Dynamic Nomogram Predicts Overall Survival in Patients With Occult Breast Cancer: a Population-based Analysis

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Research Article

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Abstract

Background: Due the rarity of occult breast cancer (OBC), no precise prognostic instruments were available to assess the overall survival (OS) in patients with OBC. The aim of this study is to construct a nomogram for predicting the OS probability in patients with OBC.

Methods: Patients who were enrolled in the Surveillance, Epidemiology, and End Results database between 2004 and 2015 were regarded as subjects and studied. We constructed a dynamic nomogram that can predict prognosis in patients with OBC based on crucial independent factors by using univariate and multivariate Cox regression analyses. C-index and calibration plots were chosen for validation. Net reclassification index (NRI), integrated discrimination improvement (IDI) and DCA (Ddecision Curve Analysis) were used to evaluate the nomogram's clinical pragmatism.

Results: Totally, 693 patients with OBC were included in this study. The nomogram integrated six independent prognostic factors through multivariate Cox regression analysis, such as surgical method, radiotherapy status, chemotherapy status, ER status, AJCC-stage and age. The prediction model exhibited robustness with the C-index 0.75 (95%CI: 0.72-0.77) in training cohort and 0.79 (95%CI: 0.76-0.82) in validation group. Moreover, the calibration curves presented favorably. The NRI values of 0.61 (95%CI: 0.28-0.99) for 5-year,0.53 (95%CI: 0.23-0.77) for 8-year OS prediction in the training cohort,0.75 (95%CI: 0.36-1.23) for 5-year and 0.6 (95%CI: 0.15-1.2) for 8-year OS prediction in the validation cohort,and the IDI values of 0.1 (95%CI: 0.04-0.17) for 5-year and 0.11 (95%CI: 0.03-0.19) for 8-year OS prediction in the training cohort, 0.21 (95%CI: 0.09-0.3) for 5-year and 0.22 (95%CI: 0.08-0.32) for 8-year OS prediction in the validation cohort,, indicated that the established nomogram performed significantly better than the AJCC stage system alone. Furthermore, DCA showed that the nomogram in our study was clinically useful and had better discriminative ability than the AJCC stage system.

Conclusions: A nomogram was developed and validated to accurately predict the individualized probability OS for patients with occult breast cancer (OBC) and is expected to offer guidance for strategic decision.

1 Introduction

Occult breast cancer (OBC), a rare clinical entity and accounting for 0.3%-1.0% of all breast cancer, presents as histologically consistent with metastatic axillary lymph node (ALN) and indiscernible primary breast lesions by clinical examination or imaging [1, 2]. Some previous studies suggested that OBC had a similar biological behavior to the metastatic axillary lymph node in breast cancer (non-OBC)[3, 4], but the clinicopathological characteristics of OBC, such as the status of hormone receptor (HR), HER2, and lymph node involvement, still remained a mystery[5–7]. Previous researches reported that patients with OBC always had tumors with triple negative subtype or three and more metastatic lymph nodes[6–10]. Retrospective and meta-analysis studies had indicated that patients with OBC had similar or more favorable prognosis than those with stage II-III or T1N1 palpable breast cancer[11, 12], but several studies

held an an adverse standpoint that OBC was associated with worse survival[12–14]. Therefore, there still had limited understanding of the effectiveness of OBC on long-term prognosis in women.

Previous studies recommended that breast-conserving surgery (BCS) with axillary lymph node dissection (ALND) plus radiotherapy (RT) had the similar long-term prognosis to mastectomy plus ALND[5, 15]. However, the current National Comprehensive Cancer Network (NCCN) guidelines recommended that patients with negative MRI findings should be treated with mastectomy plus ALND or ALND plus whole breast irradiation. On the contrary, systemic chemotherapy, endocrine therapy, or molecular targeted therapy were used to cure the stage II or III OBC disease according to previous study[16]. These findings suggested that the identification of high-risk individuals with OBC was indispensable for timely targeted interventions. However, there was no prognosis prediction models to predict individually the prognosis of OBC patients, due to lack of large, multicenter randomized clinical trials.

The American Joint Committee on Cancer (AJCC) staging system was the most common model extensively used to evaluate the prognosis of patients with non-OBC. While due to lack of evaluation in sociodemographic and clinicopathological characteristics (such as age, hormone receptor), the AJCC system had inefficiency and poor performance in predicting individual survival outcome [18–21]. For these reasons, the construction of individual prediction model is is urgently needed for patients with OBS. To predict the OS probability in patients with OBC, a nomogram, which had been widely used as a predictive method in oncology in recent years[21–24],was constructed based on thr Surveillance, Epidemiology, and End Results (SEER) database. .This model could be more accurate and personalized than the conventional TNM stage system, and is convenient for clinicians to predict the prognosis of patients.

2 Materials And Methods

2.1 Data resource

The recent version of the SEER 18 registries Custom Data (with additional treatment fields) was used as the data source for the present population-based investigation. This database consisted of 18 population-based cancer registries and covers approximately 26% of the US population across several geographic region[25]. SEER*-Stat Software version 8.3.9 (https://seer.cancer.gov/ seerstat/) (Information Management Service, Inc. Calverton, MD, USA) was used to generate the case listing. All procedures were performed in accordance with approved guidelines. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. Informed patient consent was not required to access and use SEER data.

2.2 Patients cohort

Patients diagnosed with occult breast cancer from 2004 to 2015 were enrolled in the study, and the media follow-up time was 57 months. Participants were included by following criteria: 1) breast cancer, diagnosed as the only primary malignant cancer; 2) TNM (Breast-Adjusted American Joint Committee on

Cancer, AJCC 6th) staged T0, N1-N3. Subjects were expelled by following criteria: (1) AJCC stage T1-T3, N0; (2) unknown surgical information; (3) male patients.

After the preliminary filtration, a total of 693 patients with OBC were extracted in our cohort. Patient demographic and treatment characteristics, such as age, year of diagnosis, marital status, surgery, radiotherapy and chemotherapy status, were confirmed in the current study. Tumor characteristics consisted of tumor laterality, tumor grade, AJCC stage, tumor N stage, estrogen receptor (ER) status, progesterone receptor (PR) status. Due to HER-2 status had not been recorded in the SEER database until 2010, the HER-2 status variable was not included. Figure 1 showed the entire screening process.

2.3 Endpoint and statistical analysis

Overall survival (OS) was deemed as the interval from the date of diagnosis to the date of death from any causes. Descriptive statistics were used to calculate demographic and clinical variables, student's t test was performed to describe the continuous variables, Chi-squared test was performed to describe the categorical variables. In survival analysis, univariate and multivariate Cox regression analyses were conducted. Based on the significant independent risk factors affecting OS in Cox multivariate analysis,a nomogram model was established. The nomogram estimated the OS probabilities at 3- and 5-year. Concordance index (C-index) and calibration plots wert used to assess the discriminative ability, were performed to evaluate and the calibrating ability of the Nomogram.The value of C-index ranged from 0.5 to 1.0, where 0.5 represented random chance and 1.0 indicated a perfect fit. Generally,the value of C-index greater than 0.7 indicated a reasonable estimation. The net reclassification index (NRI), integrated discrimination improvement (IDI), and decision curve analysis (DCA) were conducted to evaluate the nomogram improvements through comparing with the AJCC TNM system alone.The NRI and IDI values were performed to estimate the improvement in prognosis forecast and measure the usefulness of a new model[25]. DCA was a measurement parameter for estimating the clinical benefit of alternative models and was administrated to quantify the net benefits at different threshold probabilities for nomograms[28, 29]. Statistical significance was defined as $P < 0.05$ and all P-values were two-tailed .

3 Results

3.1 Baseline characteristics

A total of 693 patients enrolled in our cohort were randomly divided into training cohort and validation cohort (207) by a ratio of 7:3. Totally, 486 eligible candidate were randomly assigned to training cohort and 207 candidate were randomly assigned to validation cohort. The mean age was 59.4(±12.5) years, 59.5(±12.5) years and 59.3(±12.4) years old in whole population, training cohort, and validation cohort, respectively. Patients diagnosed from 2010 to 2015 (54.7%), and married women (55.4%) constituted the majority of the whole cohort. Meanwhile, the whole population had a relatively lower rate of well or moderately differentiated (4.8%), and lower rate of bilateral laterality (8.4%). Moreover, the majority of patients had IIa stage (62.2%), N1 stage (62.2%), ER-positive (50.6%) and PR-negative (54.5%) tumors. In total, among the participants included, 56.4% of them didn’t receive surgical operation, 52.4% of them

received radiotherapy and 79.2% of them received chemotherapy. There was no statistical significance between the training and validation cohorts about demographic and clinical characteristics (P > 0.05). The detailed information of these OBC patients was shown in Table 1.

3.2 Nomogram variable screening based on univariate and multivariate Cox regression analysis

As shown in Table 2, to select independent prognosis factors affecting OS,univariate and multivariate analyses were performed.Through univariate and multivariate Cox proportional hazard regression analyses, six variables were found to be statistically independent predictive factors for OBC patients. Adverse prognostic factors were the parameters age (HR, 1.03; 95% CI, 1.01-1.05; P< 0.001) and tumor stage IIIC (HR, 3.26; 95% CI, 2.06-5.15; P< 0.001) in training cohort.The favorable factors included the indexes of ER-positive tumor (HR, 0.53; 95% CI, 0.31-0.91; P<0.001), undergonging mastectomy (HR, 0.58; 95% CI, 0.35-0.96; P=0.03), chemotherapy (HR, 0.53; 95% CI, 0.33-0.83; P=0.005) and radiotherapy (HR, 0.54; 95% CI, 0.35-0.83; P=0.005) in training cohort.

3.3 Nomogram construction and validation

Based on the screening variables through Cox proportional hazard regression, the nomogram model was constructed to predict the OS at 5-year and 8-year for patients with OBC. As shown in Figure 2, the screening variables pointed to a score and we could get a total score by adding up all scores. By using the nomogram model, it was liable to calculate the 5-year and 8-year survival probability of a given patient. And most subjects in the current study had total cumulative points ranged from 120 to 300. The C-index value was 0.75 (95%CI: 0.72-0.77) in training cohort and 0.79 (95%CI: 0.76-0.82) in validation cohort (Table 3). The calibration curves of the nomogram also demonstrated the high consistency between the nomogram-predictiton and observed OS at 5-year and 8-year in both the training and validation cohorts (Figure 3A, 3B, 3C and 3D). In sum, the nomogram for OBC patients had great discriminative and calibrating abilities.

3.4 Dynamic Nomogram construction and clinical value compared with AJCC-TNM system stage

To facilitate the use of the nomogram and provide individual predictions and convenience to clinicians and patients conveniently, a dynamic nomogram (https://lkl0034.shinyapps.io /DynNomapp/) was constructed. As shown in Fig. 4, the predicted probability of OS at 5-year and 8-year for patients with OBC could be easily obtained and visualized after imputing information of the six variables which we confirmed. The R code and data for the application were attached in Supplement Data Sheet 1. For example, there is a sixty years old patients received BCS, chemotherapy and radiotherapy,, with ER-negative and grade IIIA. By using prediction online tools, we could make an estimation that the 5-year and 8-year of the overall survival were 82% (95% CI: 69%-97%) and 74% (95% CI: 58%-95%).

Moreover, we compared clinial value between the dynamic nomogram and the AJCC-TNM stage. The NRI and IDI were used to compare the accuracy between the dynamic nomogram and the AJCC-TNM stage

(Table 3). In training cohort, the NRI values for the 5-year and 8-year OS were 0.61 (95%CI: 0.28-0.99) and 0.53 (95%CI: 0.23-0.77), respectively, the IDI values for the 5-year and 8-year OS were 0.1 (95%CI: 0.04-0.17, P< 0.001) and 0.11 (95%CI: 0.03-0.19, P< 0.001), respectively. In the validation cohort, the NRI values for the 5-year and 8-year OS were 0.83 (95%CI: 0.36-1.23) and 0.6 (95%CI: 0.15-1.2), respectively,and the IDI values for the 5-year and 8-year OS were 0.21 (95%CI: 0.09-0.3, P< 0.001) and 0.22 (95%CI: 0.08-0.32, P< 0.001), respectively.

Furthermore, DCA plot indicated that the nomogram had advantage to predict the 5-year and 8-year OS, as it increased more net benefits compared with the AJCC-TNM system stage for almost all threshold probabilities in both the training and validation cohorts, and with both the treat-all-patients scheme and the treat-none scheme (Figure 5A, 5B, 5C and 5D). In summary, the above-mentioned results indicated that nomogram model could increase precision and reliability for OS prediction compared with the AJCC-TNM stage system.

4 Discussion

Based on data including 693 patients from the SEER database, we constructed a nomogram model to predict the 5-year and 8-year OS for patients with OBC. Six variables were selected by clinical significance to construct and validate the capability of the model, which could provide the basis for future clinical decisions. Measured by range along nomogram scales, age was the most important prognostic factor, followed by tumor stage, ER-status, chemotherapy, radiotherapy and surgery. To our knowledge, this was the first and largest population-based nomogram model to predict the prognosis of patients with OBC.

In our study, prognosis measurement was estimated by OS, which was a common and objective index for patients with OBC. In univariate Cox regression analysis, we found that age at diagnosis, tumor laterality, AJCC-TNM stage, surgery, radiotherapy, chemotherapy, ER status and PR status were significantly correlated with OS. To decrease the estimation bias and further confirm the independent prognosis factors on OS for patients with OBC, the multivariate Cox regression analysis was conducted. After adjusting for demographic, clinicopathological and therapeutic variables, we found that age, AJCC-TNM stage, radiotherapy, chemotherapy, ER status and surgery were still significantly associated with OS. Based on univariate and multivariate Cox regression analysis, six variables were selected to construct the prediction model.

Notably, we found that treatment patterns were the essential prognosis factors in our model. The nomogram model indicated that surgical operation played an important role to prolong the survival interval for patients with OBC, and mastectomy recipient had better OS than BCS recipient. Meanwhile, surgery strategies for OBC had been not reached consensus. Some previous research suggested mastectomy could provide the most effective local treatment for OBC patients[10, 30–32], while these findings were inconsistent with the recent studies that the application of BCS had similar OS outcome, even better than mastectomy [33–36]. This paradoxical results might be caused by selection bias, because the rate of BCS recepient was only 11.5%, which was much less than other two groups.

Furthermore, radiotherapy and chemotherapy were significantly associated with better OS, which were consistent with previous studies[37–42].

And our nomogram also demonstrated that the effect of chemotherapy might exceed that of radiotherapy.

In addition, ER-positive status played an important role to prolong the survival interval for patients with OBC, which was consistent with previous studies[6, 43, 44]. The underlying reason was that the majority of ER-positive breast cancer are luminal A and luminal B, which had achieved better prognosis[45–47]. Due to luminal A and luminal B breast cancer were sensitive to endocrine therapy, and this treatment was an important part of the comprehensive therapy of hormone receptor positive breast cancer and its efficacy had been widely accepted[48-50]. But PR status was not correlated with OS in our study, we considered that might be caused by retrospective bias, because the percent of PR-negative BC (54.5%) was 1.5 times than the percent of PR-positive BC (33.3%) in our study.

In conclusion, the nomogram model could be applied to predict the survival outcome of various cancers, which integrated clinical and demographic factors to evaluate the risk of specific diseases[18, 19, 21, 23]. In traditional, the AJCC-TNM stage system was the primary choice to predict prognosis and make clinical decision. But patients at the same stage usually had different prognosis, because AJCC-TNM stage system had not considered various variables comprehensively, such as clinical characteristics, treatment method and sociodemographic characteristics. Therefore, we compared the nomogram, which involves more variables, with the conventional AJCC-TNM stage system. The the NRI value and IDI value of the nomogram versus the TNM stage system suggested that the nomogram prediction model had better predictive capability than the TNM stage system alone. Furthermore, DCA curves demonstrated that our model forecasted survival outcome with better clinical valus and utility than the conventional staging system. In the validation cohort, the results could also be replicated favorably. In conclusion, our nomogram could provide accurate and individual prediction of OS in patients with OBC.

Although the nomogram performed well, our subject indeed had some limitations, as shown below: Firstly, the nomogram based on retrospective study, which could not prove causation and result in selection bias. Secondly, we were unable to exclude the impact of potential confounders, such as family history, comorbidities, health status, patient anxiety, BRCA gene status, which were not included in SEER database. Lastly, P value < 0.05 was used to possess the statistics sense, and no adjustment was made for multiple analysis; the chance of falsely rejecting a null hypothesis may exceed 0.05. Multicenter clinical validation was also needed to evaluate the external utility of our nomogram.

5 Conclusion

Our study aimed to construct a nomogram for predicting the prognosis in patients with OBC based on data from the SEER program. Given its favourable clinical utility and accurate prognosis prediction in comparison with conventional TNM stage system, our nomogram might be used to predict survival of

patients with OBC. However, multicenter clinical validation was also needed to evaluate the external utility of our nomogram.

Declarations

Data Availability

The datasets generated during the current study are available in the https://seer.cancer.gov.

Compliance with Ethical Standards

Conflict of interest

The authors declare that there is no interest of conflict.

Ethical approval

This study was deemed exempt from review by the Ethics Committee of the First Affiliated Hospital of Xian Jiaotong University because the database is publicly accessible.

Author Contributions

XY and KL drafted the manuscript and analyze data, SZ, WH and HS generated the figure, MD performed the background research. CZ and JH edited the manuscript. All authors have read and approved the content of the manuscript.

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Tables

Due to technical limitations, table 1 to 3 xlsx are only available as a download in the Supplemental Files section.

Figures

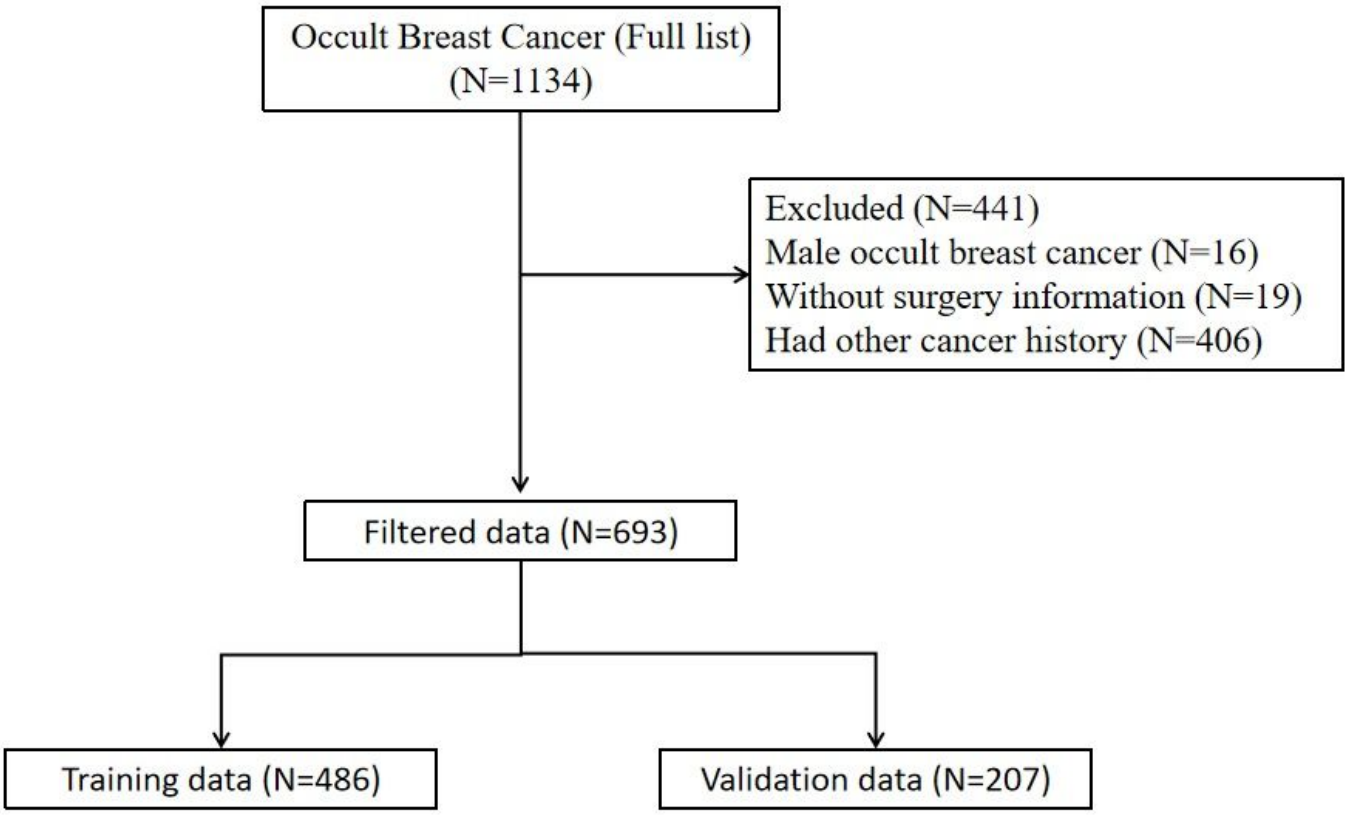

Figure 1

Eligibility, inclusion, and exclusion criteria of study population.

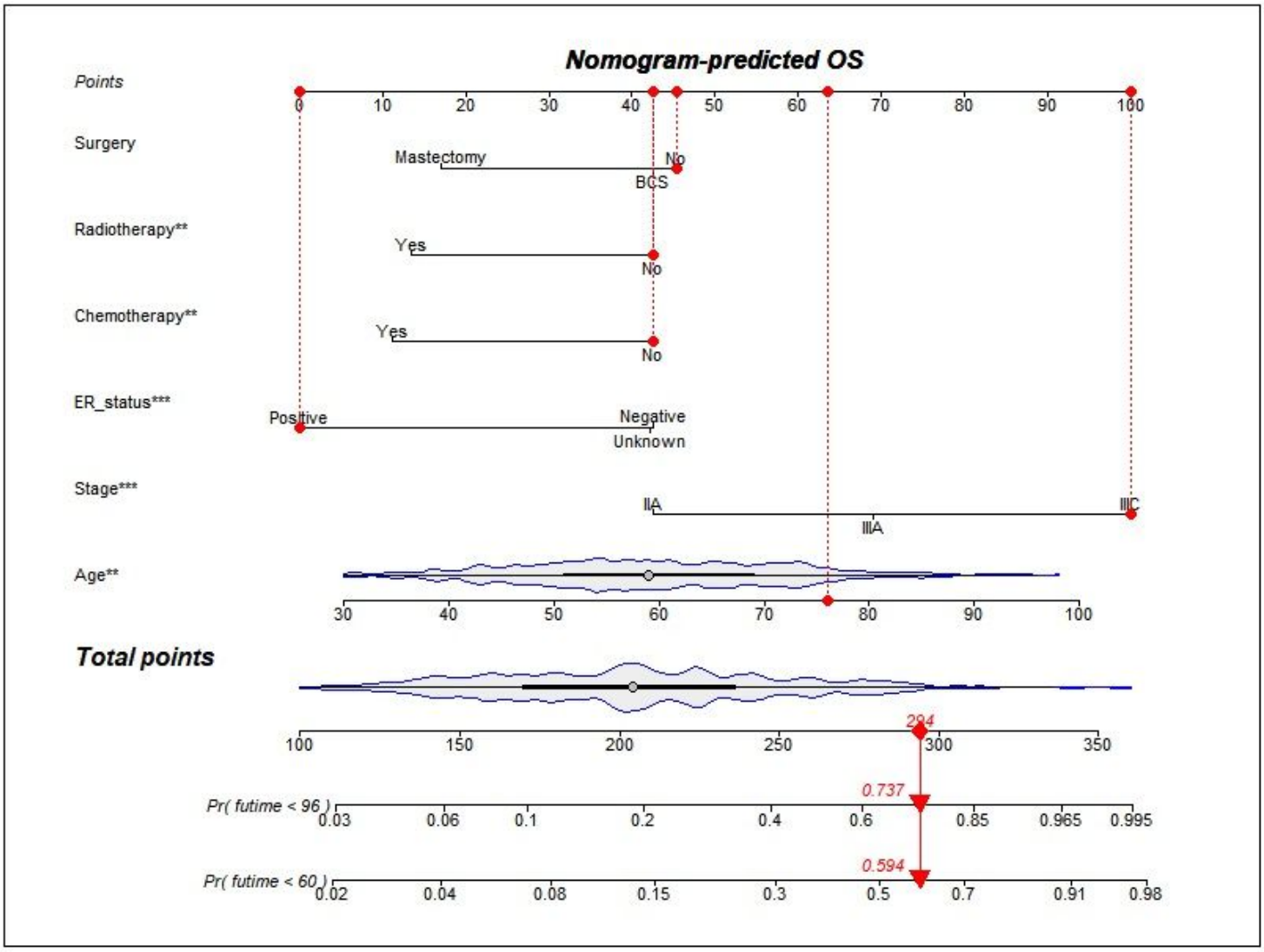

Figure 2

Nomogram prediction model for OBC patients.

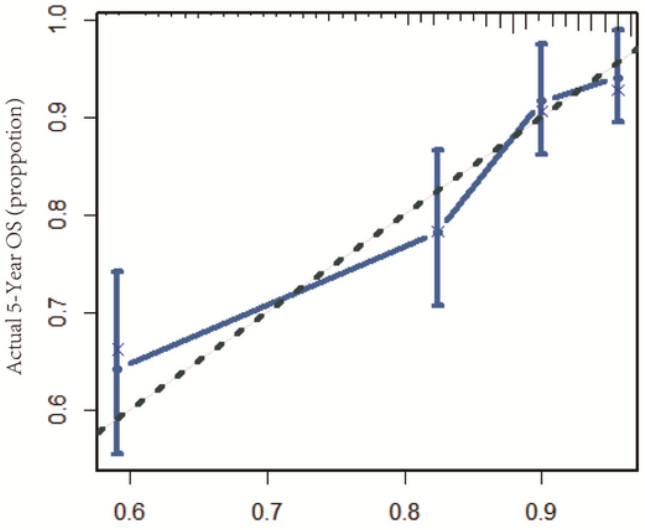

Figure3a Nomogram-Prediction Probability of 5-Year OS (Training cohort)

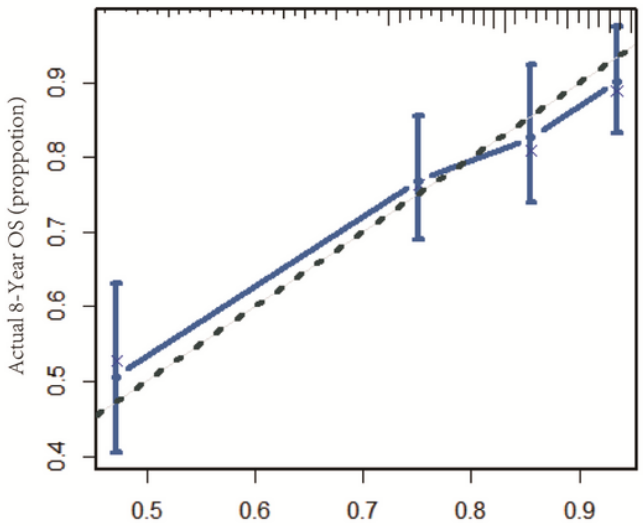

Figure3b Nomogram-Prediction Probability of 8-Year OS (Training cohort)

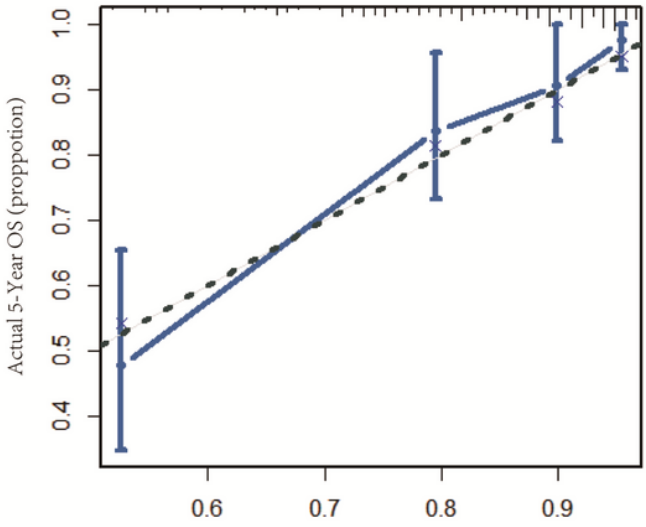

Figure3c Nomogram-Prediction Probability of 5-Year OS (Validation cohort)

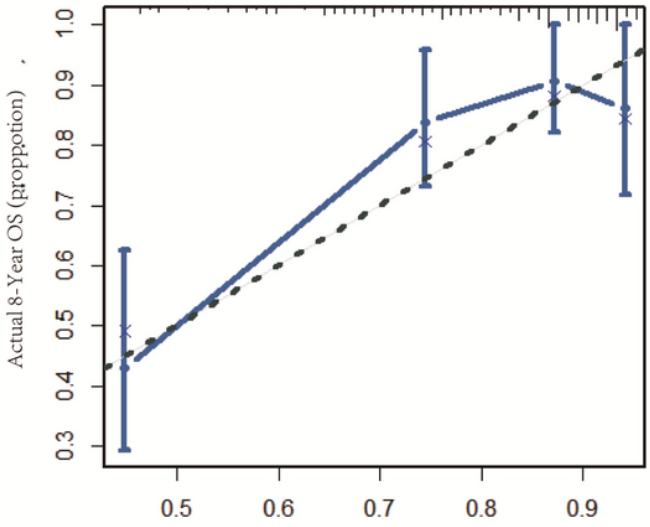

Figure3d Nomogram-Prediction Probability of 8-Year OS (Validation cohort)

Figure 3

(a) The calibration curve for predicting patient OS at 5-year in the training cohort; (b) The calibration curve for predicting patient OS at 8-year in the training cohort; (c) The calibration curve for predicting patient OS at 5-year in the validation cohort; (b) The calibration curve for predicting patient OS at 8-year in the validation cohort.

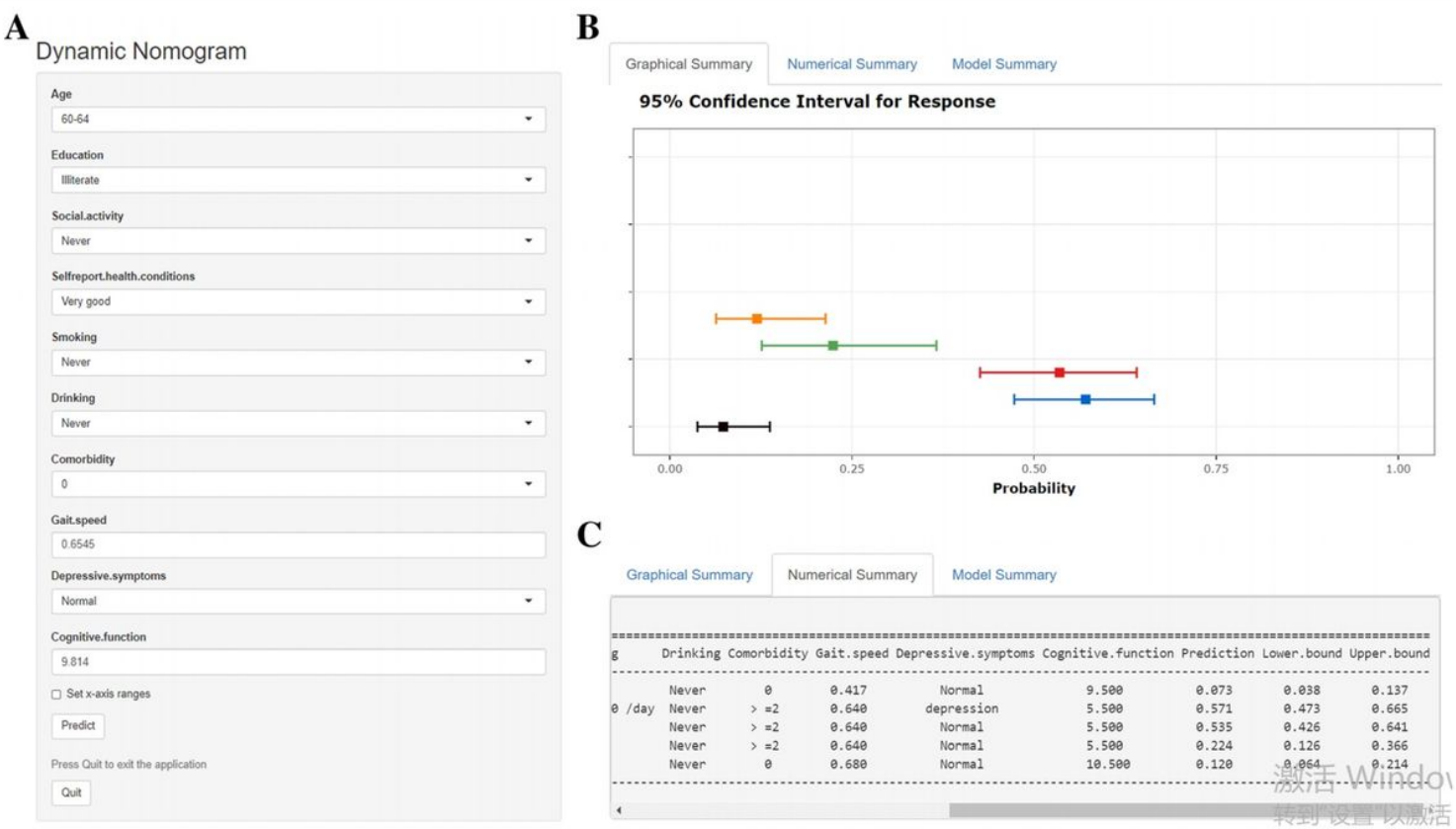

Figure 4

A case of using dynamic nomogram to probability of OS at 5-year and 8-year.

Figure 5a

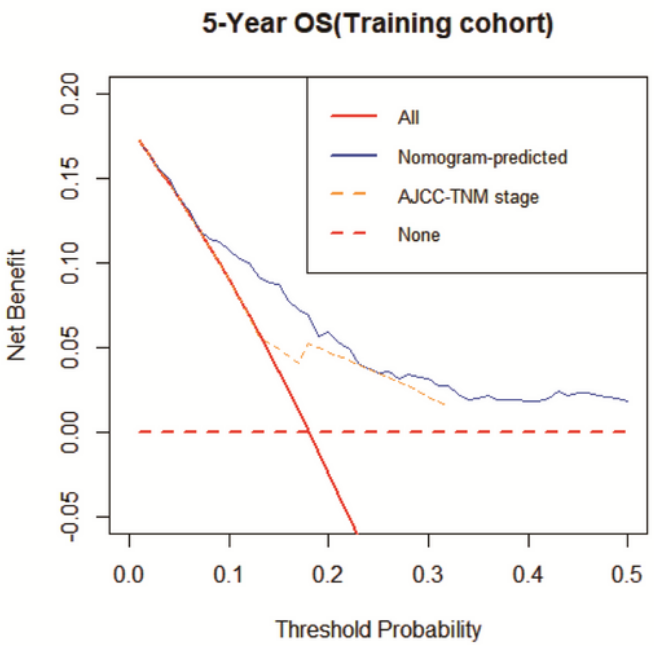

Figure 5b

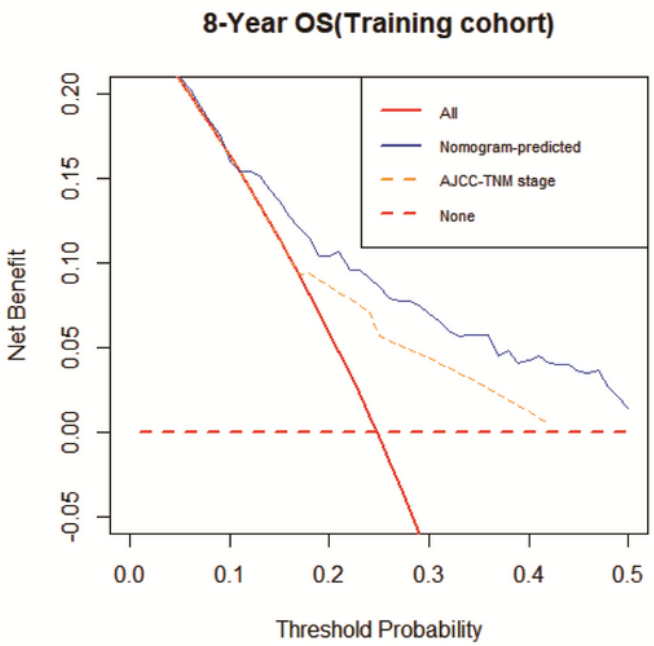

Figure 5c

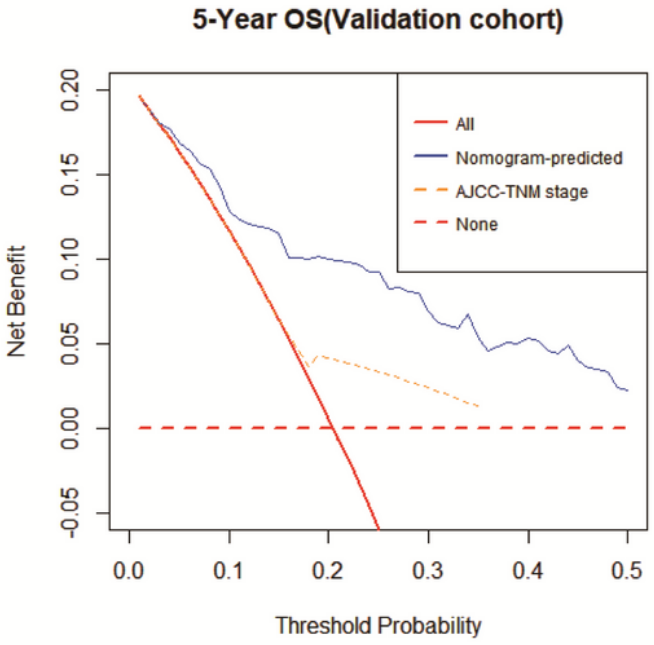

Figure 5d

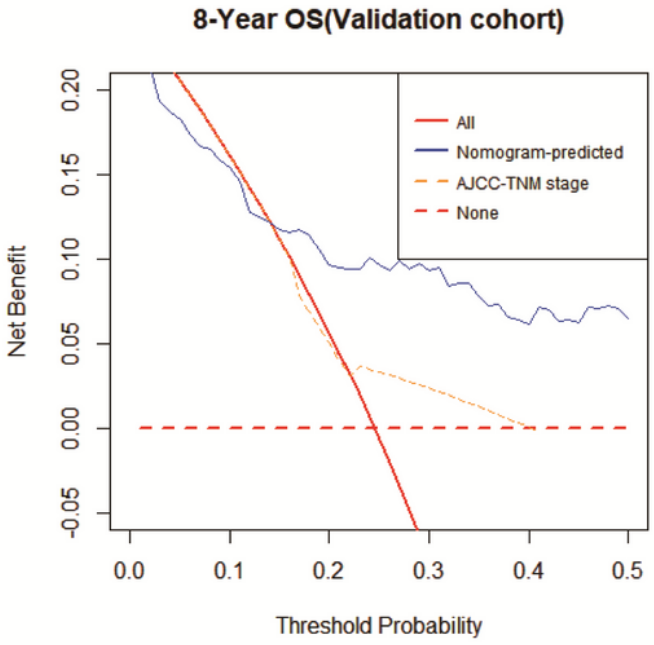

Figure 5

Decision curve analysis of the nomogram and AJCC-TNM stage system for the survival prediction of patients with OBC. (a) 5-year survival benefit in the training cohort. (b) 8-year survival benefit in the training cohort. (c) 5-year survival benefit in the validation cohort. (d) 8-year survival benefit in the validation cohort.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2CoxproportionalhazardmodelofOS.xls
- Table3.xlsx
- supplementarymaterials.rar