| Variable | Overall (n = 4,425) | Training (n = 1,894) | Internal validation (n = 812) | Temporal validation (n = 1,719) | P value |
|---|---|---|---|---|---|
| Age | | | | | 0.067 |
| < 50 | 837 (18.9) | 349 (18.4) | 164 (20.2) | 324 (18.8) | |
| 50–69 | 2,237 (50.6) | 994 (52.5) | 412 (50.7) | 831 (48.3) | |
| ≥ 70 | 1,351 (30.5) | 551 (29.1) | 236 (29.1) | 564 (32.8) | |
| Race | | | | | 0.068 |
| White | 718 (16.2) | 295 (15.6) | 145 (17.9) | 278 (16.2) | |
| Black | 3,206 (72.5) | 1,396 (73.7) | 589 (72.5) | 1,221 (71.0) | |
| Other | 501 (11.3) | 203 (10.7) | 78 (9.6) | 220 (12.8) | |
| Marital status | | | | | 0.167 |
| Married | 1,113 (25.2) | 463 (24.4) | 189 (23.3) | 461 (26.8) | |
| Unmarried | 1,900 (42.9) | 840 (44.4) | 354 (43.6) | 706 (41.1) | |
| Other | 1,412 (31.9) | 591 (31.2) | 269 (33.1) | 552 (32.1) | |
| Histological type | | | | | < 0.001 |
| Ductal | 3,851 (87.0) | 1,597 (84.3) | 707 (87.1) | 1,547 (90.0) | |
| Lobular | 195 (4.4) | 91 (4.8) | 27 (3.3) | 77 (4.5) | |
| Other | 379 (8.6) | 206 (10.9) | 78 (9.6) | 95 (5.5) | |
| Histological grade | | | | | 0.557 |
| I | 357 (8.1) | 142 (7.5) | 66 (8.1) | 149 (8.7) | |
| II | 2,110 (47.7) | 899 (47.5) | 376 (46.3) | 835 (48.6) | |
| III/IV | 1,958 (44.2) | 853 (45.1) | 370 (45.6) | 735 (42.8) | |
| T stage | | | | | 0.111 |
| T1/2 | 1,753 (39.6) | 753 (39.8) | 308 (37.9) | 692 (40.3) | |
| T3 | 768 (17.4) | 301 (15.9) | 146 (18.0) | 321 (18.7) | |
| T4 | 1,904 (43.0) | 840 (44.4) | 358 (44.1) | 706 (41.1) | |
| N stage | | | | | < 0.001 |

Data are presented as n (%). P values were calculated using Chi-square tests for categorical variables. Percentages may not sum to 100% due to rounding. Marital status “Other” includes divorced, widowed, or separated. Surgery “Unknown” indicates patients with missing data on surgical status. These 44 patients were included in the No/Unknown category for the primary analysis.

| Variable | Overall (n = 4,425) | Training (n = 1,894) | Internal validation (n = 812) | Temporal validation (n = 1,719) | P value |
|---|---|---|---|---|---|
| N0 | 824 (18.6) | 386 (20.4) | 159 (19.6) | 279 (16.2) | |
| N1 | 2,425 (54.8) | 968 (51.1) | 420 (51.7) | 1,037 (60.3) | |
| N2 | 546 (12.3) | 265 (14.0) | 112 (13.8) | 169 (9.8) | |
| N3 | 630 (14.2) | 275 (14.5) | 121 (14.9) | 234 (13.6) | |
| HER2 status | | | | | 0.036 |
| Negative | 3,351 (75.7) | 1,418 (74.9) | 597 (73.5) | 1,336 (77.7) | |
| Positive | 1,074 (24.3) | 476 (25.1) | 215 (26.5) | 383 (22.3) | |
| Bone metastasis | | | | | 0.005 |
| No | 1,729 (39.1) | 788 (41.6) | 317 (39.0) | 624 (36.3) | |
| Yes | 2,696 (60.9) | 1,106 (58.4) | 495 (61.0) | 1,095 (63.7) | |
| Brain metastasis | | | | | 0.969 |
| No | 4,058 (91.7) | 1,737 (91.7) | 743 (91.5) | 1,578 (91.8) | |
| Yes | 367 (8.3) | 157 (8.3) | 69 (8.5) | 141 (8.2) | |
| Liver metastasis | | | | | 0.122 |
| No | 3,318 (75.0) | 1,391 (73.4) | 617 (76.0) | 1,310 (76.2) | |
| Yes | 1,107 (25.0) | 503 (26.6) | 195 (24.0) | 409 (23.8) | |
| Surgery | | | | | < 0.001 |
| No | 3,448 (77.9) | 1,373 (72.5) | 615 (75.7) | 1,460 (84.9) | |
| BCS | 276 (6.2) | 148 (7.8) | 51 (6.3) | 77 (4.5) | |
| Mastectomy | 657 (14.8) | 351 (18.5) | 138 (17.0) | 168 (9.8) | |
| Unknown | 44 (1.0) | 22 (1.2) | 8 (1.0) | 14 (0.8) | |
| Chemotherapy | | | | | < 0.001 |
| No/Unknown | 1,650 (37.3) | 800 (42.2) | 347 (42.7) | 503 (29.3) | |
| Yes | 2,775 (62.7) | 1,094 (57.8) | 465 (57.3) | 1,216 (70.7) | |
| Radiation | | | | | 0.005 |
| No | 3,224 (72.9) | 1,352 (71.4) | 573 (70.6) | 1,299 (75.6) | |
| Yes | 1,201 (27.1) | 542 (28.6) | 239 (29.4) | 420 (24.4) | |

Data are presented as n (%). P values were calculated using Chi-square tests for categorical variables. Percentages may not sum to 100% due to rounding. Marital status “Other” includes divorced, widowed, or separated. Surgery “Unknown” indicates patients with missing data on surgical status. These 44 patients were included in the No/Unknown category for the primary analysis.

| Variable | Overall (n = 4,425) | Training (n = 1,894) | Internal validation (n = 812) | Temporal validation (n = 1,719) | P value |
|---|---|---|---|---|---|
| Therapy sequence | | | | | < 0.001 |
| Adjuvant | 212 (4.8) | 123 (6.5) | 41 (5.0) | 48 (2.8) | |
| Neoadjuvant | 1,135 (25.6) | 482 (25.4) | 199 (24.5) | 454 (26.4) | |
| Other | 3,078 (69.6) | 1,289 (68.1) | 572 (70.4) | 1,217 (70.8) | |
| Nodes positive | | | | | < 0.001 |
| 1–3 | 3,029 (68.5) | 1,386 (73.2) | 594 (73.2) | 1,049 (61.0) | |
| 4–9 | 1,396 (31.5) | 508 (26.8) | 218 (26.8) | 670 (39.0) | |
| Nodes examined | | | | | < 0.001 |
| 1–3 | 750 (16.9) | 387 (20.4) | 153 (18.8) | 210 (12.2) | |
| 4–9 | 108 (2.4) | 62 (3.3) | 27 (3.3) | 19 (1.1) | |
| ≥ 10 | 3,567 (80.6) | 1,445 (76.3) | 632 (77.8) | 1,490 (86.7) | |

Data are presented as n (%). P values were calculated using Chi-square tests for categorical variables. Percentages may not sum to 100% due to rounding. Marital status “Other” includes divorced, widowed, or separated. Surgery “Unknown” indicates patients with missing data on surgical status. These 44 patients were included in the No/Unknown category for the primary analysis.

In the SEER cohort, the age distribution was as follows: 50.6% of patients were 50–69 years old, 30.5% were ≥ 70 years, and 18.9% were under 50 years. Invasive ductal carcinoma was the predominant histological type (87.0%). HER2-negative status was observed in 75.7% of cases. Regarding T stage, 39.6% of patients had T1–2 tumors, 17.4% had T3 tumors, and 43.0% had T4 tumors. For N stage, 18.6% were N0, 54.8% were N1, 12.3% were N2, and 14.2% were N3. Bone metastases were present in 60.9% of patients, while liver and brain metastases were observed in 25.0% and 8.3%, respectively. Regarding treatment, chemotherapy was administered to 62.7% of patients, while 22.1% underwent surgery (including 6.2% BCS and 14.8% mastectomy), and 27.1% received radiotherapy (Table 1).

# Survival Analysis

Univariable and multivariable Cox regression analyses were performed in the training cohort (n = 1,894) to identify independent prognostic factors for OS and BCSS. Eleven clinicopathological parameters showed significant associations with OS or BCSS in univariate analysis and were subsequently entered into the multivariate Cox regression model, which confirmed their independent contributions with category-specific associations varying between OS and BCSS (Table 2). The final predictors were incorporated into a nomogram to estimate 3-year (36-month) survival probabilities for OS and BCSS. N stage was not retained in the multivariate model because its overall association with survival was not statistically significant in the univariable analysis (global P = 0.218).

Table 2
Univariate and multivariate Cox regression analyses for OS and BCSS in the training cohort

| Variable | OS Univariate HR (95% CI) | P | OS Multivariate HR (95% CI) | P | BCSS Univariate HR (95% CI) | P | BCSS Multivariate HR (95% CI) | P |
|---|---|---|---|---|---|---|---|---|
| Age | | | | | | | | |
| < 50 | Ref | — | Ref | — | Ref | — | Ref | — |
| 50–69 | 1.21 (1.05–1.39) | 0.008 | 1.23 (1.06–1.42) | 0.006 | 1.17 (1.01–1.35) | 0.034 | 1.20 (1.03–1.40) | 0.021 |
| ≥ 70 | 1.58 (1.36–1.83) | < 0.001 | 1.45 (1.23–1.71) | < 0.001 | 1.39 (1.19–1.63) | < 0.001 | 1.38 (1.16–1.65) | < 0.001 |
| Race | | | | | | | | |
| White | Ref | — | Ref | — | Ref | — | Ref | — |
| Black | 0.80 (0.69–0.91) | 0.001 | 0.82 (0.71–0.95) | 0.008 | 0.78 (0.68–0.90) | 0.001 | 0.79 (0.68–0.92) | 0.003 |
| Other | 0.78 (0.64–0.95) | 0.012 | 0.82 (0.67–1.01) | 0.060 | 0.78 (0.64–0.96) | 0.020 | 0.80 (0.64–0.99) | 0.039 |
| Marital status | | | | | | | | |
| Married | Ref | — | Ref | — | Ref | — | Ref | — |
| Unmarried | 0.84 (0.74–0.95) | 0.007 | 0.89 (0.78–1.02) | 0.089 | 0.83 (0.73–0.95) | 0.005 | 0.88 (0.76–1.01) | 0.070 |
| Other | 1.25 (1.10–1.43) | 0.001 | 1.16 (1.00-1.34) | 0.047 | 1.18 (1.03–1.36) | 0.018 | 1.11 (0.95–1.29) | 0.189 |
| Grade | | | | | | | | |
| I | Ref | — | Ref | — | Ref | — | Ref | — |
| II | 1.19 (0.98–1.45) | 0.078 | 1.28 (1.02–1.60) | 0.032 | 1.28 (1.03–1.59) | 0.026 | 1.33 (1.04–1.70) | 0.023 |
| III/IV | 1.31 (1.08–1.60) | 0.007 | 1.78 (1.42–2.24) | < 0.001 | 1.50 (1.21–1.86) | < 0.001 | 1.94 (1.51–2.50) | < 0.001 |
| T stage | | | | | | | | |
| T1/2 | Ref | — | Ref | — | Ref | — | Ref | — |

HR, hazard ratio; CI, confidence interval; OS, overall survival; BCSS, breast cancer-specific survival. Ref indicates the reference category; — indicates not applicable.

| Variable | OS Univariate HR (95% CI) | P | OS Multivariate HR (95% CI) | P | BCSS Univariate HR (95% CI) | P | BCSS Multivariate HR (95% CI) | P |
|---|---|---|---|---|---|---|---|---|
| T3 | 1.06 (0.91–1.23) | 0.434 | 1.09 (0.94–1.27) | 0.260 | 1.13 (0.96–1.32) | 0.132 | 1.15 (0.98–1.35) | 0.082 |
| T4 | 1.26 (1.13–1.40) | < 0.001 | 1.25 (1.10–1.41) | 0.001 | 1.31 (1.17–1.47) | < 0.001 | 1.28 (1.12–1.46) | 0.002 |
| HER2 status | | | | | | | | |
| Negative | Ref | — | Ref | — | Ref | — | Ref | — |
| Positive | 0.70 (0.62–0.79) | < 0.001 | 0.67 (0.58–0.77) | < 0.001 | 0.72 (0.64–0.82) | < 0.001 | 0.66 (0.57–0.77) | < 0.001 |
| Bone metastasis | | | | | | | | |
| No | Ref | — | Ref | — | Ref | — | Ref | — |
| Yes | 1.44 (1.30–1.59) | < 0.001 | 1.28 (1.13–1.46) | < 0.001 | 1.56 (1.40–1.74) | < 0.001 | 1.32 (1.15–1.51) | < 0.001 |
| Brain metastasis | | | | | | | | |
| No | Ref | — | Ref | — | Ref | — | Ref | — |
| Yes | 1.52 (1.28–1.81) | < 0.001 | 1.37 (1.13–1.66) | 0.001 | 1.57 (1.31–1.88) | < 0.001 | 1.38 (1.13–1.69) | 0.002 |
| Liver metastasis | | | | | | | | |
| No | Ref | — | Ref | — | Ref | — | Ref | — |
| Yes | 1.62 (1.45–1.81) | < 0.001 | 1.63 (1.43–1.86) | < 0.001 | 1.72 (1.53–1.93) | < 0.001 | 1.66 (1.44–1.91) | < 0.001 |
| Surgery | | | | | | | | |
| No/Unknown | Ref | — | Ref | — | Ref | — | Ref | — |
| Yes | 0.62 (0.55–0.69) | < 0.001 | 0.68 (0.55–0.85) | 0.001 | 0.59 (0.52–0.67) | < 0.001 | 0.63 (0.49–0.80) | < 0.001 |
| Chemotherapy | | | | | | | | |
| No/Unknown | Ref | — | Ref | — | Ref | — | Ref | — |

HR, hazard ratio; CI, confidence interval; OS, overall survival; BCSS, breast cancer-specific survival. Ref indicates the reference category; — indicates not applicable.

| Variable | OS Univariate HR (95% CI) | P | OS Multivariate HR (95% CI) | P | BCSS Univariate HR (95% CI) | P | BCSS Multivariate HR (95% CI) | P |
|---|---|---|---|---|---|---|---|---|
| Yes | 0.60 (0.54–0.66) | < 0.001 | 0.62 (0.55–0.70) | < 0.001 | 0.62 (0.56–0.69) | < 0.001 | 0.64 (0.56–0.73) | < 0.001 |

HR, hazard ratio; CI, confidence interval; OS, overall survival; BCSS, breast cancer-specific survival. Ref indicates the reference category; — indicates not applicable.

## Nomogram Construction

The regression coefficients used for risk score calculation are shown in Supplementary Table S2. The nomograms for predicting 3-year OS and BCSS were developed using the independent prognostic factors identified through multivariate analysis (Fig. 2). Each predictor was assigned a point value, and the sum of all points (total points) was used to estimate the corresponding 3-year survival probability. Higher total points indicated lower predicted survival probability in both models.

The predictive performance of the nomograms was evaluated using time-dependent ROC analysis across all cohorts (Fig. 3). For OS, the AUC values at 1, 2, and 3 years were 0.712, 0.700, and 0.705 in the training cohort; 0.714, 0.703, and 0.706 in the internal validation cohort; 0.721, 0.724, and 0.717 in the temporal validation cohort (2018–2021); and 0.708, 0.700, and 0.683 in the external validation cohort. For BCSS, the corresponding AUC values were 0.714, 0.707, and 0.711 (training); 0.713, 0.706, and 0.713 (internal validation); 0.721, 0.723, and 0.717 (temporal validation); and 0.668, 0.672, and 0.648 (external validation). The temporal validation cohort showed numerically higher AUC values than the other cohorts; however, no formal between-cohort comparisons were performed. Overall, discrimination was maintained in the temporal validation cohort. All AUC values exceeded 0.64, indicating modest-to-acceptable discrimination across all cohorts. ROC curves for the temporal validation cohort are shown in Supplementary Figure S1.

The C-index for OS was 0.655 (95% CI: 0.637–0.673) in the training cohort, 0.648 (95% CI: 0.621–0.675) in the internal validation cohort, 0.681 (95% CI: 0.663–0.699) in the temporal validation cohort, and 0.657 (95% CI: 0.613–0.686) in the external validation cohort. For BCSS, the corresponding C-index values were 0.662 (95% CI: 0.644–0.680), 0.657 (95% CI: 0.630–0.684), 0.686 (95% CI: 0.667–0.704), and 0.652 (95% CI: 0.611–0.683), respectively (Table 3). The temporal validation cohort showed numerically higher C-index values, further supporting the model's acceptable predictive performance in patients diagnosed in recent years.

Table 3
Harrell's concordance indices (C-index) of the nomograms for OS and BCSS prediction in the training, internal validation, temporal validation, and external validation cohorts

| Cohort | N | OS C-index (95% CI) | BCSS C-index (95% CI) |
|---|---|---|---|
| Training | 1,894 | 0.655 (0.637–0.673) | 0.662 (0.644–0.680) |
| Internal validation | 812 | 0.648 (0.621–0.675) | 0.657 (0.630–0.684) |
| Temporal validation | 1,719 | 0.681 (0.663–0.699) | 0.686 (0.667–0.704) |
| External validation | 374 | 0.657 (0.613–0.686) | 0.652 (0.611–0.683) |

C-index, Harrell's concordance index; OS, overall survival; BCSS, breast cancer-specific survival; CI, confidence interval.

## Model Validation

Calibration was favorable in the training and internal validation cohorts, and acceptable in the temporal and external validation cohorts, although estimates in the external cohort were less precise due to limited sample size (Fig. 4). Calibration plots for the temporal validation cohort are shown in Supplementary Figure S2.

Decision curve analysis (DCA) indicated modest incremental net benefit of the nomograms over the treat-all and treat-none strategies across a range of threshold probabilities in the training, internal validation, temporal validation, and external validation cohorts (Fig. 5). DCA for the temporal validation cohort is shown in Supplementary Figure S3.

Risk stratification based on the nomograms effectively classified patients into high- and low-risk groups with significantly different survival outcomes across all cohorts (log-rank $p < 0.001$ for all comparisons) (Fig. 6). Kaplan-Meier survival curves for the temporal validation cohort are shown in Supplementary Figure S4. These findings support the prognostic discrimination and potential clinical utility of the nomograms for predicting survival in BCLM patients across different time periods and populations.

## Discussion

The management of breast cancer with lung metastasis (BCLM) involves multimodal strategies including surgery, systemic chemotherapy, radiotherapy, endocrine therapy, and molecularly targeted agents. Despite therapeutic advances, prognosis remains poor, with a median survival of 25 months in contemporary cohorts. Accurate prognostic assessment is therefore critical for personalizing treatment. Current prognostic tools for BCLM are limited, with the AJCC TNM staging system serving as the primary reference. However, its utility is constrained as all patients with lung metastases are uniformly classified as stage IV, offering minimal discriminatory stratification. Using data from the SEER database (2010–2021) and an independent external cohort, we identified lung metastasis-specific prognostic variables and developed a nomogram with validation across multiple cohorts, including a temporal validation cohort of patients diagnosed between 2018 and 2021. This model exhibited acceptable discriminatory performance for both overall survival (OS) and breast cancer-specific survival (BCSS), offering clinically relevant insights for decision-making.

Patient age emerged as an independent prognostic factor for both OS and BCSS. Younger patients had significantly longer median OS compared to older patients, suggesting better survival among younger individuals. Although younger women are more susceptible to aggressive breast cancer, older patients show higher incidence of lung metastasis(14). Age-related increases in breast cancer-specific mortality are particularly evident beyond 70 years(15), potentially due to delayed diagnosis, larger tumor size, and higher rates of lymph node involvement(16).

Racial disparities were observed in this cohort. Non-Hispanic Black (NH-Black) women were more likely to be diagnosed at advanced stages compared to Non-Hispanic White (NH-White) women(17). Higher mortality among NH-Black women in the southeastern U.S. may reflect regional variations in healthcare access, education, and socioeconomic status(18). Interestingly, Black patients showed a survival advantage compared to White patients in multivariable analysis (HR = 0.82, 95% CI: 0.71–0.95). The reasons for this finding remain unclear and warrant further investigation. As the SEER registry predominantly comprises White and Black individuals, generalizability to other racial/ethnic groups requires further study.

Marital status showed heterogeneous associations with survival in this cohort. Previous studies have reported better survival outcomes among married patients, attributed to earlier symptom detection, emotional support, and timely treatment initiation(19, 20). However, in the present multivariable analysis, the unmarried category was not independently associated with OS or BCSS (OS: HR = 0.89, P = 0.089; BCSS: HR = 0.88, P = 0.070), whereas the 'other' category showed an endpoint-specific association with OS (HR = 1.16, P = 0.047).

Limited research exists on the association between molecular subtypes and lung metastasis risk. A study of 3,726 early-stage patients revealed varying lung metastasis rates across subtypes: 9.1% in $HR^+/HER2^-$, 17.7% in $HR^+/HER2^+$, 24.1% in $HR^-/HER2^+$, and 15.7% in triple-negative disease(9). Significant survival differences were observed, with $ER^+$, $PR^+$, and $HER2^+$ status conferring mortality risk reductions of 48.9%, 44.2%, and 25.8%, respectively(21). In our study, HER2-positive status was associated with improved survival in both OS and BCSS ($HR \approx 0.67$, $P < 0.001$), reflecting the protective effect of HER2-targeted therapies. Crosstalk between HR and HER2 pathways may explain differential treatment responses. For instance, $HR^+/HER2^+$ patients show lower pathological complete response (pCR) rates after neoadjuvant therapy, suggesting HER2-mediated enhancement of ER signaling that may diminish the efficacy of endocrine therapy(22). This implies possible bypass activation of HER2 downstream pathways in metastatic settings(23).

Surgical intervention was associated with improved OS and BCSS. Randomized trials have evaluated locoregional treatment of the primary tumor in de novo metastatic breast cancer, but the survival benefit remains uncertain(24), though surgery may inadvertently promote pro-invasive gene expression(25). In our cohort, patients who underwent surgery had significantly longer median survival compared to non-surgical cases (log-rank $P < 0.001$), suggesting that surgery may be associated with improved outcomes in selected patients, although this association should not be interpreted causally due to potential treatment-selection bias.

Chemotherapy was associated with improved median survival compared to patients without systemic treatment; however, this finding may reflect treatment selection bias and should be interpreted with caution. Detailed data on specific chemotherapy regimens were unavailable, limiting further stratified analysis. Additional independent prognostic factors included T stage, tumor grade, and metastatic involvement of bone, brain, and liver.

A major strength of this study is the inclusion of a temporal validation cohort comprising patients diagnosed between 2018 and 2021. Most existing prognostic models for BCLM have been developed using historical data without assessing performance in contemporary populations—a critical gap, as treatment paradigms have evolved substantially over the past decade with the widespread adoption of HER2-targeted therapies, CDK4/6 inhibitors, and more precise radiotherapy. Encouragingly, our nomogram showed numerically higher performance in this temporal cohort, with C-index values of 0.681 (OS) and 0.686 (BCSS) and AUC values ranging from 0.721 to 0.724 (OS) and 0.717 to 0.723 (BCSS). These findings suggest that the models not only performs well in historical data but also maintained acceptable predictive accuracy in recently diagnosed patients, further supporting its potential clinical utility in contemporary clinical practice. This temporal validation approach directly addresses concerns about model obsolescence due to temporal shifts in patient characteristics and treatment patterns.

This study extends previous BCLM prognostic models by focusing on HR-positive disease and incorporating internal, temporal, and independent external validation cohorts. The models demonstrated consistent predictive accuracy across all cohorts, with C-index values ranging from 0.648 to 0.686 and AUC values ranging from 0.648 to 0.724. Notably, the temporal validation cohort showed numerically higher performance than the other cohorts, suggesting that the models may be well-suited for contemporary patients, although this observation may also reflect differences in case mix and follow-up patterns. The external validation cohort (n = 374) from Guangxi Medical University Cancer Hospital further supported the transportability of the models to an independent Chinese population, with C-index values of 0.657 (OS) and 0.652 (BCSS). This multi-cohort validation strategy further strengthens the evidence base for the nomograms' potential clinical applicability.

Several limitations should be acknowledged. First, the retrospective design introduces potential selection and information biases. Second, the SEER database lacks information on endocrine therapy, which is a cornerstone of treatment for $HR^+$ breast cancer. This omission may affect survival predictions and limit the nomograms' utility for guiding endocrine-based treatment decisions. Third, our nomogram includes post-treatment variables, so it is intended for risk stratification after initial management rather than for pre-treatment prediction. Fourth, the external validation cohort was derived from a single Chinese institution, which may limit generalizability to other populations. Fifth, the lower AUC for BCSS in the external cohort (0.648–0.672) suggests that discriminative ability may vary across populations, highlighting the need for further validation in diverse settings. Sixth, for BCSS, non-breast cancer deaths were treated as censored events, which does not account for competing mortality risks—particularly relevant in older patients with comorbidities. Seventh, predictor selection was partly based on univariable screening, which may have introduced selection instability. Finally, the grouping of 'unknown' with 'no' for treatment variables may introduce misclassification bias, and detailed data on Ki-67, socioeconomic factors, and specific treatment regimens were not available. Future studies incorporating these variables and competing-risk methods are warranted.

## Conclusion

We developed and validated a nomogram for predicting prognosis in $HR^+$ BCLM patients using data from the SEER database (2010–2021) and an independent external cohort. The models demonstrated acceptable predictive performance when evaluated in the training, internal validation, temporal validation (2018–2021), and external validation cohorts, with the temporal validation cohort, representing the most recent patient population, showing the numerically highest C-index values (OS: 0.681; BCSS: 0.686) and supporting its applicability to

contemporary practice. This tool may support post-treatment prognostic assessment and risk stratification, but should not be interpreted as a tool for selecting specific treatments. By integrating clinicopathological and treatment-related factors, the nomograms provides a practical framework for personalized prognostic assessment in $HR^+$ BCLM. Future studies incorporating endocrine therapy and other emerging biomarkers are warranted to further enhance its clinical utility.

# Abbreviations

BC
breast cancer
BCLM
breast cancer with lung metastasis
SEER
Surveillance,Epidemiology,and End Results program
ROC
receiver operating characteristic
DCA
decision curve analysis
OS
overall survival
BCSS
breast cancer-specific survival
K-M
Kaplan-Meier.

# Declarations

### Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2013 revision). The external validation study using data from Guangxi Medical University Cancer Hospital was approved by the Research Ethics Committee of Guangxi Medical University Cancer Hospital (Approval No. KY2025677). Written informed consent was obtained from all participants included in the external validation cohort. For the SEER database, which consists of publicly available, de-identified data, additional institutional review and informed consent were not required, as the use of this registry data falls under Category 4 of the NIH Exemption Criteria for secondary analysis of existing anonymous data (45 CFR 46).

### Consent for publication

All authors have reviewed the final version of this manuscript and consent to its submission for publication.

### Availability of data and materials

The datasets supporting this study were retrieved from the publicly accessible Surveillance, Epidemiology, and End Results (SEER) Program (https://seer.cancer.gov), maintained by the National Cancer Institute's Division of

Cancer Control and Population Sciences (DCCPS). The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

All authors declare no potential conflicts of interest with respect to the investigation, authorship, and/or publication of this study.

**Authors' Contributions**

Sihang Lin is a major contributor to study design, data interpretation, and manuscript writing. Lixia Liu, Jiayu Guan, Yanan Mo, Jie Wang, Siyu Luo, and Huawei Yang carried out statistical analysis and manuscript writing. All authors read and approved the final manuscript.

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**Clinical trial number**

Not applicable.

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## Figures

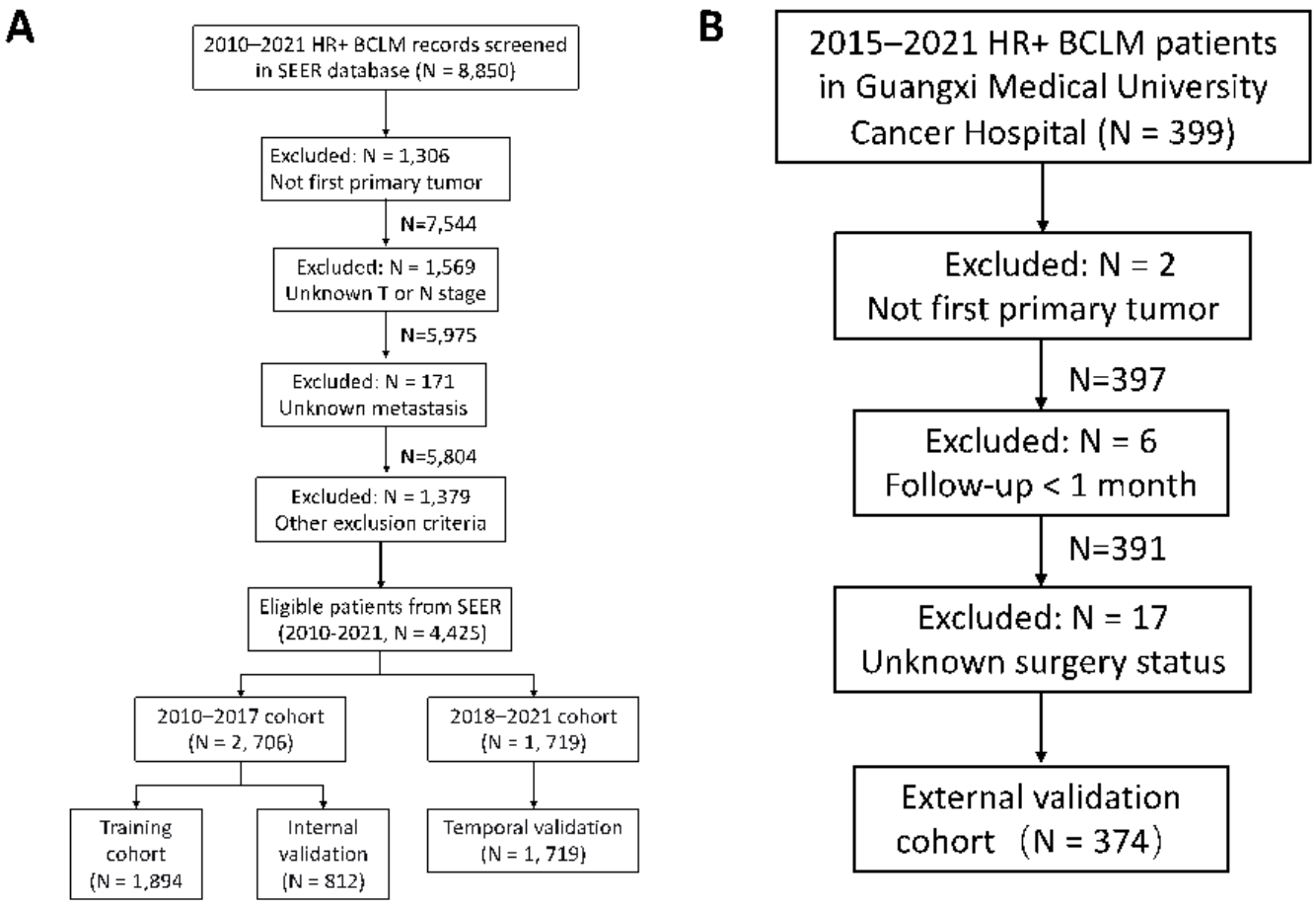
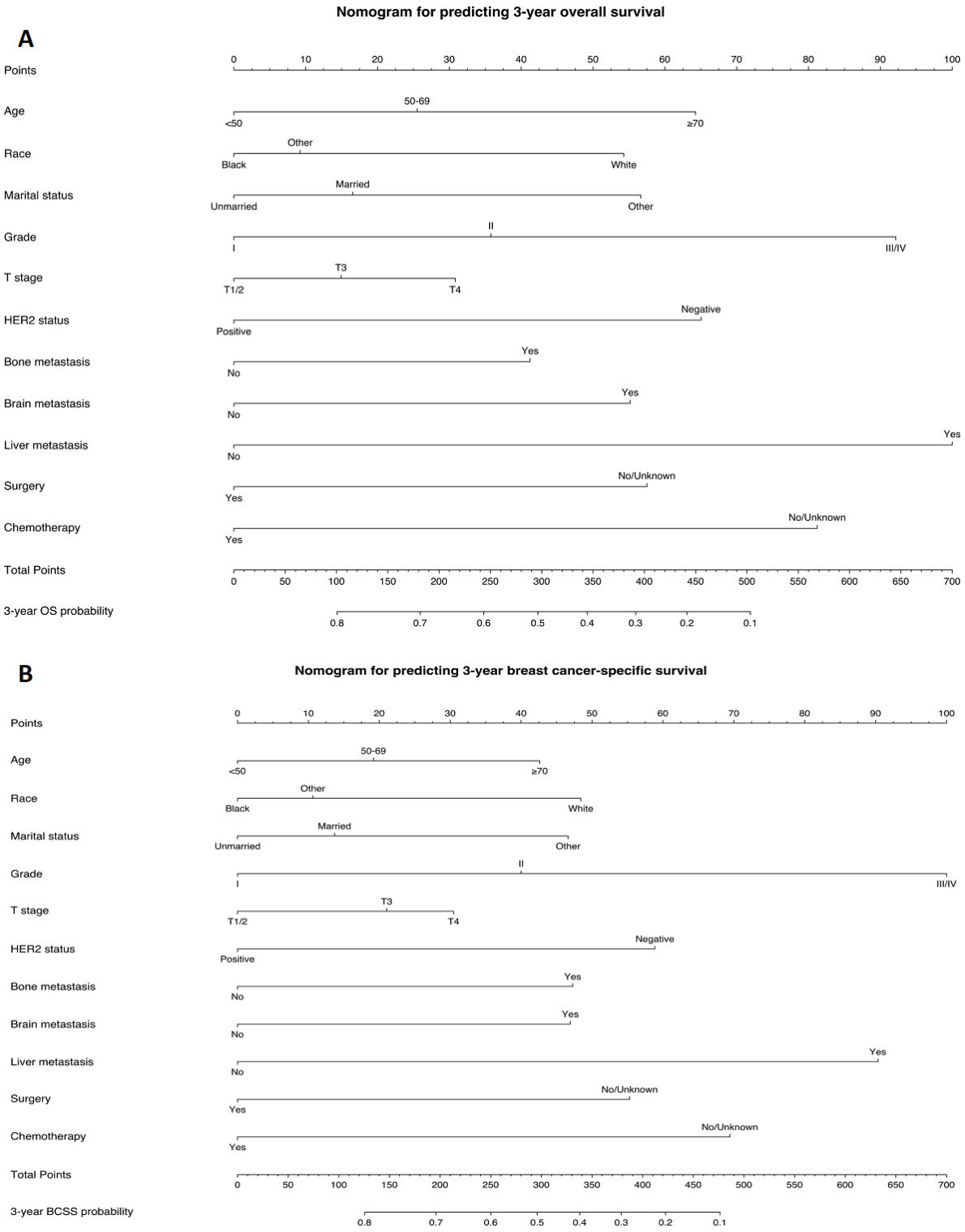



**Figure 1**

**Flowcharts of patient selection for the SEER database and external validation cohorts.**

(A) Of 8,850 HR-positive BCLM records initially screened in the SEER database (2010–2021), 4,425 patients met the final eligibility criteria. Patients diagnosed between 2010 and 2017 (n = 2,706) were randomly divided into the training cohort (n = 1,894, 70%) and internal validation cohort (n = 812, 30%), whereas patients diagnosed between 2018 and 2021 (n = 1,719) comprised the temporal validation cohort.

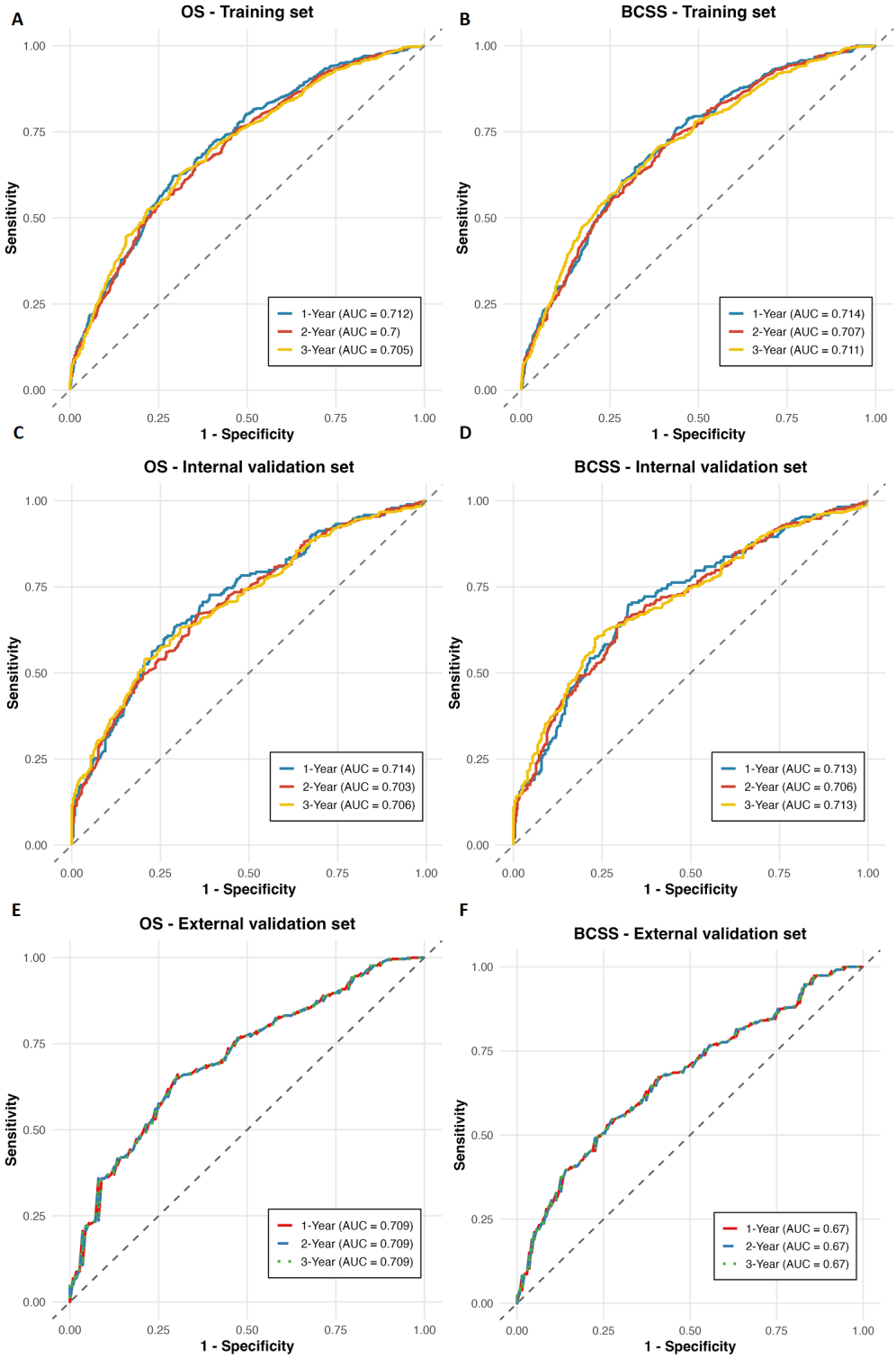
(B) Among 399 patients initially identified at Guangxi Medical University Cancer Hospital (2015–2021), 374 were included in the external validation cohort after exclusions.




## Figure 2

**Nomograms for predicting 3-year (A) overall survival (OS) and (B) breast cancer-specific survival (BCSS) in HR⁺ breast cancer patients with lung metastasis.**

Each predictor was assigned a point value; the total points were summed and mapped to the corresponding 3-year survival probability. Higher total points indicate poorer prognosis. T1/2 indicates T1–T2. Surgery and chemotherapy were categorized as Yes versus No/Unknown.

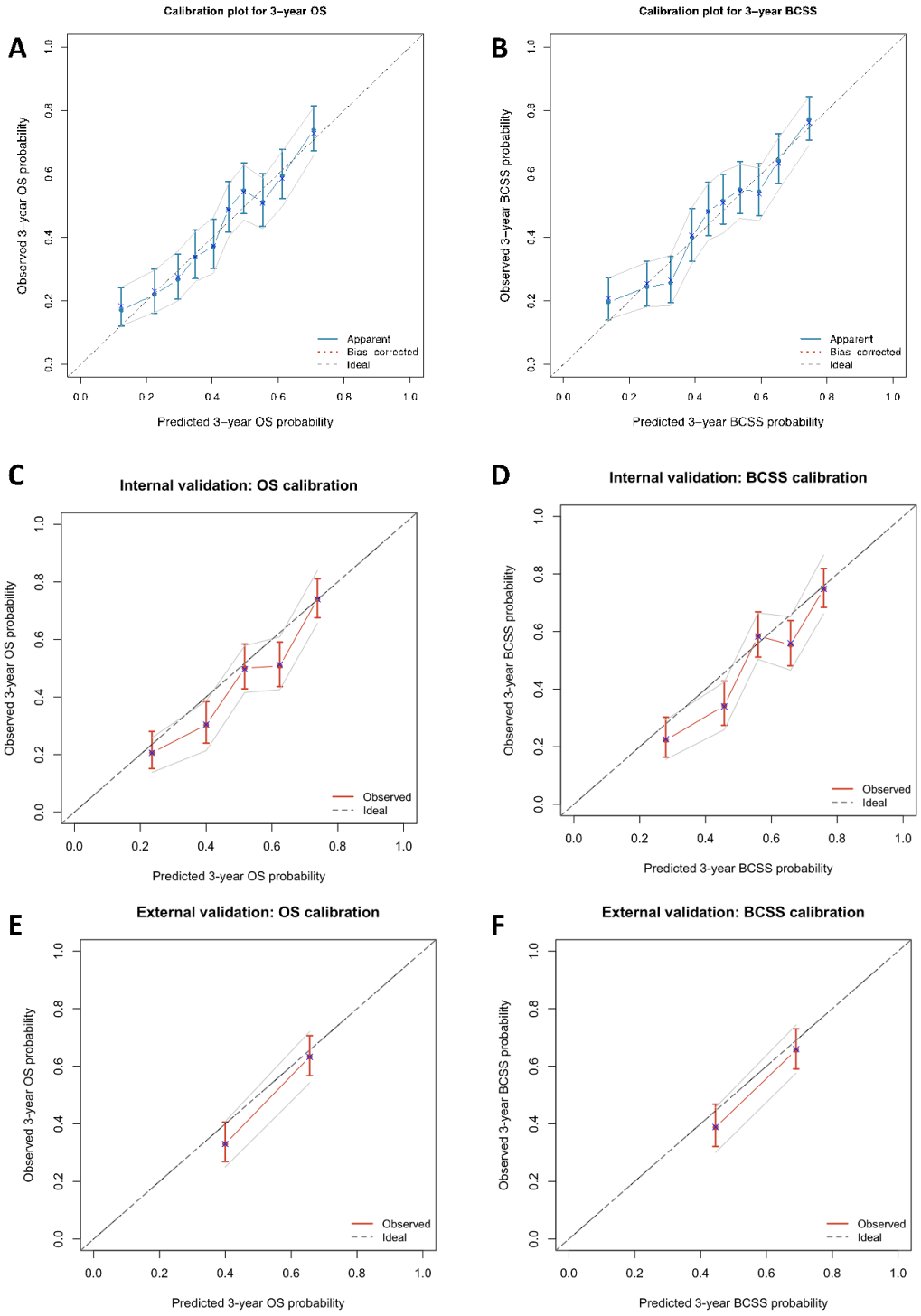



## Figure 3

**Time-dependent ROC curves for the nomograms in the training, internal validation, and external validation cohorts.**

Panels A, C, and E show OS, whereas panels B, D, and F show BCSS in the training, internal validation, and external validation cohorts, respectively. AUC values are shown for 1-, 2-, and 3-year predictions. The dashed diagonal line represents a random classifier (AUC = 0.5). The nomograms demonstrated acceptable to moderate

discriminative ability across all cohorts, with AUC values ranging from 0.700 to 0.714 in the training cohort, 0.703 to 0.714 in the internal validation cohort, and 0.648 to 0.708 in the external validation cohort.




## Figure 4

**Calibration plots for 3-year OS and BCSS predictions in the training, internal validation, and external validation cohorts.**

Panels A, C, and E show OS calibration, whereas panels B, D, and F show BCSS calibration in the training, internal validation, and external validation cohorts, respectively. The x-axis represents the predicted survival probability, and the y-axis represents the observed survival probability. The dashed diagonal line indicates perfect calibration. In the training cohort, the apparent and bootstrap bias-corrected curves generally followed the ideal line, indicating favorable calibration. In the internal and external validation cohorts, the observed calibration estimates were close to the ideal line, although estimates in the external cohort were less precise because of the limited sample size.

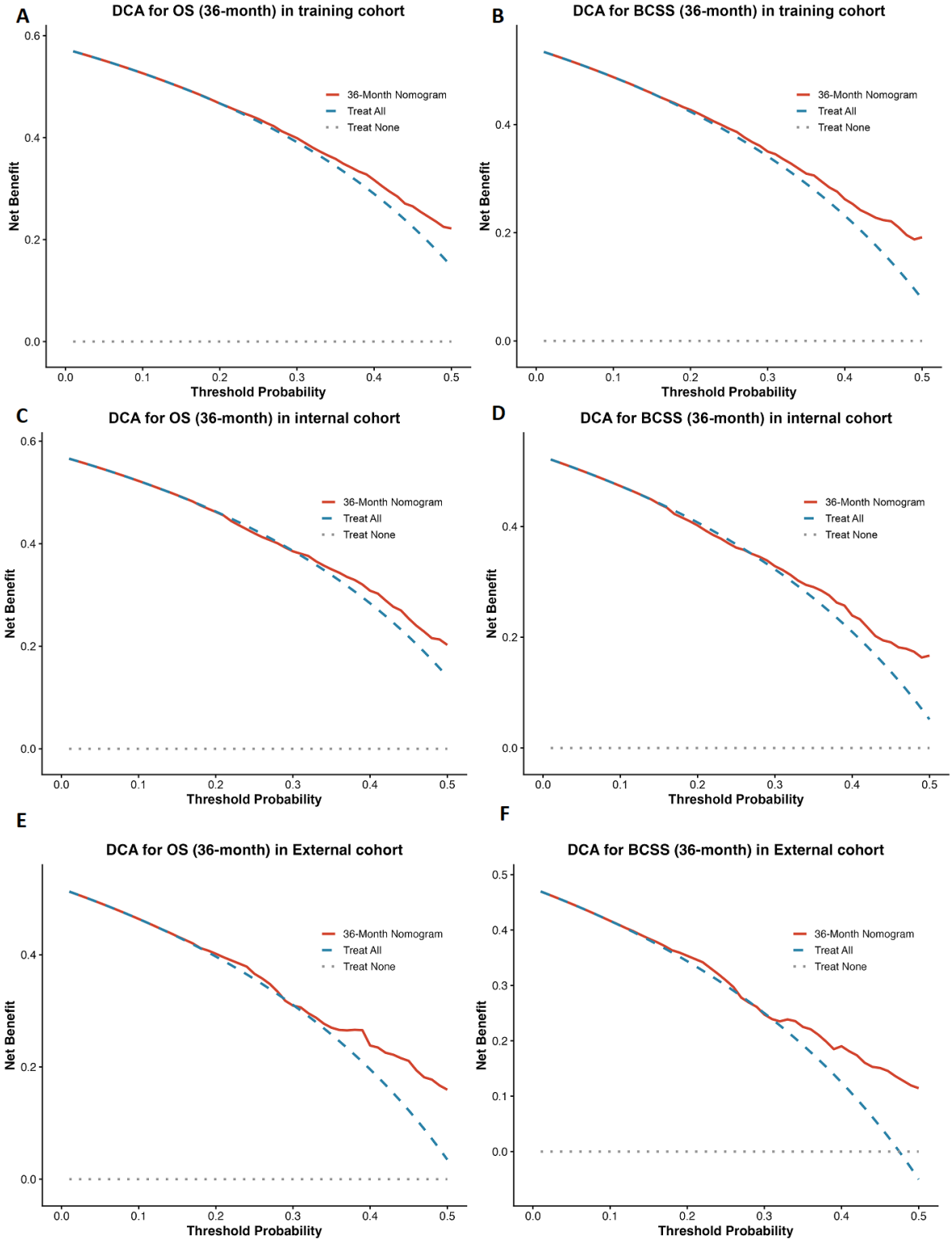
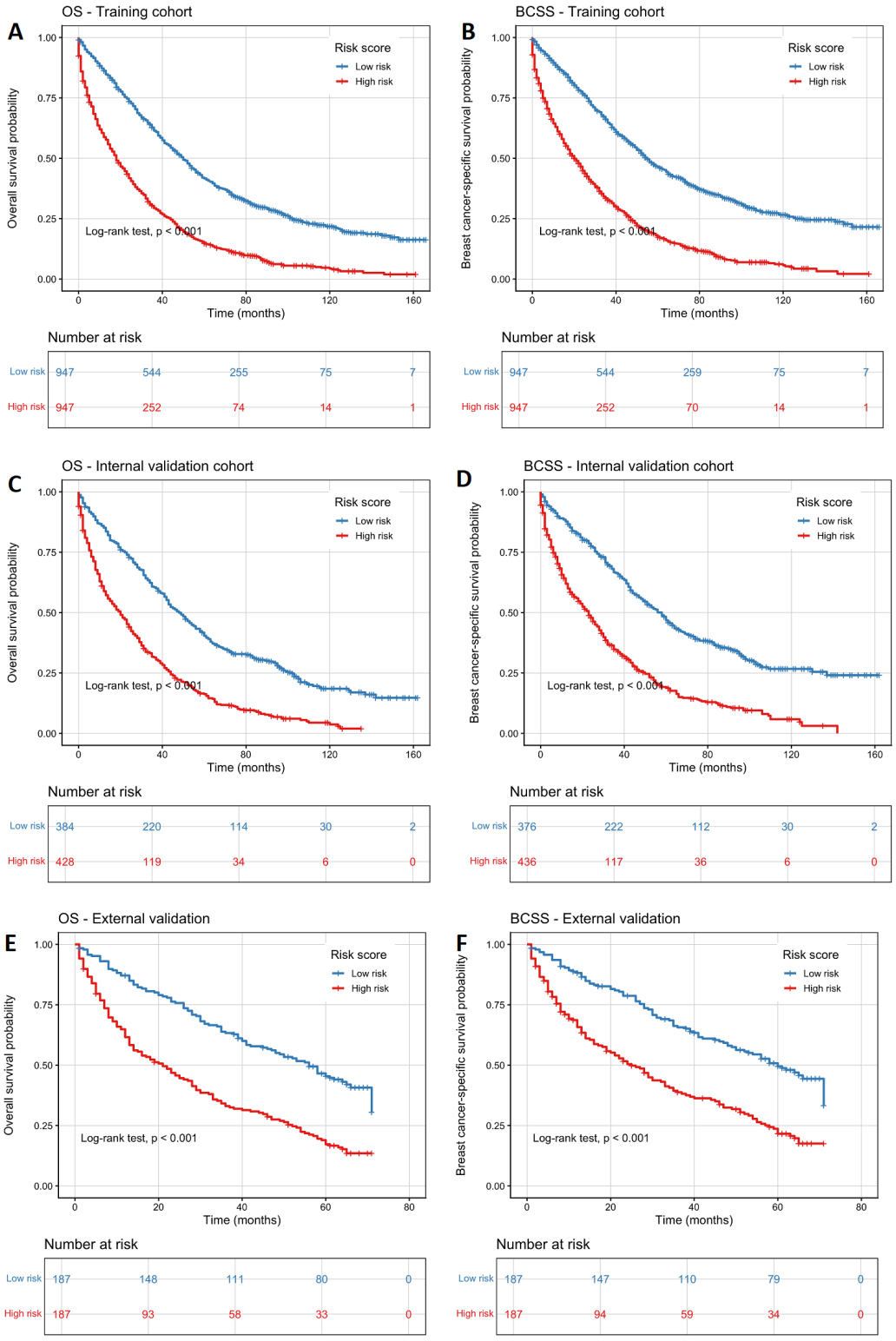


Figure 5

**Decision curve analysis (DCA) for 3-year (A) OS and (B) BCSS predictions in the training, internal validation, and external validation cohorts.**

Panels A, C, and E show OS, whereas panels B, D, and F show BCSS in the training, internal validation, and external validation cohorts, respectively. The y-axis represents the net benefit, and the x-axis represents the threshold probability. The nomograms curve (red) is compared with the “treat all” (blue dashed) and “treat none” (gray dotted) strategies. The nomograms demonstrated modest incremental net benefit over the treat-all and treat-none strategies across a range of threshold probabilities in all cohorts, indicating potential clinical utility.




## Figure 6

Kaplan–Meier survival curves for OS and BCSS according to risk stratification.

Panels A, C, and E show OS, whereas panels B, D, and F show BCSS in the training, internal validation, and external validation cohorts, respectively. Patients were divided into high- and low-risk groups based on the median risk score derived from the training cohort. The number at risk is presented below each curve. P values

were calculated using the log-rank test, and the low-risk group demonstrated significantly better survival than the high-risk group in all cohorts (all log-rank P < 0.001).

## Supplementary Files

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- Supplementary.docx