A Nomogram Individually Predicts the Overall Survival of Patients with Breast Cancer after Surgery—a Retrospective Study in the SEER Database and China

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Research Article

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Abstract

**Background:** Patients with breast cancer have a poor prognosis. We want to construct a more elaborative and validate nomograms for predicting overall survival in patients with breast cancer.

**Methods:** A total of 68363 breast cancer patients who underwent surgery between 2011 and 2015 were recruited from the Surveillance Epidemiology, and End Results (SEER) database. After eliminating lacking clinical information, 60445 eligible breast cancer patients were randomly divided into the training cohort (n=42327) and the internal validation cohort (n=18118) in a ratio of 7:3. The endpoint of this study was overall survival (OS). Multivariate Cox proportional hazards regression models was performed to identify independent risk factors of OS in the training cohort, and then the nomogram was constructed. The nomogram predictive performance was evaluated by the Harrell's concordance index (C-index), the time-dependent receiver operating characteristics (ROC) curve (AUC), calibration curve, decision curve analysis (DCA) and clinical impact curve. Moreover, the nomogram was verified by the internal validation cohort and external validation cohort.

**Results:** Age, gender, grade, 7th AJCC stage, ER status, PR status, Her-2 Status, breast subtype were found to be independent risk factor of OS (P<0.05). The nomogram integrating these eight factors was constructed and proved excellent discrimination capability in the training cohort (C-index, 0.724 (95% CI, 0.716-0.732)) which was demonstrated in the internal validation cohort (C-index, 0.717 (95% CI, 0.705-0.729) and external validation cohort (C-index, 0.793 (95% CI, 0.724-0.862)). Calibration curve for the probability of 1-, 3- and 5-year OS demonstrated good concordance between nomogram prediction and actual observed results in both the training and validation cohort. Besides, the DCA and clinical impact curve indicated the clinical usefulness of our constructed nomogram.

**Conclusions:** We developed a nomogram that integrate clinicopathological variables, which can precisely predict the 1-, 3- and 5-year OS of breast cancer patients after surgery. Validation uncovered preeminent discrimination power for the nomogram, indicating that it presents satisfactory clinical application. Therefore, the nomogram can help clinicians in formulating the suitable therapy strategies for individual patients.

**Background**

Breast cancer is one of the most common malignancies in the worldwide and the second leading cause of cancer death in female patients [1, 2]. The incidence of breast cancer has been increasing gramatically in recent decades, and the exact pathogenesis remains not clearly known yet. With the continuous progress of various treatment modalities in latest years, but the prognosis of breast cancer is still remains poor.

The American Joint Committee on Cancer (AJCC) TNM staging system is globally recognized and widely used to predict disease progression and design effective therapeutic strategies of breast cancer patients [3, 4], but it is largely influenced by a variety of conclusive clinicopathological characteristics, for
example age, gender, histological differentiation and breast subtype, which may also have a favorable impact on survival in patients[5, 6]. If the prognosis could be accurately predicted in breast cancer patients after resection, comprehensive scientific treatment would be taken timely to high-risk patients to increase the survival and decrease the mortality.

The nomogram is considered as a useful and reliable clinical tool to help clinicians and patients estimate the overall survival probability and make personalized decisions by incorporating vital clinical indicators to predict the survival outcome of certain cancers individually[7, 8]. The good accuracy and simplicity of the prediction of the nomogram make it a new standard to guide the treatment of cancer patients[9].

In this study, our aim is to build a more elaborative nomogram to predict the overall survival rates of breast cancer patients with relatively large cohort in 1-, 3- and 5-year, based the surveillance, epidemiology, and end results (SEER) database.

**Methods**

**Study population selection and design**

We acquired the study population from the SEER (Version 8.3.8) program records of the National Cancer Institute (https://seer.cancer.gov/). The SEER database can provide more information about demographic, tumor location, tumor size and morphology, diagnosis stage, treatment, prognosis and so on of millions of cancer patients, which provides excellent data for clinical research of tumors. The 1975-2016 year SEER (submitted in November 2018)) became useable on April 2019.

The inclusion criteria were as follows: (1) patients aged at diagnosis ≥14 years who underwent surgery at the site of the primary tumor; (2) pathology histological diagnosis was breast cancer; (3) year of diagnosis between 2011-2015; (4) complete clinicopathological follow-up data. The exclusion criteria were (1) patients diagnosed according to exfoliative cytology; (2) patients with unknown 7th AJCC stage, ER status, PR status, Her2 status, breast subtype, survival time and follow-up vital status. Ultimately, the data of 60,445 patients were enrolled and analysed in this study from the SEER database. Furthermore, the eligible breast cancer patients were randomly split into two groups in a ratio of 7:3, the training cohort (n=42,327) and internal validation cohort (n=18,118). In addition, a Chinese cohort (n=332) from Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University was used for external validation. Our study procedure is shown in Figure 1.

Extraction of demographic and clinicopathological characteristics from SEER database, containing age at diagnosis, gender, year of diagnosis, tumor site, behavior recode, grade, histology diagnostic confirmation, 7th AJCC stage, ER (estrogen receptor) status, PR (progesterone receptor) status, Her2 (human epidermal growth factor receptor-2) status, breast subtype, survival months and follow-up vital status. The Chinese cohort follow-ups ended in April 29, 2020 or the date of patient death, whichever came first. The overall survival time (OS) was defined as the time from diagnosis to death for any reason or last follow-up.
The analysis of data from SEER is not limited by medical ethics review and does not require informed consent. The external validation cohort was approved by the hospital ethics committee, but because it was a retrospective study, informed consent was not required (project number: K20210809). All procedures conducted in studies involving human participants met the 1964 declaration of Helsinki and its subsequent amendments or similar ethical standards.

**Statistical Analyses**

Categorical variables were described as frequency and proportion. Continuous variables were described as mean (standard deviation, SD) or median (interquartile range, IQR). In order to compare the basic characteristics between training cohort and validation cohort, chi-square test or Fisher's exact test was used for categorical variables, student's t-test was used for normal distribution variables, and Mann-Whitney U-test was used for non-normal distribution variables. Univariate and multivariate Cox proportional risk regression model was used to recognize independent risk factors of OS in the training cohort (P<0.05). The survival differences were compared between groups using Kaplan-Meier curves. These independent risk factors were used to construct nomogram for breast cancer patients. The nomogram was validated internally (training cohort) and externally (internal validation cohort and external validation cohort). The calibration curves were used to compare the correlation between actual and predicted survival outcomes [9]. Both the Harrell's concordance index (C-index) and area under the time-dependent receiver operating characteristics (ROC) curve (AUC) can be used to assess the discrimination accuracy of the nomogram [10]. The decision curve analyses (DCA) and clinical impact curve were used to evaluate the clinical usefulness and benefits of the predictive model [11].

The SPSS 22.0 and the R software (version 4.0.3) were used for all statistical analysis. Two-tailed test P-value less than 0.05 was considered statistically significant.

**Results**

**Study population characteristics**

The demographic and clinicopathological characteristics of the breast cancer patients are listed in Table 1. The median follow-up time of all patients were 48.0 months, and 6091 (10.1%) breast cancer patients died of all causes. On the basis of age at diagnosis, all patients were be segmented into two groups: <60 year (42.9%), ≥60 year (57.1%). Most of patients presented with pathological moderately differentiated grade II (44.2%), 7th AJCC stage I (54.4%) at the time of diagnosis. Of these, 45677 (75.5%) patients of breast subtype were Luminal A.

**Independent prognostic factors of OS**

In the training cohort, the results of univariate and multivariate analysis are shown in Table 2. The multivariate analysis revealed that age, gender, grade, 7th AJCC stage, ER status, PR status, Her-2 status, breast subtype were found to be independent risk factor of OS (P<0.05). It's more intuitionistic to present the results as a forest plot (Figure 2).
Figure 3 displays the Kaplan-Meier survival curve in training cohort. The patients with above 60 years old, ER negative, PR negative, Her-2 negative and triple negative had shorter survival time (P<0.05). The grade IV and 7th AJCC stage IV group had the worst prognosis (P<0.0001).

**Nomogram Construction**

Based on the multivariate Cox regressions analyses results, a nomogram was constructed (Figure 4) for predicting OS in training cohort. The nomograms indicated that 7th AJCC stage contributed most to OS. Just to make it easier to use the nomogram, every variable was allocated a score that a vertical line is drawn upward to ascertain the number of points of each variable value. Add these numbers and find the corresponding position on the total point axis, a straight line is drawn downward to the survival axis to ascertain the possibility of OS. For example, the patient was less than 60 years old, grade II, 7th AJCC stage III, ER status negative, PR status negative, Her-2 status positive and the breast subtype was luminal B. Her total points were 13.2, and the probability of 1-year OS survival, 3-year OS survival, 5-year OS survival was more than 95%, 87%, 75%, respectively, on the basis of the nomogram.

**Nomogram Validation**

The discrimination performance of nomogram was 0.724 (95%CI, 0.716-0.732), which was confirmed in the internal validation cohort (C-index, 0.717 (95%CI, 0.705-0.729) and external validation cohort (C-index, 0.793 (95%CI, 0.724-0.862), respectively. Moreover, the nomogram proved better differentiated ability for OS compared with the 7th AJCC stage in both the training cohort (AUC: 0.726, 0.634, respectively, Figure 5A), internal validation cohort (AUC: 0.716, 0.613, respectively, Figure 5B) and external validation cohort (AUC: 0.716, 0.613, respectively, Figure 5C).

The calibration curve for predicting 1-, 3-, or 5-years OS present a good concordance of the nomogram predicted probability with actual observations in both the training cohort, internal and external validation cohort (Figure 6). Ultimately, the DCA curves was carried out to indicated the clinical net benefits of the nomogram with that of the 7th AJCC stage, grade (Figure 7A, 7B, 7C). The nomogram predict the OS probabilities showed largest net benefits in the training, internal and external validation cohort (Figure 7D, 7E, 7F).

**Discussion**

In this study, we construct a nomogram to predict the OS of breast cancer patients after surgery, which integrated age at diagnosis, gender, grade, 7th AJCC stage, ER status, PR status, Her-2 status, and breast subtype. Furthermore, the nomogram was validated using the internal and external validation cohort. This nomogram was more significantly predictive (AUC: 0.735) than the 7th AJCC stage (AUC: 0.634). In addition, the calibration curve showed that the predicted 1-, 3- and 5-year OS closely related to the actual observations, whether it is in training, internal and external validation cohort. Similarly, the DCA curve manifested it had largest net benefits and promising clinical applicability.
According to the results of multivariate cox regression analysis, eight clinicopathological characteristics were found to be independent dangerous factors, containing age at diagnosis, gender, grade, 7th AJCC stage, ER status, PR status, Her-2 status and breast subtype. The nomogram reveals that the 7th AJCC stage is the most important variable affecting OS, which is mainly due to the 7th AJCC stage, including tumor size, lymph node metastasis and distant metastasis, which are very important factors affecting the prognosis of breast cancer[12, 13]. Our results indicated that patients who were older than 60 years, the older they were, the worse the prognosis was. As similar with our consequences, age was proved to be a significant association with OS in several other studies[14-16]. One possible reason for this that OS might be influenced by age not only associated with the clinical course of a disease, but also with age-related complications[17]. Moreover, aging might facilitate the growth of tumor cells by suppressing the immune system[18]. As can be seen from the nomogram, breast cancer patients who are negative for ER and PR had a poor prognosis, which is in accordance with other findings[19, 20]. Histological grade showed undifferentiated tumors and triple negative breast cancer, which has been recognized as an index of a poor prognosis in breast cancer patients[16, 21].

The nomogram is a imaging exhibition of a statistical prediction model that provides survival probability of a particular outcome[22, 23]. Therefore, the parameters should be readily retrievable and gaugeable. What's more, the nomogram has enough discriminant capability, and the prediction is in good agreement with the actual observation. In terms of prognosis, nomogram of other tumors has also been proved to be economical and practical. Fang et al.[24]established the nomogram by combining age, tumour size, differentiation, N stage, M stage with tumor location to precisely predict OS of gastroenteropancreatic neuroendocrine neoplasms. Kong et al.[6] integrating age at diagnosis, T stage, N stage, and M stage to construct a credible and powerful nomogram to predict prognosis for adrenocortical carcinoma patients after surgery. There is growing evidence has shown that the nomogram presents a better predictive capacity than the traditional AJCC TNM stage in numerous tumors[24-26]. In comparison with the extensively used AJCC TNM stage, our nomogram is not merely simple and convenient, but also provides a accurate individual prognosis for different patients. Therefore, the nomogram will help clinicians to estimate personalized survival probability and make with optimize therapeutic schedule.

In addition to the reliable data sources of nomogram, our study has several advantages. Firstly, the clinicopathological characteristic of breast cancer patients that we collected from SEER database was abundant and comprehensive, therefore assuring construct the accurate and reliable prognostic nomogram. Secondly, the nomogram presents superior discrimination ability in predicting OS compared with 7th AJCC stage. The effectiveness and practicability of the nomogram was verified by the internal and external validation corhor. Finally, this research employed eight clinicopathological variables that are easily to obtain and extensively used in clinical practice, which bring simple and convenient for using of the nomogram.

This study had the following shortcomings. First, this is a retrospective study from the SEER database, selection bias was hardly inevitable. Second, we can not get more clinical information from SEER database, such as vascular invasion, radiotherapy, chemotherapy and laboratory data, which, if
contained, the sensitivity and specificity of nomogram can be improved. Third, the lack of clinical data and follow-up may affect the discrimination and prediction ability of nomogram. We should design a prospective experiment to further verify the nomogram in future.

Conclusions

In summary, construction of nomogram to predict the postoperative OS in breast cancer patients. Our user-friendly nomogram, an easy-to-use tool for risk evaluation and survival prediction in personalized breast cancer patients, which can precisely and efficiently provide individualized counseling, timely surveillance, and clinical evaluation.

Abbreviations

SEER: Surveillance Epidemiology, and End Results; OS: overall survival; C-index: Harrell’s concordance index; AUC: time-dependent receiver operating characteristics curve; DCA: decision curve analysis; AJCC: American Joint Committee on Cancer; ER: estrogen receptor; PR: progesterone receptor; Her-2: human epidermal growth factor receptor-2.

Declarations

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Author contributions

Yufen Zheng: Designed the project, collected datas and performed data analysis, wrote the manuscript. Minya Jin and Shiyong Chen: Designed the project, performed data analysis and wrote the manuscript. Yijun Feng and Juping Du: Performed data analysis and wrote the manuscript. Jun Li: Supervised the project, administrative support and wrote the manuscript. Jing Wang: Designed the project, supervised the project and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.
Ethics approval and consent to participate

The analysis of data from SEER is not limited by medical ethics review and does not require informed consent. The external validation cohort was approved by the Taizhou Hospital of Zhejiang Province ethics committee, but because it was a retrospective study, informed consent was not required. All procedures conducted in studies involving human participants met the 1964 declaration of Helsinki and its subsequent amendments or similar ethical standards.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables
| Variable | Total cohort n=60445 | Training cohort n=42327 | Internal validation cohort n=18118 | External validation cohort n=332 |
|----------|---------------------|-------------------------|-------------------------------------|----------------------------------|
| Age (Years) | | | | |
| <60 | 25965(42.9%) | 18236(43.0%) | 7729(42.6%) | 268(80.7%) |
| ≥60 | 34480(57.1%) | 24091(57.0%) | 10389(57.4%) | 64(19.3%) |
| Grade | | | | |
| Grade I | 15976(26.4%) | 11068(26.1%) | 4908(27.1%) | 13(3.9%) |
| Grade II | 26766(44.2%) | 18886(44.6%) | 7880(43.5%) | 164(49.4%) |
| Grade III | 17613(29.1%) | 12315(29.0%) | 5298(29.2%) | 155(46.7%) |
| Grade IV | 90(0.1%) | 58(0.1%) | 32(0.2%) | 0(0.0%) |
| 7th AJCC T stage | | | | |
| T0 | 41(0.1%) | 29(0.1%) | 12(0.1%) | 0(0.0%) |
| T1 | 38854(64.3%) | 27277(64.4%) | 11577 (63.9%) | 133(40.1%) |
| T2 | 17156(28.3%) | 11943(28.2%) | 5213(28.8%) | 183(55.1%) |
| T3 | 3212(5.3%) | 2253(5.3%) | 959(5.3%) | 16(4.8%) |
| T4 | 1182(2.0%) | 825(2.0%) | 357(2.0%) | 0(0.0%) |
| 7th AJCC N stage | | | | |
| N0 | 44061(72.9%) | 30938(73.1%) | 13123(72.4%) | 157(47.3%) |
| N1 | 12399(20.5%) | 15187(35.2%) | 3779(20.9%) | 106(31.9%) |
| N2 | 2604(4.3%) | 8620(20.4%) | 784(4.3%) | 38(11.5%) |
| N3 | 1381(2.3%) | 949(2.3%) | 432(2.4%) | 31(9.3%) |
| 7th AJCC M stage | | | | |
| M0 | 60263(99.7%) | 42200(99.7%) | 18063(99.6%) | 305(91.9%) |
| M1 | 182(0.3%) | 127(0.3%) | 55(0.4%) | 27(8.1%) |
| 7 th AJCC stage | | | | |
| I | 32929(54.4%) | 23112(54.6%) | 9817(54.1%) | 74(22.2%) |
| II | 21464(35.5%) | 15019(35.4%) | 6445(35.5%) | 201(60.5%) |
| III | 5870(9.7%) | 4069(9.6%) | 1801(9.9%) | 56(16.8%) |
|      |        |        |        |        |
|------|--------|--------|--------|--------|
| IV   | 182(0.3%) | 127(0.3%) | 55(0.3%) | 1(0.3%) |
| ER Status |        |        |        |        |
| Positive  | 50921(84.2%) | 35625(84.1%) | 15296(84.5%) | 246(74.0%) |
| Negative  | 9524(15.8%) | 6702(15.9%) | 2822(15.5%) | 86(26.0%) |
| PR Status |        |        |        |        |
| Positive  | 44464(73.5%) | 31139(73.5%) | 13325(73.5%) | 214(64.5%) |
| Negative  | 15981(26.4%) | 11188(26.5%) | 4793(26.5%) | 118(35.5%) |
| Her-2 Status |        |        |        |        |
| Positive  | 8217(13.5%) | 5697(13.4%) | 2520(13.9%) | 121(36.4%) |
| Negative  | 52228(86.5%) | 36630(86.6%) | 15598(86.1%) | 211(63.6%) |
| Breast Subtype |        |        |        |        |
| Luminal A | 45677(75.5%) | 32003(75.6%) | 13674(75.4%) | 140(42.2%) |
| Luminal B | 5759(9.5%) | 3965(9.4%) | 1794(9.9%) | 34(10.2%) |
| Her-2 enriched | 2458(4.0%) | 1732(4.1%) | 726(4.1%) | 119(35.8%) |
| Triple negative | 6551 (10.8%) | 4627(10.9%) | 1924(10.6%) | 39(11.8%) |
| Vital status |        |        |        |        |
| Alive  | 54354(89.9%) | 38066(89.9%) | 16288(89.8%) | 290(87.4%) |
| Dead   | 6091 (10.1%) | 4261(10.1%) | 1830(10.2%) | 42(12.6%) |
| Median follow-up time(Months, 25th–75th percentile) | 48.0(34.0-65.0) | 49.0(34.0-65.0) | 48.0(34.0-64.0) | 71.0(64.3-83.0) |

AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, Human epidermal growth factor 2-neu.
Table 2. Univariate and multivariate analyses of overall survival in the training corhort

| Variable                  | OS |                |                |
|---------------------------|----|----------------|----------------|
|                           |    | Univariate     | Multivariate   |
|                           |    | HR(95%CI)       | HR(95%CI)      |
|                           |    | P Value         | P Value        |
| Age (Years)               | 2.400(2.240-2.570) | 0.000          | 2.920(2.720-3.130) | 0.000 |
| Grade                     | 1.570(1.510-1.640) | 0.000          | 1.250(1.190-1.310) | 0.000 |
| 7 th AJCC stage           | 2.010(1.940-2.090) | 0.000          | 2.020(1.940-2.110) | 0.000 |
| ER status                 | 0.440(0.420-0.470) | 0.000          | 0.780(0.630-0.960) | 0.019 |
| PR Status                 | 0.510(0.480-0.540) | 0.000          | 0.780(0.710-0.860) | 0.000 |
| Her-2 Status              | 0.890(0.810-0.980) | 0.013          | 0.650(0.590-0.710) | 0.000 |
| Breast Subtype            | 1.340(1.310-1.380) | 0.000          | 1.080(1.000-1.170) | 0.048 |

AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, Human epidermal growth factor 2-neu; OS, overall survival.

Figures

Figure 1
Flowchart of sample selection for this study. AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results; ER, estrogen receptor; PR, progesterone receptor; Her-2, Human epidermal growth factor 2-neu.

Figure 2
The effects of different prognostic factors was described by forest plot. AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; Her-2, Human epidermal growth factor 2-neu.

Figure 3
Kaplan-Meier OS curve of the female patients stratified by characteristics in the training cohort. (A) Age; (B) Grade; (C) 7th AJCC stage; (D) ER status; (E) PR status; (F) Her-2 status; (G) Breast Subtype. AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; Her-2, Human epidermal growth factor 2-neu; OS, overall survival.

**Figure 4**

A nomogram predicting the 1-, 3- and 5-year OS survival of postoperative breast cancer patients in the training cohort. AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; Her-2, Human epidermal growth factor 2-neu; OS, overall survival.

**Figure 5**

The ROC curves in the training cohort (A), internal validation cohort (B) and external validation cohort (C). AUC, area under the time-dependent receiver operating characteristics curve.

**Figure 6**

Calibration plot of the nomogram for predicting OS of breast cancer patients. (A) 1-year, (B) 3-year, and (C) 5-year OS according to the training cohort. (D) 1-year, (E) 3-year, and (F) 5-year OS according to the internal validation cohort. (G) 1-year, (H) 3-years, and (G) 5-years OS according to the external validation cohort. The performance is estimated by bootstrap 1,000 repetitions. The X-axis plots the nomogram-predicted survival; the Y-axis plots the actual survival. OS, overall survival.

**Figure 7**

Decision curve analysis and clinical impact curve. Decision curve analysis for the nomogram in the training cohort (A), internal validation cohort (B) and external validation cohort (C). The horizontal solid black line represents the assumption that no patients will experience the event, and the solid gray line represents the assumption that all patients will relapse. Clinical impact curve of the nomogram for OS prediction in the training cohort (D), internal validation cohort (E) and external validation cohort (F).

**Supplementary Files**

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• Highlights.doc
• GraphicalAbstractImage.pdf
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