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Retrospective Study

A nomogram for predicting overall survival in Chinese triple-negative breast cancer patients after surgery

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Abstract

BACKGROUND

There are few nomograms for the prognosis of Chinese patients with triple-negative breast cancer (TNBC).

AIM

To construct and validate a nomogram for the overall survival (OS) of Chinese TNBC patients after surgery.

METHODS

This study used the data of SEER*stat 8.3.5 and selected Chinese patients with TNBC operated on between 2010 and 2015. Univariable and multivariable Cox proportional hazard regression models were used. The identified variables were integrated to form a predictive nomogram and risk stratification model; it was assessed with C-indexes and calibration curves.

RESULTS

The median and maximal OS of the 336 patients was 39 and 83 mo, respectively. The multivariable analysis showed that age ($P = 0.043$), marital status ($P = 0.040$), tumor localization ($P = 0.030$), grade ($P = 0.035$), T classification ($P = 0.012$), and N classification ($P = 0.002$) were independent prognostic factors. The six variables were combined to construct a 1-, 3-, and 5-year OS nomogram. The C-indexes of the nomogram to predict OS were 0.766 and compared to the seventh edition staging system, which was higher (0.766 vs. 0.707, $P < 0.001$). In order to categorize patients into different prognostic groups, a risk stratification model was created. There was a significant difference between the Kaplan-Meier curves of the entire cohort and each disease stage according to the nomogram.

CONCLUSION

The nomogram provided a prognostic superiority over the traditional TNM system. It could help clinicians make individual OS or risk predictions for Chinese TNBC patients after surgery.

INTRODUCTION

Breast cancer (BC) is the most common malignancy diagnosed in women worldwide, with 2,088,849 new cases and 626,679 deaths in 2018 [1]. BC has several risk factors, including genetic causes, aging, reproductive history, hormone exposure, lifestyle factors, medical history, and radiation exposure [2-4]. The management of BC is multidisciplinary [2, 5, 6]. Endocrine therapy can be used to prevent the recurrence of hormone (estrogen and/or progesterone) receptor-positive BC, while anti-HER2 therapies can be used to improve the prognosis of HER2-positive BC [2]. In the United States, therefore, the 5-year survival rate for women with localized BC is 99%, 85% for women with regional spread, and 27% for women with distant metastases. [2, 4]. Factors affecting prognosis include tumor and disease characteristics, age, response to therapy, race, ethnicity, and body mass [2]. Triple-negative BC (TNBC) is characterized by the absence of hormone receptor expression and HER2 overexpression [7-9]. TNBC represents approximately 15%-20% of

all BCs and generally has more aggressive biology, earlier onset of metastatic disease, visceral metastases, rapidly progressive disease, the inefficacy of endocrine therapy, short response duration to available therapies, and inferior survival outcomes [10-12]. The survival of patients with TNBC is influenced by age at diagnosis, tumor stage, positive lymph node ratio, and Ki-67 [13]. Ovcaricek *et al* [14] showed that age and nodal status are prognostic factors in such patients, while Pistelli *et al* [15] showed that tumor size and lymphovascular invasion are prognostic factors for TNBC. Owing to the malignant behavior of TNBC and in order to achieve a better prognostic assessment, stratifying patients with TNBC based on their individual characteristics is important. Nomograms are useful and convenient tools for cancer patients to quantify and predict risk and prognosis [16-18]. Many prognostication nomograms have been developed and validated for BC patients based on traditional clinicopathological features [19, 20]. Hwang *et al* [19] limited their nomogram to pathological complete response after neoadjuvant chemotherapy, while Luo *et al* [20] included radiomics in their nomogram, which might not be readily available in all hospitals. Furthermore, most models were developed using Caucasian patients, not Asians. A SEER-based study showed that Chinese women had better 10-year survival than Caucasians [21]; similar results were observed in Japanese women [22]. A study suggested that the prognosis of TNBC was similar between Asians and Caucasians, but the sample size was small [23]. There are currently few nomograms for Chinese patients with TNBC. Yang *et al* [24] and Shi *et al* [25] developed such a nomogram, but their predictive value was fair at best. Wang *et al* [26] developed a nomogram specifically for TNBC patients with de novo metastasis. Thus, the present study aimed to establish and validate a nomogram for TNBC in Chinese patients after surgery. This tool could help improve the management of TNBC in Chinese women.

MATERIALS AND METHODS

Study design and patient selection

This study used the data from SEER*stat 8.3.5 and patients undergoing TNBC surgery between 2010 and 2015 were included. The inclusion conditions were 1) Chinese patients with histologically confirmed primary TNBC, 2) >18 years of age at diagnosis, and 3) underwent primary tumor resection. The exclusion criteria were 1) male BC, 2) missing follow-up information, 3) missing data regarding tumor stage, histologic grade, tumor size, therapy, or marital status, or 4) distant metastasis.

Statistical analysis

Categorical data were presented as n (%) and analyzed using the chi-square test. Univariable comparisons of survival data were performed using the Kaplan-Meier method and compared using the log-rank test and Cox analyses. Based on the univariable Cox analyses ($P < 0.10$) and considering clinically relevant factors, multivariable analysis using the Cox risk regression model with backward elimination was performed. Using the results of the multivariate analysis, variables with P-values of ≤ 0.05 were chosen for development of the nomograms.

To create the nomogram, we used 1-, 3-, and 5-year OS. We calculated the C-indexes and generated calibration plots using 1,000 bootstrap resamples to assess the nomogram's predictive accuracy. Using the average score of each patient in the nomogram, the risk stratification model was developed to group the patients into two prognostic groups. The analyses were all performed with R (<http://www.r-project.org>) and Empower (R, v 3.6.3) (www.empowerstats.com, XY Solutions, Inc., Boston, MA, USA). Two-tailed P-values < 0.05 were considered statistically significant. The details of the nomogram and recursive partitioning analysis (RPA) are presented as an appendix.

RESULTS

Patient characteristics

Finally, 336 patients were identified from the SEER database according to the screening queries (Figure 1). The median age was 57 years (range: 28-100 years). The median follow-up time was 39 mo. The 1-, 3- and 5-year survival rates were 94.0%, 53.6%, and 29.8%, respectively. Tumors ≥ 3 cm accounted for 16.4% of the cases. Among the 336 patients,

101 (30.1%) patients were unmarried, and 171 (50.9%) had left-sided cancer. Demographics, clinicopathological characteristics, and therapy are summarized in Table 1.

Identification of independent prognostic factors

The univariable Cox regression analyses demonstrated that age at diagnosis, marital status, laterality, histologic grade, T classification, N classification, and radiotherapy were associated with OS. An unmarried status ($P = 0.016$) and right-side BC ($P = 0.003$) were associated with poorer survival (Supplementary Figure S1). These factors were brought into the multivariable Cox regression analysis. Age at diagnosis ($P = 0.043$), marital status ($P = 0.040$), tumor localization ($P = 0.030$), grade ($P = 0.035$), T classification ($P = 0.012$), and N classification ($P = 0.002$) were used to develop the nomogram.

Constructing and validating the nomogram

The Nomogram was composed of six independent factors (Figure 2). Give a score for each category on the point scale axis (Table S1). By adding up each score and projecting the total score onto the lowest scale, an overall score can be calculated to estimate each patient's OS at 1-, 3-, and 5 years.

The C-index of the nomogram was higher than the C-index of the 7th version of the AJCC-TNM staging system (0.766 vs. 0.707, $P < 0.01$), indicating that predictive accuracy of the nomogram was acceptable. Furthermore, calibration plots of the nomogram (Figure 3) demonstrated that the predicted OS closely matched the actual observations. The decision curve analysis is an analysis of net benefits that calculates the true-positive rate in relation to the weighted false-positive rate for different thresholds of risk that a clinician or patient may accept. This analysis was used to evaluate the 5-year OS of TNBC patients. See Figure 4, all models had higher net returns than the "treat all" strategy. In most of the decision threshold probabilities, the Nomogram decision model has a higher net benefit than the TNM phase model.

Risk stratification system

The results supported the predictive efficacy of the nomogram for OS. Therefore, we calculated the total score based on the Nomogram prediction score. Patients were divided

into two groups based on median: low risk (total score <101.028) and high risk (total score ≥101.028). In the entire cohort, the 5-year OS rates of the patients with low and high risk were 31.9% and 27.8%, respectively (Figure 5).

In order to validate the supplementary role of the risk stratification system to the 7th version of the AJCC-TNM staging system, we stratified the training cohort according to the TNM stage. Therefore, no significant distinction was found for stage III ($P = 0.21$). Moreover, within each TNM stage, there were significant differences between Kaplan-Meier curves in the survival predicted by the row plots (Figure 5).

DISCUSSION

The AJCC-TNM staging classification is the most widely used system for risk stratification and the selection of the treatment strategy for cancer patients [27,28]. Still, this classical system does not accurately identify survival differences among cancer subtypes [29]. In addition, the TNM staging system ignores many factors that were confirmed to be highly associated with OS. At present, there are few nomograms for the prognosis of Chinese patients with TNBC. The aim of this study is to construct and validate a nomogram for OS of Chinese TNBC patients after surgery. The results suggest that the nomogram developed in this study provided a clear prognostic value superiority over the traditional TNM system. The nomogram could help clinicians make individual survival or risk prediction for Chinese TNBC patients after surgery and give necessary treatment recommendations.

Few independent studies have been conducted on nomogram survival to predict postoperative survival in Chinese TNBC patients; the sample size was small and the prognostic factors were insufficient [24, 25, 29]. Thus, the present study used the survival data of the SEER database. The SEER registry, the largest population-based cancer patient database in the United States, was covering about 26% of patients diagnosed with cancer [30,31]. Patient data from the latest version of SEER published in 2015 (covering 18 registries, 1973-2015) were collected using SEER*Stat 8.3.5 under strict inclusion and exclusion criteria.

Four independent prognostic factors were identified through univariable and multivariable Cox regression analyses, including age at diagnosis, marital status, laterality, histologic grade, T classification, and N classification. These variables were finally incorporated into the nomogram. The findings were consistent with previous studies on survival risk factors for TNBC patients but not identical. The nomogram by Jiang *et al* [29] included age, tumor grade, and TNM stage. Yang *et al* [24] included stromal tumor-infiltrating lymphocytes, tumor size, nodal status, and Ki-67 index. Finally, Shi *et al* [25] included albumin-to-globulin ratio, neutrophil-to-lymphocyte ratio, positive lymph nodes, and tumor size.

The nomogram developed here showed that the N classification made the largest contribution to prognosis. The N3 stage was highly associated with a poor prognosis in Chinese TNBC patients. A previous study demonstrated that among lymph node-positive TNBCs, the lymph node ratio appeared to be a stronger predictor of mortality than pathological lymph nodes stage (HR: 0.80 for pN3 vs. pN1, and 3.05 for >0.65 vs. <0.21 Lymph node ratio) [13].

This study also found that the survival of Chinese TNBC patients was associated with tumor laterality. Left-sided cancer had better OS than right-sided. There is a slight excess of BC in the left breast compared with the right [32, 33], but previous studies have been hampered by small numbers or limited geographic or demographic populations. Since the laterality difference is quite small, it has been difficult to appreciate the clinical or biologic characteristics associated with left BC predominance [34]. In addition, several studies have linked marital status to cancer outcomes in soft tissue sarcoma and small intestinal adenocarcinoma rectal cancer [35, 36]. The present study also had clear survival discrimination in patients with different marital statuses, probably due to reproductive factors [2].

The necessary identification and calibration evaluations are necessary to ensure the validity of Nomogram, to maximize its generalizability, to avoid overfitting. Discrimination is usually evaluated with the C-index, and calibration is assessed by comparing the agreement between predicting and actual patient survival. The results

suggested that the nomogram developed in this study had a better predicting and discriminating ability compared with traditional staging systems. Apart from that, a decision curves analysis was performed to examine the clinical net benefit in Chinese TNBC patients' prognosis when using the nomogram. The results showed that The model is improved the clinical net benefit of all threshold probabilities [37, 38].

Finally, a system was constructed to classify the patients into two risk subgroups based on the predicted total scores. In this study, when applying the risk stratification system to evaluate patients of the same stage, it could discriminate OS in stages I and II but not in stage III patients. One important reason might be the small sample size. Thus, the Nomogram risk stratification system is an accurate and reliable prognostic model supported by all results. It is beneficial for clinicians to identify high-risk patients and conduct necessary adjunctive therapy.

There were some limitations to this study. First, this was a retrospective study based on the SEER database, which possesses its limitations [39]. There is a possible selection bias regarding the variables included in the nomogram. The SEER database does not contain information on modern gene-array technology or some important molecular factors, such as PD-L1 expression or microsatellite status, which have been proven to be associated with OS in colon cancer [40]. Subsequent analysis might improve the study design in the future. Finally, the sample of Chinese patients with TNBC was small in the SEER database. In addition, they were individuals of Chinese descent but living in the United States of America. Therefore, they cannot completely represent the Chinese living in China. Future studies should aim at validating the results in China.

CONCLUSION

In conclusion, a novel nomogram for predicting OS after surgery in Chinese TNBC patients was developed and validated. The included factors are all easy to obtain in the clinical setting, and the prognostic model is convenient to use. This nomogram provides a clear prognostic superiority over the AJCC-TNM 7. It is the first model suitable for risk stratification in long-term survival for Chinese TNBC patients.

ARTICLE HIGHLIGHTS

Research background

Triple-negative Breast cancer (TNBC) represents approximately 15%-20% of all BCs and generally has more aggressive biology, earlier onset of metastatic disease, visceral metastases, rapidly progressive disease, the inefficacy of endocrine therapy, short response duration to available therapies, and inferior survival outcomes. Nomograms are useful and convenient tools for cancer patients to quantify and predict risk and prognosis, at present, there are few nomograms for Chinese TNBC patients. Thus, the present study aimed to establish and validate a nomogram for TNBC in Chinese patients after surgery. This tool could help improve the management of TNBC in Chinese women.

Research motivation

To explore a nomogram for predicting overall survival in Chinese triple-negative breast cancer patients after surgery.

Research objectives

To construct and validate a nomogram for the overall survival (OS) of Chinese TNBC patients after surgery.

Research methods

This study used the data of SEER*stat 8.3.5 and selected Chinese patients with TNBC operated on between 2010 and 2015. Univariable and multivariable Cox proportional hazard regression models were used. A predictive nomogram and risk stratification model was constructed by integrating the identified variables; it was assessed with C-indexes and calibration curves.

Research results

The median and maximal OS of the 336 patients was 39 and 83 mo, respectively. The multivariable analysis showed that age ($P = 0.043$), marital status ($P = 0.040$), tumor localization ($P = 0.030$), grade ($P = 0.035$), T classification ($P = 0.012$), and N classification ($P = 0.002$) were independent prognostic factors. The six variables were combined to construct a 1-, 3-, and 5-year OS nomogram. The C-indexes of the nomogram to predict OS were 0.766, which was higher than that of the seventh edition TNM staging system (0.766 vs. 0.707, $P < 0.001$). Using the average score of each patient in the nomogram, the risk stratification model was developed to group the patients into two prognostic groups. There was a significant difference between the Kaplan-Meier curves of the entire cohort and each disease stage according to the nomogram. Future studies should aim at validating the results in China.

Research conclusions

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Research perspectives

The sample of Chinese patients with TNBC was small in the SEER database. In addition, they were individuals of Chinese descent but living in the United States of America. Therefore, they cannot completely represent the Chinese living in China. Future studies should aim at validating the results in China.

ACKNOWLEDGEMENTS

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