Establishment and validation of novel clinical prognosis nomograms for luminal A breast cancer patients with bone metastasis

QiHao Tu
Affiliated Hospital of Medical College Qingdao University

Chuan Hu
Affiliated Hospital of Medical College Qingdao University

Hao Zhang
Affiliated Hospital of Medical College Qingdao University

Chen Peng
Affiliated Hospital of Medical College Qingdao University

Meng Kong
Affiliated Hospital of Medical College Qingdao University

MengXiong Song
Affiliated Hospital of Medical College Qingdao University

Chong Zhao
Affiliated Hospital of Medical College Qingdao University

YuJue Wang
Qingdao University Medical College

Jianyi Li
Affiliated Hospital of Medical College Qingdao University

ChuanLi Zhou
Affiliated Hospital of Medical College Qingdao University

Chao Wang
Affiliated Hospital of Medical College Qingdao University

XueXiao Ma (✉ drmaxuexiao@163.com)
The Affiliated Hospital of Qingdao University

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Abstract

Purpose

Overall survival (OS) and cancer-specific survival (CSS) of luminal A breast cancer (BC) patients with bone metastasis remain poor and vary dramatically from person to person. Our goal was to build two universally applicable nomograms to accurately predict OS and CSS for luminal A patients with bone metastasis.

Methods

The data of luminal A BC patients with bone metastases between 2010 and 2015 were collected from the Surveillance, Epidemiology, and End Results (SEER) database collected from the Surveillance, Epidemiology, and End Results (SEER) database for luminal A BC patients with bone metastasis between 2010 and 2015. Univariate and multivariate Cox regression analyses were to assess and identify independent risk factors of OS and CSS. Integrating all significant predictors, nomograms and risk groups stratification model were developed. The performance of the nomogram was validated with concordance index (C-index), calibration plots, and decision curve analyses (DCA) for discriminative ability, calibration and clinical utility, respectively.

Results

3171 luminal A BC patients with bone metastasis were included. Through univariate and multivariate Cox regression analyses, 12 variables were identified as both independent OS- and CSS-related factors, including age, race, primary site, histology grade, tumor size, surgery, brain metastasis, liver metastasis, lung metastasis, estrogen receptor status, progesterone receptor status and insurance. Our nomograms for 1-, 3- and 5-year survival were based on those significant prognostic factors to develop. The C-indexes of OS- and CSS-nomograms in the training cohort were 0.701 and 0.704, respectively. Similar results were obtained in the validation cohort. The calibration curves and DCA presented satisfactory calibration and clinical utility.

Conclusion

Two nomograms have good discrimination, calibration and clinical utility, can accurately and effectively predict the prognosis of patients, and may benefit for clinical decision-making. In high-risk patients, more aggressive therapy and closer surveillance should be considered.

Background
Breast cancer (BC) is the second most diagnosed cancer (11.6% of the cancer cases), second only to lung cancer, and accounts for a quarter of all female cancer cases [1]. Among females, BC is not only the most generally diagnosed cancer, but also the main cause of cancer death [1]. The well-known classification criteria for BC is depending on the status of molecular markers ER (estrogen receptor), PR (progesterone receptor), Ki-67 and Her2 (human epidermal growth factor receptor 2) [2]. Breast cancers can be divided into molecular subtypes of Triple negative, luminal A, Luminal B and HER2, with luminal A subtype being the most common one[3].

The main cause of death for BC patients is not the primary tumor but the occurrence of distant metastasis [4]. A cancer statistic among Hispanics/Latinos showed approximately over 30% of BC patients would have distant non-nodal metastases [5]. A population-based research including about 300,000 patients indicated that the bone metastasis (3.28%) takes the leading place in distant metastasis secondary to BC, which will develop in almost 3/4 of stage-IV BC patients[6], negatively affecting the patient’s mobility, survival expectancy and life quality. Poor prognosis is largely caused by skeletal-related events (SRE), mainly presenting as severe pain, pathologic fractures, spinal cord compression and hypercalcemia [7, 8].

Indeed, tumor treatment has made great progress as medical technology further develops. However, accurate prediction and standard treatments for luminal A subtype BC patients with bone metastasis are lacking. Moreover, limitations of conventional predictors including RPA / GPA classification and TMN stage, old risk grouping, regression tree analyses or probability tables have gradually revealed. To supply the most appropriate and feasible clinical treatment, there is an urgent need for convenient and effective tool to accurately predict prognosis. With advantages compared to old predictors, nomograms have been applied effectively for a long time in outcomes predicting based on data collected from clinic and laboratory [9, 10]. Furthermore, in several disciplines, studies which compared different models have showed that nomograms based upon univariate and multivariate Cox regression, are superior to other methodologies[11]. As a popular and effective prediction model, nomogram enables clinicians to evaluate the prognosis and choose optimized treatment plan. The study is to develop new nomograms to predict the prognosis of luminal A subtype BC patients with bone metastasis.

**Methods**

**Patient Selection and grouping**

The demographics, clinical and laboratory information of the luminal A patients with bone metastasis in the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to June 2015 were collected. There’s no need for informed consent in our study since the unidentified data was free from medical ethics review. The inclusion criteria were as follows: (1) patients diagnosed by immunohistochemistry; (2) patients with primary luminal A BC; (3) patients with bone metastasis. The exclusion criteria were as follows: (1) under 18 years old when diagnosed; (2) follow-up time < 2months; (3) key information lacking. Finally, 3171 patients were selected and randomly allocated into two groups by R software with a
ratio of 7:3. Descriptive statistics were used to summarize the status and the features of the training and validation datasets.

**Variable selection and declaration**

Following variables were selected in our study: follow time, tumor size, race, gender, age at diagnosis, primary site, grade, laterality, histologic type, T, N stage, treatment, metastasis, cause of death, status of life, ER, PR, treatment marital and insurance. Some variables were analyzed and adjusted considering their type, performance and occurrence rates in clinical manifestation, as well as the actual data volume. Tumor size was regrouped into three subcollections (below 36mm, 36–85 mm, above 85 mm). Patients were then divided into three subcollections based on their ages (< 55, 55–78, > 78). Race was classified as the white, black or others. Histology was divided as infiltrating duct carcinoma (IDC), infiltrating duct and lobular carcinoma (IDC + ILC) or others. Primary site was stratified as lower-inner, upper-inner or lower-outer quadrant of breast, central portion of breast, breast NOS and others. T stage was regrouped into two subgroups (T1-2, T3-4). N stage was regrouped into two subgroups (N0, N1-3).

**Nomogram development and statistical analyses**

Patients who had no ending events during the follow-up were also included in the analysis. OS or CSS was recognized as the endpoint of the study. OS was calculated from diagnosis to death led by any cause or the end of follow-up while CSS was from diagnosis to death caused by cancer [12]. Baseline characteristics comparison was performed by chi-square test and risk factors for OS or CSS were evaluated by univariate Cox regression. Multivariate Cox regression was then conducted based on the results of univariate analysis. As a set of independent prognostic factors get screened, the nomograms for the OS and CSS of 1, 3 and 5 years were further constructed.

Aiming at the most simplified model with strongest predicting capability, we conducted the establishment of the model under rigorous programmable decision so that its building procedure could get internally validated [13]. Meanwhile, we validated the models internally with the 1000 bootstrap resamples and conducted external validation on the validation cohort. The level of discrimination in this cohort was quantified and measured using concordance index (C-index) and its 95% confidence interval (95% CI). The model’s distinguishing ability improves when its C-index increases from 0.5 to 1. The maximum value of the C-index is 1.0, which indicates the model’s perfect ability in correctly discriminating outcome. The consistency of the predicted results with the actual was further determined by Calibration plot.

Subsequently, the clinical utility of the nomogram was assessed by decision curve analysis (DCA) with by quantifying quantified net benefits under various threshold probabilities [14], which was decided by the difference between the expected benefit and expected lose in association with every treatment strategy and proposed testing [15]. The patients of the training and validation datasets were categorized into group of high-risk or low-risk in line with their nomogram-derived risk scores. The survival curve upon a log-rank test was used to evaluate the utility of nomogram in prognosis predicting. R software (www.r-project.org, version 3.6.1) and the IBM SPSS 25.0 software were applied for all statistical analyses as above.
Results

Grouping and baseline characteristics

The flow chart of the process of patient inclusion, exclusion and grouping is shown in Fig. 1. According to the criteria in the method, 3,171 BC patients with bone metastasis were finally obtained. The R software was used to randomly divide all patients into training group (N = 2,223) and validation group (N = 948) at a ratio of 7: 3. Mean age and follow time of all were 60 years old (range, 21–97) and 30.2 months. In terms of race, 78.4%(n = 2,485), 13.7%(n = 435) and 7.9%(n = 251) of patients were white, black and other races, respectively. The most general histological type was infiltrating duct carcinoma (IDC) (n = 2,285, 72.1%). Moderate differentiation (Grade II) (n = 1,710, 53.9%) accounted for more than half proportion, with poor differentiation (Grade III-IV) (n = 1048, 33.0%) and good differentiation (Grade I) (n = 413, 13.0%) following. Regarding size, majority of patients with tumor size greater than 20 mm (n = 2,772, 71.6%). Among the socioeconomic factors, only a few patients have no insurance (n = 118, 3.7%). In the training group, almost half of all patients received chemotherapy (n = 1,058, 47.6%). Only 849 patients (38.2%) received surgery, 962 patients (43.3%) receiving radiotherapy. Detailed demographics and clinical information of the training and validation groups were summarized in Table 1.
Table 1
Demographic, Clinical and laboratory features of patients diagnosed as luminal A with bone metastasis

| Variable          | Training set (n = 2,223) | Validating set (n = 948) | P-value |
|-------------------|--------------------------|--------------------------|---------|
| **Follow time (mo)** |                          |                          |         |
| Mean              | 30.4                     | 29.8                     |         |
| Range             | 2–83                     | 2–83                     |         |
| **Number of events** |                          |                          |         |
| Live              | 1059 (47.6%)             | 462 (48.7%)              |         |
| Dead              | 1164 (52.4%)             | 486 (51.3%)              |         |
| **Age (y)**       |                          |                          | 0.387   |
| 55-               | 776 (34.9%)              | 307 (32.4%)              |         |
| 55–78             | 1220 (54.9%)             | 539 (56.9%)              |         |
| 78+               | 227 (10.2%)              | 102 (10.8%)              |         |
| **Race**          |                          |                          | 0.748   |
| White             | 1743 (78.4%)             | 742 (78.3%)              |         |
| Black             | 300 (13.5%)              | 135 (14.2%)              |         |
| Other             | 180 (8.1%)               | 71 (7.5%)                |         |
| **Grade**         |                          |                          | 0.340   |
| I                 | 292 (13.1%)              | 121 (12.8%)              |         |
| II                | 1190 (53.5%)             | 520 (54.9%)              |         |
| III               | 734 (33.0%)              | 307 (32.4%)              |         |
| IV                | 7 (0.3%)                 | 0                        |         |
| **Laterality**    |                          |                          | 0.260   |
| Left              | 1138 (51.2%)             | 474 (50.0%)              |         |
| Right             | 1085 (48.8%)             | 473 (49.9%)              |         |
| Bilateral         | 0                        | 1 (0.01%)                |         |
| **Histological type** |                        |                          | 0.731   |
| IDC               | 1607 (72.3%)             | 678 (71.5%)              |         |
| IDC + ILC         | 136 (6.1%)               | 65 (6.9%)                |         |
| Variable                  | Training set (n = 2,223) | Validating set (n = 948) | P-value |
|---------------------------|--------------------------|--------------------------|---------|
| Other                     | 480 (21.6%)              | 205 (21.6%)              |         |
| T stage                   |                          |                          | 0.806   |
| T1-2                      | 1183 (53.2%)             | 509 (53.7%)              |         |
| T3-4                      | 1040 (46.8%)             | 439 (46.3%)              |         |
| N stage                   |                          |                          | 0.867   |
| N0                        | 522 (23.5%)              | 220 (23.2%)              |         |
| N1-3                      | 1701 (76.5%)             | 728 (76.8%)              |         |
| Size (mm)                 |                          |                          | 0.083   |
| 20-                       | 973 (43.8%)              | 454 (47.9%)              |         |
| 20–50                     | 1019 (45.8%)             | 396 (41.8%)              |         |
| 50+                       | 231 (10.4%)              | 98 (10.3%)               |         |
| Primary site              |                          |                          | 0.134   |
| Breast, NOS               | 487 (21.9%)              | 252 (26.6%)              |         |
| Central portion of breast | 180 (8.1%)               | 66 (7.0%)                |         |
| Lower-inner quadrant of breast | 94 (4.2%)         | 41 (4.3%)                |         |
| Lower-outer quadrant of breast | 140 (6.3%)           | 55 (5.8%)                |         |
| Upper-inner quadrant of breast | 179 (8.1%)           | 64 (6.8%)                |         |
| Upper-outer quadrant of breast | 619 (27.8%)         | 248 (26.2%)              |         |
| other                     | 524 (23.6%)              | 222 (23.4%)              |         |
| Surgery                   |                          |                          | 0.734   |
| Yes                       | 849 (38.2%)              | 356 (37.6%)              |         |
| No                        | 1374 (61.8%)             | 592 (62.4%)              |         |
| Radiation                 |                          |                          | <0.0001 |
| Yes                       | 962 (43.3%)              | 516 (54.4%)              |         |
| No                        | 1261 (56.7%)             | 432 (45.6%)              |         |
| Chemotherapy              |                          |                          | 0.322   |
| Yes                       | 1058 (47.6%)             | 433 (45.7%)              |         |
| No                        | 1165 (52.4%)             | 515 (54.3%)              |         |
| Variable | Training set (n = 2,223) | Validating set (n = 948) | P-value |
|----------|--------------------------|--------------------------|---------|
| Brain    |                          |                          | 0.009   |
| Yes      | 103 (4.6%)               | 25 (2.6%)                |         |
| No       | 2120 (95.4%)             | 923 (97.4%)              |         |
| Liver    |                          |                          | 0.026   |
| Yes      | 347 (15.6%)              | 119 (12.6%)              |         |
| No       | 1876 (84.4%)             | 829 (87.4%)              |         |
| Lung     |                          |                          | 0.947   |
| Yes      | 469 (21.1%)              | 199 (21.0%)              |         |
| No       | 1754 (78.9%)             | 749 (79.0%)              |         |
| ER       |                          |                          | 0.097   |
| Positive | 2208 (99.3%)             | 936 (98.7%)              |         |
| Negative | 15 (0.7%)                | 12 (1.3%)                |         |
| PR       |                          |                          | 0.973   |
| Positive | 1903 (85.6%)             | 813 (85.8%)              |         |
| Negative | 317 (14.3%)              | 134 (14.1%)              |         |
| Borderline| 3 (0.1%)                 | 1 (0.1%)                 |         |
| Insurance|                          |                          | 0.007   |
| Yes      | 2127 (95.7%)             | 926 (97.7%)              |         |
| No       | 96 (4.3%)                | 22 (2.3%)                |         |
| Marital status |                  |                          | 0.004   |
| Yes      | 1127 (50.7%)             | 428 (45.1%)              |         |
| No       | 1096 (49.3%)             | 520 (54.9%)              |         |

**Confirmation of prognostic factors and development nomograms**

We first conducted a univariate analysis to screen for relevant significant variables. The results of the univariate analysis on the training group can be viewed in Table 2. We obtained the significant P value, HR (hazards ratio) and 95% confidence intervals (CI) of the relative importance of each independent variable, including demographic, clinical and socioeconomic factors. Subsequently, we conducted a multivariate Cox regression analysis of significance variables. Through univariate and multivariate Cox
regression analyses, 12 independent variables, in significant association with OS and CSS, were identified including age, race, histology grade, tumor size, primary site, surgery, brain metastasis, liver metastasis, lung metastasis, ER status, PR status and insurance. The results of the multivariate Cox regression analysis of OS and CSS on the training group are shown in Table 3. Ultimately, the significant variables mentioned above were included to build the nomogram. The nomograms of OS and CSS are shown in Figs. 2 and 3. Nomogram is a quite user-friendly predictive tool which enables clinician or patient to determine the survival probability by calculating the scores of covariate and then draw a line vertically downward [16]. The scores assigned to each factors were listed in Table 4.
Table 2
Univariate Cox regression analysis of overall survival and cancer-specific survival in the training group

| Variable       | OS     | CSS     |
|----------------|--------|---------|
|                | OS     | CSS     |
|                | HR     | 95%CI   | P  | HR     | 95%CI   | P  |
| Age(y)         |        |         |     |        |         |     |
| < 55           | reference | reference |     |         |         |     |
| 55–78          | 1.230  | 1.082–1.399 | 0.002 | 1.215  | 1.045–1.413 | 0.011 |
| > 78           | 2.187  | 1.812–2.639 | 0.000 | 1.922  | 1.542–2.397 | 0.000 |
| Size(mm)       |        |         |     |        |         |     |
| < 36           | reference | reference |     |         |         |     |
| 36–85          | 1.154  | 1.020–1.305 | 0.023 | 1.143  | 1.004–1.302 | 0.043 |
| > 85           | 1.601  | 1.327–1.933 | 0.000 | 1.644  | 1.351–1.999 | 0.000 |
| Race           |        |         |     |        |         |     |
| Black          | reference | reference |     |         |         |     |
| Other          | 0.614  | 0.478–0.790 | 0.000 | 0.667  | 0.514–0.866 | 0.002 |
| White          | 0.575  | 0.491–0.672 | 0.000 | 0.590  | 0.499–0.697 | 0.000 |
| Primary Site   |        |         |     |        |         |     |
| Breast, NOS    | reference | reference |     |         |         |     |
| Central portion| 0.670  | 0.522–0.860 | 0.002 | 0.684  | 0.527–0.888 | 0.004 |
| Lower-outer quadrant | 0.803  | 0.677–0.952 | 0.011 | 0.788  | 0.659–0.943 | 0.009 |
| Grade          |        |         |     |        |         |     |
| I              | reference | reference |     |         |         |     |
| II             | 1.319  | 1.082–1.607 | 0.006 | 1.301  | 1.056–1.603 | 0.014 |
| III            | 1.885  | 1.539–2.309 | 0.000 | 1.937  | 1.564–2.398 | 0.000 |
| IV             | 2.478  | 1.091–5.628 | 0.030 | 2.746  | 1.206–6.252 | 0.016 |
| T stage        |        |         |     |        |         |     |
| T1,T2          | reference | reference |     |         |         |     |
| T3,T4          | 1.299  | 1.157–1.457 | 0.000 | 1.288  | 1.141–1.454 | 0.000 |
| Surgery        |        |         |     |        |         |     |
| Variable                     | OS                                      | CSS                                     |
|------------------------------|-----------------------------------------|-----------------------------------------|
|                              | HR | 95%CI | P  | HR | 95%CI | P  |
| No                           | reference | reference |    |    | reference |    |
| Yes                          | 0.539 | 0.476–0.609 | 0.000 | 0.533 | 0.468–0.608 | 0.000 |
| **Chemotherapy**             |    |    |    |    |    |    |
| No                           | reference | reference |    |    | reference |    |
| Yes                          | 0.859 | 0.765–0.964 | 0.010 |    |    |    |
| **Brain metastasis**        |    |    |    |    |    |    |
| No                           | reference | reference |    |    | reference |    |
| Yes                          | 2.506 | 1.996–3.147 | 0.000 | 2.607 | 2.060–3.299 | 0.000 |
| **Liver metastasis**        |    |    |    |    |    |    |
| No                           | reference | reference |    |    | reference |    |
| Yes                          | 2.174 | 1.884–2.509 | 0.000 | 2.330 | 2.010–2.701 | 0.000 |
| **Lung metastasis**         |    |    |    |    |    |    |
| No                           | reference | reference |    |    | reference |    |
| Yes                          | 1.666 | 1.463–1.898 | 0.000 | 1.642 | 1.431–1.884 | 0.000 |
| **ER**                      |    |    |    |    |    |    |
| Negative                    | reference | reference |    |    | reference |    |
| Positive                    | 0.244 | 0.141–0.423 | 0.000 | 0.219 | 0.127–0.380 | 0.000 |
| **PR**                      |    |    |    |    |    |    |
| Negative                    | reference | reference |    |    | reference |    |
| Positive                    | 0.551 | 0.473–0.641 | 0.000 | 0.517 | 0.442–0.604 | 0.000 |
| **Insurance**               |    |    |    |    |    |    |
| No                           | reference | reference |    |    | reference |    |
| Yes                          | 0.721 | 0.558–0.931 | 0.012 | 0.681 | 0.524–0.886 | 0.004 |
| **Marital status**          |    |    |    |    |    |    |
| No                           | reference | reference |    |    | reference |    |
| Yes                          | 0.770 | 0.686–0.864 | 0.000 | 0.807 | 0.715–0.911 | 0.001 |

Nomograms validation and risk stratification
The performance of the nomograms was validated with C-index, calibration plots, and DCA for discriminative ability, accurate prediction and clinical utility, respectively. The C-index of this model in the training group was 0.701 (95% CI: 0.688–0.720) for the OS model, 0.704 (95% CI, 0.688–0.720) for the CSS model. In the validation group, the C-index of OS was 0.665 (95% CI: 0.63–0.692), while that of CCS was 0.678 (95% CI, 0.651–0.705), underlying the good discriminating ability of the nomograms in the training and verification group. The prediction curves of OS and CSS in the training and validation groups at 1, 3, and 5 years were close to the standard curve (Y = X), indicating that the prediction results of nomograms have a significant correlation with the actual observation (Fig. 4). DCA of 1-, 3- and 5-year OS and CSS showed that the nomograms had a higher net benefit in the training cohort and validation cohort, respectively (Figs. 5 and 6). According to our OS nomogram and CSS nomogram, risk scores were calculated for each luminal A patient with bone metastasis. In addition, it has been tested by the Kaplan-Meier survival curve that patients of low-risk group present better prognosis than those in high-risk group (Figs. 7 and 8).

**Table 3** Multivariate Cox regression analysis of overall survival and cancer-specific survival in the training group
| Variable        | OS | CSS |
|-----------------|----|-----|
|                 | HR | 95%CI | P | HR | 95%CI | P |
| **Age (y)**     |    |       |
| <55             | 1  | 1     |
| 55-78           | 1.218 | 1.068-1.390 | 0.003 | 1.204 | 1.031-1.405 | 0.019 |
| >78             | 2.476 | 2.039-3.006 | 0.000 | 2.137 | 1.697-2.692 | 0.000 |
| **Size (mm)**   |    |       |
| <36             | 1  | 1     |
| 36-85           | 1.131 | 0.998-1.282 | 0.053 | 1.078 | 0.925-1.257 | 0.337 |
| >85             | 1.363 | 1.118-1.661 | 0.002 | 1.292 | 1.014-1.645 | 0.038 |
| **Race**        |    |       |
| Black           | 1  | 1     |
| Other           | 0.650 | 0.503-0.839 | 0.001 | 0.724 | 0.553-0.946 | 0.018 |
| White           | 0.641 | 0.546-0.752 | 0.000 | 0.686 | 0.578-0.815 | 0.000 |
| **Primary Site**|    |       |
| Breast, NOS     | 1  | 1     |
| Central portion | 0.744 | 0.578-0.958 | 0.022 | 0.767 | 0.589-0.998 | 0.048 |
| Lower-inner quadrant | 1.021 | 0.825-1.264 | 0.846 | 1.044 | 0.834-1.308 | 0.706 |
| Lower-outer quadrant | 0.823 | 0.693-0.978 | 0.027 | 0.811 | 0.676-0.974 | 0.025 |
| Other           | 0.975 | 0.833-1.142 | 0.752 | 0.980 | 0.829-1.158 | 0.811 |
| **Grade**       |    |       |
| I               | 1  | 1     |
| II              | 1.297 | 1.063-1.583 | 0.010 | 1.293 | 1.048-1.597 | 0.017 |
| III             | 1.755 | 1.425-2.160 | 0.000 | 1.806 | 1.450-2.249 | 0.000 |
| IV              | 1.817 | 0.789-4.182 | 0.160 | 1.949 | 0.843-4.506 | 0.119 |
| **T stage**     |    |       |
| T1,T2           | 1  |       |
| T3,T4           | 1.061 | 0.906-1.241 | 0.463 |
|               | No       | 1       | 1       |
|---------------|----------|---------|---------|
| **Brain metastasis** |          |         |         |
| No            | 1        | 1       |         |
| Yes           | 0.601    | 0.528-0.683 | 0.000  |
| **Liver metastasis** |          |         |         |
| No            | 1        | 1       |         |
| Yes           | 1.977    | 1.560-2.506 | 0.000  |
| **Lung metastasis** |          |         |         |
| No            | 1        | 1       |         |
| Yes           | 1.910    | 1.643-2.221 | 0.000  |
| **ER**        |          |         |         |
| Negative      | 1        | 1       |         |
| Positive      | 0.272    | 0.156-0.477 | 0.000  |
| **PR**        |          |         |         |
| Negative      | 1        | 1       |         |
| Positive      | 0.634    | 0.543-0.740 | 0.000  |
| Borderline    | 2.336    | 0.739-7.388 | 0.149  |
| **Insurance** |          |         |         |
| No            | 1        | 1       |         |
| Yes           | 0.755    | 0.581-0.980 | 0.035  |
| **Marital**   |          |         |         |
| No            | 1        |         |         |
| Yes           | 0.916    | 0.807-1.040 | 0.176  |

**Table 4** Value assignment of the independent prognostic factors contained in the OS- and CSS-nomograms
| Prognostic factors          | OS | CSS |
|----------------------------|----|-----|
| **Age (y)**                |    |     |
| <55                        | 59 | 65  |
| 55-78                      | 68 | 73  |
| >78                        | 100| 100 |
| **Size (mm)**              |    |     |
| <36                        | 59 | 65  |
| 36-85                      | 65 | 70  |
| >85                        | 73 | 79  |
| **Race**                   |    |     |
| Black                      | 59 | 65  |
| Other                      | 40 | 49  |
| White                      | 39 | 47  |
| **Primary Site**           |    |     |
| Breast, NOS                | 59 | 65  |
| Central portion of breast  | 46 | 53  |
| Lower-inner quadrant of breast | 68 | 73 |
| Lower-outer quadrant of breast | 54 | 61 |
| Upper-inner quadrant of breast | 58 | 62 |
| Upper-outer quadrant of breast | 58 | 64 |
| Other                      | 50 | 55  |
| **Grade**                  |    |     |
| I                          | 59 | 65  |
| II                         | 71 | 76  |
| III                        | 85 | 91  |
| IV                         | 86 | 95  |
| **Surgery**                |    |     |
Discussion

For patients of BC with bone metastasis, the long-term survival and life quality in the later period are still not optimistic, and yet convenient and accurate prognostic predicting tool lacks. Recent studies point that the prediction ability of nomogram may be superior to that of traditional, categorical predictive models for various outcomes associated with cancer [17–19]. To take a step further, we performed the first large-cohort and comprehensive retrospective study based on wide multicenter, where the OS and the CSS of luminal A patients with bone metastasis (n = 3,171) selected from the SEER database were retrospectively analyzed. Through univariate and multivariate Cox regression analyses, 12 independent variables
associated with the OS and CSS were finally identified. Two nomograms established based on these significant prognosis predicting indicators showed high levels of discrimination and calibration in clinical utility.

Although BC bone metastasis is still incurable, our survival curves showed that the survival probability for patients of low-risk group is significantly higher than those of high-risk group. Therefore, it appears to be crucial to identify the risk factors for facilitating the prognosis predicting. Consistent with previous studies, our study suggests that age is a strong independent prognostic factor and young age is an advantageous factor for good prognosis [20, 21]. Besides, a report focusing on the OS time trends indicates that every incremental year of age is in independent and significant association with a higher risk of death [22]. On the contrary, old age may be a disadvantageous factor with poor status and age-related comorbidities. In addition, some targeted therapy or other intensive systemic treatment may be contraindicated to the old patients who are vulnerable to more frequent causes of death. In line with our conclusion, it has been previously reported that race is a significant survival predictor [23]. Parada H et al. [24] pointed that racial differences in gene expression might lead to the survival disparity of BC patients. Our study shows that, insurance status is also a significant variable. In many states of the USA, health insurance not only compensated patients for surgery but also reduced the cost of systemic adjuvant treatments. And insurance status has shown its impact on stages of diagnosis in previous study [25]. Moreover, Pan et al. [23] developed that in addition to the impact on diagnosis, uninsured status was also demonstrated to be an unfavorable factor of poor OS and CSS.

In our conclusion, tumor size, tumor primary site and histology grade were recognized as risk factors of great importance in affecting the prognosis of BC patients, which were in accordance with previous studies [26–29]. With our regression analyses, brain, liver and lung metastasis were also independent predictors of prognosis, among which brain metastasis was most likely to result in poor prognosis, followed by liver and lung metastasis. When considering all BC patients as an entire population, a cohort study has found that different distant metastatic sites presented similar trends in affecting survival [30]. Moreover, the effective implications of ER and PR status have been demonstrated by some large-scale studies in predicting patients’ prognosis and responding to BC endocrine therapy [31, 32]. Seho et al. [33] also concluded that lack expression of either ER or PR was in association with worse prognosis, especially among patients with node-positive luminal A subtype.

For cancer patients who have metastasized, whether to perform surgery is still controversial. Similar to previous reports, our research showed that non-surgical luminal A patients with bone metastasis had unfavorable prognosis. Generally, surgical treatment for primary lesion is recognized as a palliative therapy for BC patients with metastasis. Gnerlich et al. [34] showed an association between receiving surgery and improved survival for BC patients with metastasis. Xiong et al. [35] pointed that the prognosis of certain stage IV BC patients, especially those with bone- or soft tissue-only metastasis, could be improved by surgical removal of primary lesions. Moreover, for BC patients with bone metastasis, surgery can not only prolong the survival time but also improve life quality to some extent. And it is generally believed that chemotherapy can exert similar effect by reducing cancer-related complications
through killing or inhibiting cancer cells, thereby relapse delayed and survival time prolonged. However, chemotherapy failed to be identified as a significant predictor for either OS or CSS in our multivariate analysis. In fact, our conclusion is not an exception with support of other studies, where no benefit of adjuvant chemotherapy was detected in luminal A BC patients [36, 37]. The Panel of the St Gallen International Expert Consensus insisted that was less useful in Luminal A subtype patients for their less responsiveness to chemotherapy [38]. In addition, consistent with our results, a retrospective cohort study suggested that there was no significant effect of radiotherapy in improving survival of BC with metastasis [39].

Our nomograms were based on twelve independent and significant prognosis factors selected from univariate and multivariate Cox regression analyses with satisfied level of discrimination, calibration and clinical utility, which can help predict the survival probability and expected benefits of different treatments, so that the most suitable one can be selected and the prognosis can get improved. In addition, there are many kinds of predictors included in our nomograms, implying that the luminal A with bone metastasis is a complex disease with considerable individual differences. In recent years, against the increasing emphasis on personalization of cancer treatment strategies, our nomograms can make accurate individualized predictions for each luminal A subtype patient with bone metastasis.

However, there are several limitations in the present research. First, our nomograms were based on a retrospective cohort obtained from SEER-base, which inevitably creates bias. Second, the data may lack some potentially important variables and key indicators, such as hormone therapy, targeted therapy, recurrence, and other advanced technologies. Third, some data are missing or not in detail, especially specific locations of bone metastasis and types of surgery. These deficiencies remain to be further improved in future studies.

**Conclusions**

Our study identified twelve independent prognostic factors for OS and CSS of luminal A BC patients with bone metastasis. The nomograms we developed, can accurately and effectively predict the survival information of patients, and may facilitate for clinical decision-making.

**Abbreviations**

BC: Breast cancer; OS: Overall survival; CSS: Cancer-specific survival; SEER: Surveillance, Epidemiology, and End Results; ER: Estrogen receptor; PR: Progesterone receptor; Her2; Human epidermal growth factor receptor 2; C-index: Concordance index; DCA: Decision curve analysis.

**Declarations**

**Availability of data and materials**
The data analyzed during the study are available from the SEER data set repository and/or authors.

**Ethics approval and consent to participate**

The study protocol was approved by the SEER program from the National Cancer Institute, US (reference number 15260-Nov2018). There’s no need for informed consent in our study since the unidentified data was free from medical ethics review.

**Consent for publication**

Not applicable

**Competing interests**

All authors declare that they have no potential conflict of interest.

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**Authors’ contributions**

QH T and C H had idea of and designed this study. QH T, C H and H Z collected data. QH T, C P and M K analyzed data. QH T, C H and YJ W generated the figures and tables. QH T wrote the manuscript. C H, YJ W, MX S, JY L, CL Z, C W and C Z helped to review and revision of the manuscript. XX M supervised the research. All authors reviewed the results and approved the final version of the article.

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