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Development and Validation of an Individualized Nomogram for Predicting Overall Survival in Patients With Typical Lung Carcinoid Tumors

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Objective: We aim to develop and validate an effective nomogram prognostic model for patients with typical lung carcinoid tumors using a large patient cohort from the Surveillance, Epidemiology, and End Results (SEER) database.

Materials and Methods: Data from patients with typical lung carcinoid tumors between 2010 and 2015 were selected from the SEER database for retrospective analysis. Univariate and multivariate Cox analysis was performed to clarify independent prognostic factors. Next, a nomogram was formulated to predict the probability of 3- and 5-year overall survival (OS). Concordance indexes (*c*-index), receiver operating characteristic analysis and calibration curves were used to evaluate the model.

Results: The selected patients were randomly divided into a training and a validation cohort. A nomogram was established based on the training cohort. Cox analysis results indicated that age, sex, T stage, N stage, surgery, and bone metastasis were independent variables for OS. All these factors, except surgery, were included in the nomogram model for predicting 3- and 5-year OS. The internally and externally validated *c*-indexes were 0.787 and 0.817, respectively. For the 3-year survival prediction, receiver operating characteristic analysis showed that the areas under the curve in the training and validation cohorts were 0.824 and 0.795, respectively. For the 5-year survival prediction, the area under the curve in the training and validation cohorts were 0.812 and 0.787, respectively. The calibration plots for probability of survival were in good agreement.

Conclusion: The nomogram brings us closer to personalized medicine and the maximization of predictive accuracy in the prediction of OS in patients with typical lung carcinoid tumors.

Key Words: bronchial carcinoid tumor, SEER, outcomes, nomogram

(*Am J Clin Oncol* 2020;43:607–614)

Lung cancer is the main cause of tumor-related mortality worldwide, 1% to 2% of which are carcinoid tumors. The past 30 years have witnessed a growth in the incidence of carcinoid tumors of the lung,[1] which may be a result of increasing cancer screenings and the application of imaging and bronchoscopy. The revised 2015 World Health Organization classification morphologically graded typical carcinoids as low-grade tumors.[2] Multiple prognostic parameters have been shown to have an impact on the survival of lung carcinoid tumors. The 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system appears to be superior to the 7th in predicting prognosis of lung carcinoid tumors.[3,4] Metastatic status, tumor size, histologic subtype, mitotic counts and Ki-67 index have been found to serve as prognostic factors in patients with carcinoids.[5–7] Age, ipsilateral mediastinal subcarinal lymph node status and surgical methods have also been shown to have an impact on prognosis.[7] However, there is no prognostic model in typical lung carcinoid tumors combining prognostic parameters.

The nomogram prognostic model is a statistical predictive model with a graphic representation, able to integrate multiple factors and decode the probability of an event more easily than traditional evaluation standards.[8] Nomogram models bring us closer to personalized medicine and the maximization of predictive accuracy.[9,10] Currently, nomograms are being used to provide individualized treatment for the majority of malignancies.[11–14] Therefore, in the present study, population-based data from the Surveillance, Epidemiology, and End Results (SEER) database were used to formulate and validate a combined individualized nomogram for the prediction of overall survival (OS) in patients with typical lung carcinoid tumors. To the best of our knowledge, this is the first attempt to construct a prediction nomogram based on clinicopathologic data of cases with typical lung carcinoid tumors.

MATERIALS AND METHODS

Study Population

Population consisted of all patients with typical carcinoid carcinoma were obtained from the SEER database, which provides data on cancer statistics in the United States. Data in the current study were extracted from the SEER 18 Regs (1975-2016 varying). The inclusion criteria were as follows: carcinoid cases (histologic code 8240) diagnosed between 2010 and 2015, only one primary tumor, the location of tumor was in lung and bronchus. Cases age 17 years old or younger, or

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The data in this research was obtained from SEER database, which is supported by the Surveillance Research Program in NCI's Division of Cancer Control and Population Sciences. All text within NCI products is free of copyright and may be reused without permission.

Supported by grants from the Natural Science Foundation of Shandong Province (no. ZR2017MH062) and the Science and Technology for People's Livelihood Project of Qingdao (no. 17-3-3-33-nsh). The funding agency played no role in this study.

Z.Y. and S.D.: Conception and design. W.Z.: Collection and assembly of data. J.L.: Development of methodology. J.L. and S.D.: Data analysis and interpretation. All authors: Manuscript writing and final approval of manuscript.

The authors declare no conflicts of interest.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.amjclinicaloncology.com.

ISSN: 0277-3732/20/4309-0607
DOI: 10.1097/COC.0000000000000715

diagnosed made by death certificate and autopsy were exclusive of our research. The variables in our analysis included age, sex, race, marital status, survival months, vital status, T stage (AJCC, 7th ed.), N stage (AJCC, 7th ed.), M stage (AJCC, 7th ed.), SEER Summary stage 2000, surgery, and distant metastasis to the lung, liver, brain, and bone. OS was defined as the interval between diagnosis and death or time of the last follow-up.

Nomogram Construction

The selected patients were divided into a training cohort (n = 1798) and a validation cohort (n = 768) by performing the package of caret (Classification and Regression Training) in R version 3.6.1. The formulating of the nomogram was based on data in the training set. Variables significantly related to prognosis were identified by univariate and multivariate Cox regression analyses. The results of Cox analyses were visualized by forest plots via GraphPad Prism 5.0. The ultimate multivariate Cox regression model was used to construct the nomogram prognostic model via rms package in R version 3.6.1.

Model Validation

The validation of the nomogram model was performed by 3 criteria using the training set as well as validation set. First, the prediction performance was evaluated by concordance index (*c*-index). *C*-index is a value ranging from 0 to 1; a high *c*-index (> 0.71) suggests relatively good performance of the model.[12] Second, calibration curves were carried out to assess the agreement between predicted and actual proportion in 3- and 5-year survival. A calibration curve that is closer to the ideal curve indicates a perfectly calibrated model.[13] Third, receiver operating characteristic (ROC) analysis based on risk score was applied using survival ROC and tidy verse package in R version 3.6.1. Area under the curve (AUC) implies prediction ability of nomogram model. A larger AUC (> 0.71) indicates more accurate predictions for prognosis.

Statistical Analysis

All computations were performed in GraphPad Prism 5.0 and R 3.6.1 (www.Rproject.org). *P*-value of <0.05 was considered statistically significant. Cox proportional hazard regression models were used in the univariate and multivariate analysis to identify independent prognostic factors. The nomogram was formulated and validated based on Cox regression models. Survival curves were drawn in Kaplan-Meier method by survival package in R 3.6.1.

RESULTS

Demographics and Clinicopathologic Characteristics of the Training and Validation Cohorts

A total of 2566 typical lung carcinoid patients from the SEER database between 2010 and 2015 were included in the present study. The enrolled patients were divided into a training (n = 1798) and a validation cohort (n = 768) using the caret package in R version 3.6.1. Log-rank method was used and χ^2 values were calculated for every possible division of the population in X-tile software, a bioinformatics tool for cutoff value optimization based on outcome data.[15] Then this software selected the optimal cut-point of our data, and transformed the age value into 3 categorical variables: below 62, 62-77, and above 77 years (Supplemental Data Content 1, http://links.lww.com/AJCO/A336). As shown in Table 1, the demographic and clinicopathologic characteristics of these 2 cohorts were similar, and no significant difference was observed in the survival analysis results drawn by GraphPad Prism 5.0 (log-rank test; $P = 0.6446$) between the training and validation cohorts (Supplemental Data Content 2, http://links.lww.com/AJCO/A336).

TABLE 1. Demographics and Clinicopathologic Characteristics of Patients With Lung Carcinoid Tumors

Characteristics	Training Set (n = 1798), n (%)	Validation Set (n = 768), n (%)
Age (y)		
< 62	894 (49.7)	380 (49.5)
62-77	728 (40.5)	305 (39.7)
> 77	176 (9.8)	83 (10.8)
Sex		
Male	569 (31.6)	235 (30.6)
Female	1229 (68.4)	533 (69.4)
Race		
White	1585 (88.2)	678 (88.3)
Black	140 (7.8)	60 (7.8)
Others/unknown	73 (0.4)	30 (3.9)
Marital status		
Yes	997 (55.5)	432 (56.3)
No	801 (44.5)	336 (43.7)
Tumor stage		
Localized	1180 (65.6)	493 (64.2)
Regional	343 (19.1)	169 (22.0)
Distant	233 (13.0)	90 (11.7)
Other	42 (2.3)	16 (2.1)
T stage		
T1	1041 (57.9)	422 (55.0)
T2	373 (20.8)	175 (22.8)
T3	168 (9.3)	83 (10.8)
T4	119 (6.6)	41 (5.3)
Tx	97 (5.4)	47 (6.1)
N stage		
N0	1528 (85.0)	646 (84.1)
N1	111 (6.2)	57 (7.4)
N2	97 (5.4)	39 (5.1)
N3	18 (1.0)	5 (0.7)
Nx	44 (2.4)	21 (2.7)
M stage		
M0	1638 (91.1)	695 (90.5)
M1	160 (8.9)	73 (9.5)
Surgery		
Yes	909 (50.6)	391 (50.9)
No/unknown	889 (49.4)	377 (49.1)
Bone metastasis		
Yes	31 (1.7)	16 (2.1)
No/unknown	1767 (98.3)	752 (97.9)
Brain metastasis		
Yes	13 (0.7)	6 (0.8)
No/unknown	1785 (99.3)	762 (99.2)
Liver metastasis		
Yes	38 (2.1)	19 (2.5)
No/unknown	1760 (97.9)	749 (97.5)
Lung metastasis		
Yes	77 (4.3)	27 (3.5)
No/unknown	1721 (95.7)	741 (96.5)

Identification of Prognostic Factors in the Training Cohort

To explore the effect of clinicopathologic characteristics on patient survival, univariate Cox analysis was used in the training cohort. The results showed that age, sex, marital status, tumor stage, T stage, N stage, M stage, surgery, and metastasis to the bone, brain, and liver were considered risk factors for the OS of patients with typical carcinoids (Fig. 1A). Multivariate Cox analysis was then performed on these significant prognostic factors. Forest plots indicated that age, sex, T stage, N stage, surgery, and

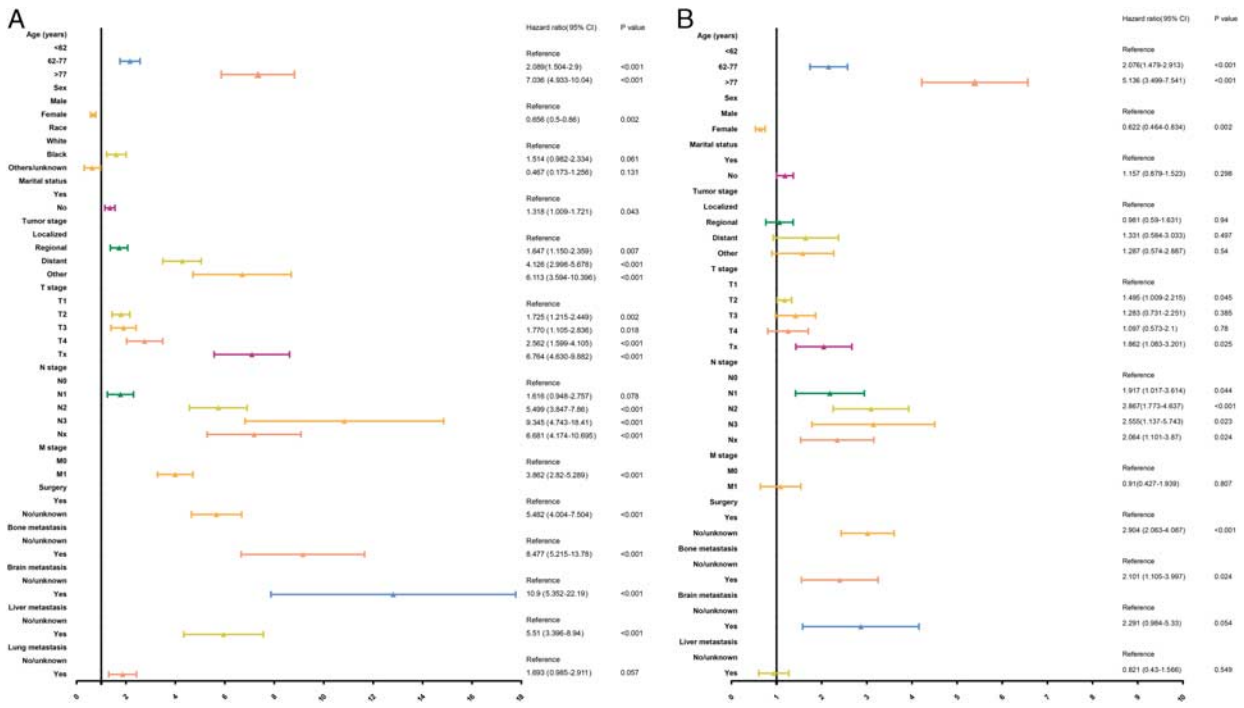

FIGURE 1. Hazard ratio of overall survival for patients with typical lung carcinoid tumors based on Cox regression analysis. A, Univariate analysis of the training cohort. B, Multivariate analysis of the training cohort. CI indicates confidence interval. full color online

bone metastasis were independent variables for OS (Fig. 1B). In addition, Kaplan-Meier curve analysis was carried out to validate the predictive abilities of these factors (Figs. 2A–L). The results showed that longer OS was associated with younger age ($P < 0.0001$), female sex ($P = 0.0021$), white race ($P = 0.012$), married status ($P = 0.0419$), lower T, N, and M stage ($P < 0.0001$), lower tumor stage ($P < 0.0001$), surgery ($P < 0.0001$), and no metastasis to the bone, brain, and liver ($P < 0.0001$). Lung metastasis had no significant impact on OS ($P = 0.0543$) (Supplemental Data Content 2, http://links.lww.com/AJCO/A336).

Construction of Nomogram Prognostic Model in the Training Cohort

To work out a quantitative approach to the prediction of individual probability for 3- and 5-year OS, a nomogram model that integrated all the clinicopathologic independent risk factors except surgery was formulated (Fig. 3), to improve the applicability of this model for a wide variety of patients initially presenting to clinic and waiting for systemic evaluation.[16] To calculate the final risk score, the scores of the items depicted in the nomogram should be added up. As seen in Figure 3, age contributed most to prognosis, followed by N stage, T stage, bone metastasis, and sex.

Validation of Predictive Accuracy of Nomogram in the Training and Validation Cohorts

To validate the robustness of the nomogram model, the *c*-index was first calculated in this model. High *c*-indexes were observed in both the training (0.787) and validation cohorts (0.817). Next, the calibration curves were found to be closer to the ideal curves with regard to 3- and 5-year survival probability, which suggested a good predictive ability of the nomogram (Figs. 4A–D). Next, the survival package was used to calculate the risk score in the training and validation cohorts. To be exact, survival package in R 3.6.1 was performed to generate the risk score for each patient and obtain the optimum cutoff scores in 2 cohorts. Patients with risk score of cutoff value or lower in each set were classified into the low-risk group (1117 in the training set and 395 in the validation set), while the left ones in each set were divided into the high-risk group (681 in the training set and 373 in the validation set). Kaplan-Meier curves showed longer survival times in high-risk populations (Figs. 5A, B). Furthermore, ROC analysis based on the risk score was used to assess the predictive accuracy of the nomogram: The 3-year survival AUC of the nomogram in the training and validation cohorts was 0.824 and 0.795, respectively, while the 5-year survival AUC was 0.812 and 0.787, respectively (Figs. 6A, B). These results demonstrated a good discrimination ability of the nomogram.

DISCUSSION

In the present study, an individualized nomogram including routinely available information such as sex, age, T stage, N stage, and bone metastasis, was built to predict OS in a large cohort of patients with typical lung carcinoid tumors. Favorable validation results were obtained from *c*-index, and calibration and ROC curves.

Kaplan-Meier curve analysis showed that lung metastasis had no significant impact on OS. This result was not consistent with that of Wolin,[17] who found that patients with metastatic lung neuroendocrine tumors had shorter survival times than those with localized lung neuroendocrine tumors. A possible explanation for this might be the limited study population of this study. In the process of model construction, age had the highest weight in the multivariate Cox analysis, suggesting its vital role in the prediction model. Older patients were found to have a high risk and a shorter OS (62 to 77 y: hazard ratio [HR] = 2.076, 95% confidence interval [CI] = 1.479-2.913;

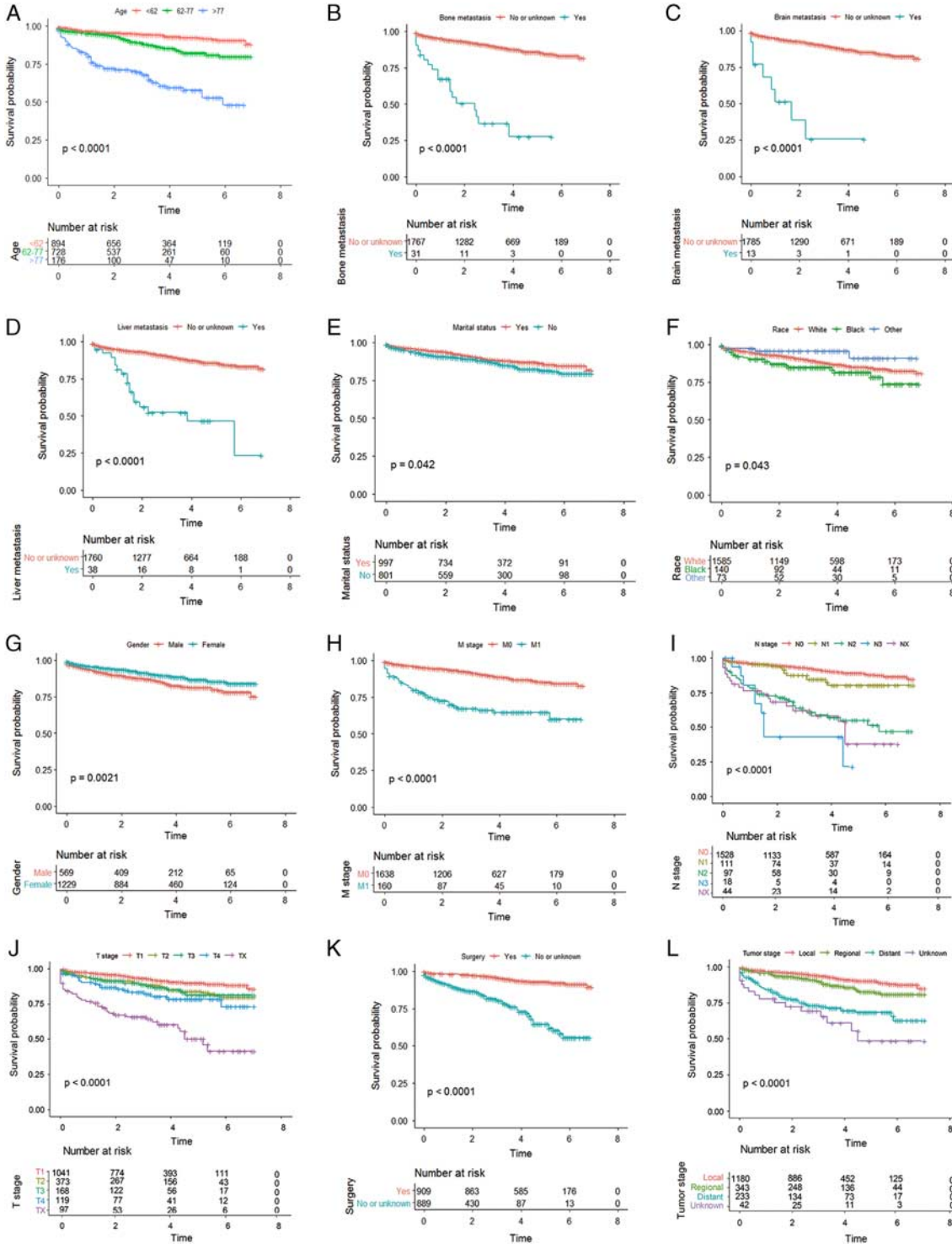

FIGURE 2. Kaplan-Meier survival curves of overall survival based on age (A), bone metastasis (B), brain metastasis (C), liver metastasis (D), marital status (E), race (F), sex (G), M stage (H), N stage (I), T stage (J), surgery (K), and tumor stage (L). full color online

above 77 y: HR = 5.136, 95% CI = 3.499-7.541). This result was consistent with the findings of other studies,[13,18,19] in which older age led to lower survival rates in cancer. The multivariate Cox analysis results showed that sex was another independent factor for OS, and female patients appeared to have a better prognosis than their male counterparts (females: HR = 0.604, 95% CI = 0.45-0.806). This result was in agreement with earlier observations in other subtypes of lung cancer,[13,20,21] including non–small cell lung cancer (NSCLC), small cell lung cancer, and large cell neuroendocrine

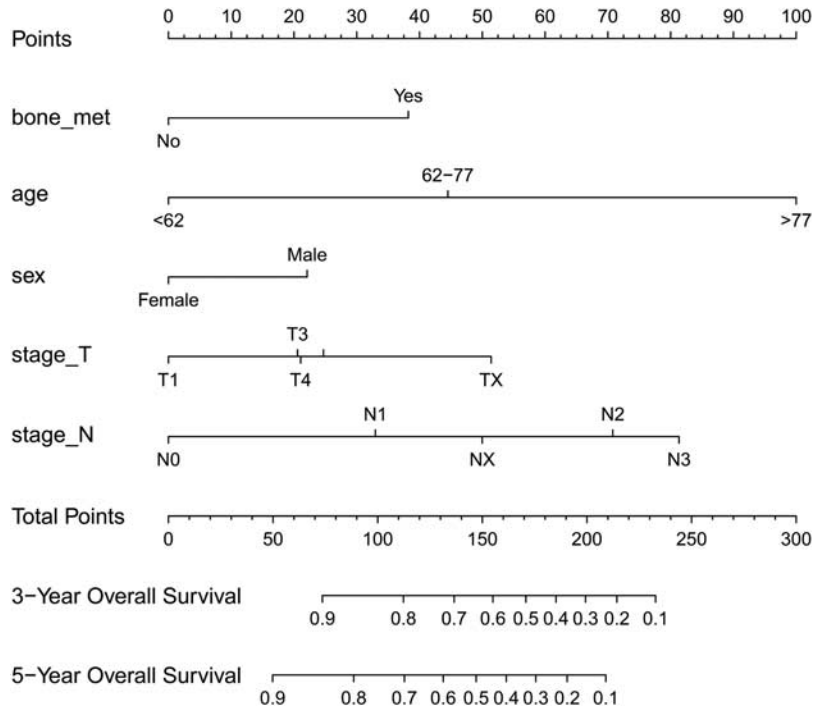

FIGURE 3. Nomogram for the prediction of 3- and 5-year overall survival in patients with typical lung carcinoid tumors.

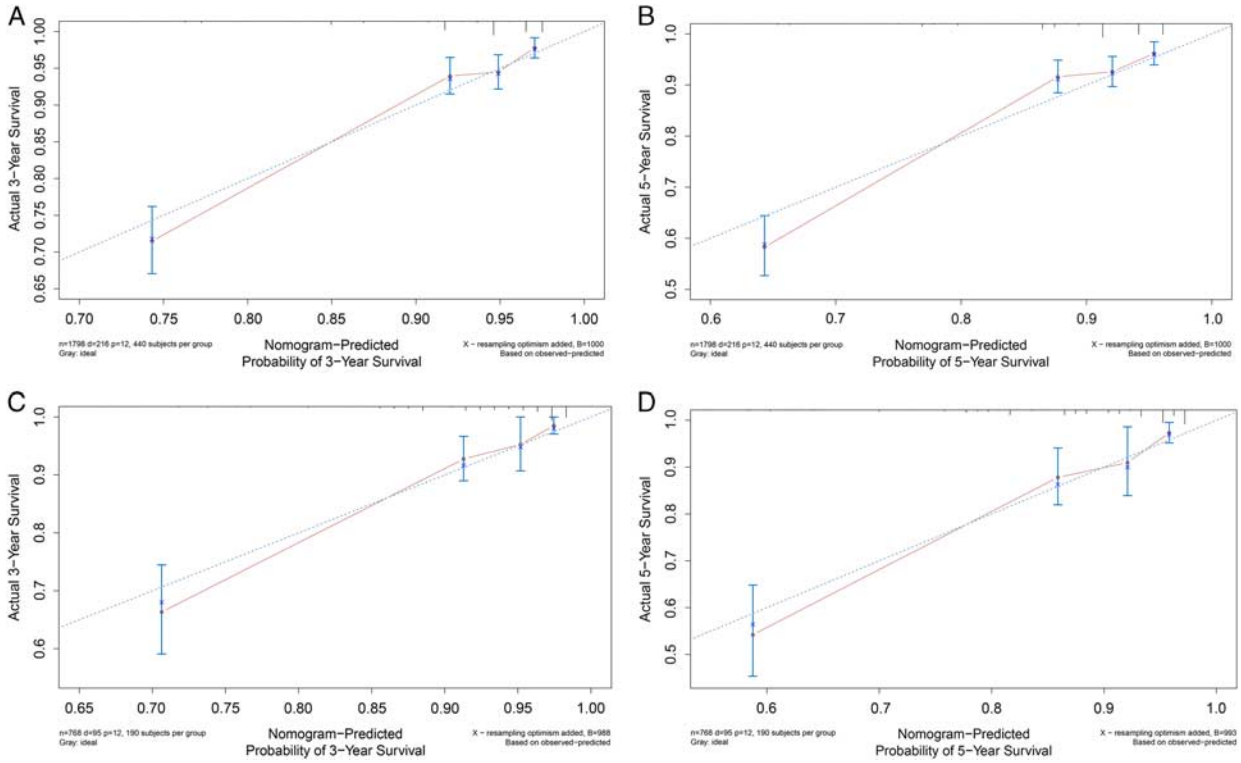

FIGURE 4. Calibration curves of the nomogram predicting 3- and 5-year overall survival (OS) in patients with typical lung carcinoid tumors. A, Calibration curve of 3-year OS in the training cohort. B, Calibration curve of 5-year OS in the training cohort. C, Calibration curve of 3-year OS in the validation cohort. D, Calibration curve of 5-year OS in the validation cohort. full color online

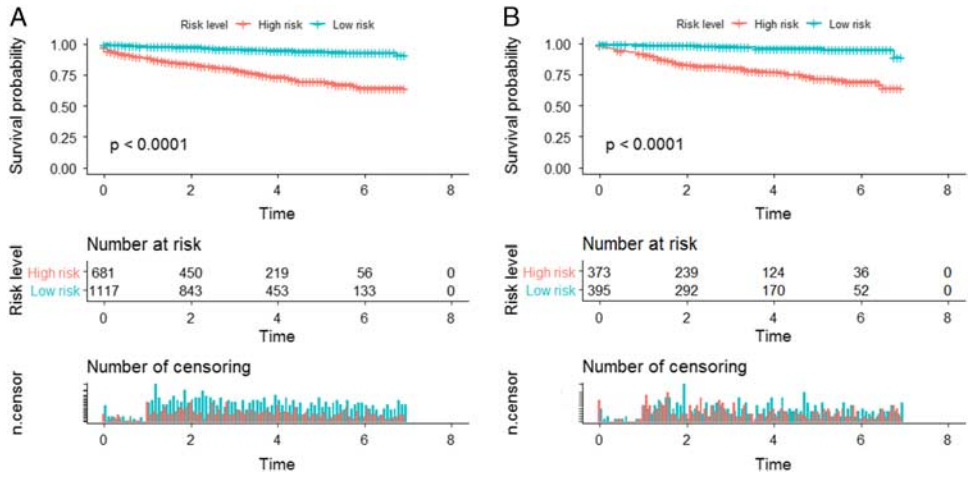

FIGURE 5. Kaplan-Meier survival curves showing overall survival probability stratified by risk group. A, Kaplan-Meier survival curves of the training cohort. B, Kaplan-Meier survival curves of the training cohort. full color online

carcinoma, indicating that the male sex is associated with poorer prognosis, despite the higher incidence in women than in men of lung cancer in the United States.[22,23]

T stage (AJCC, 7th ed.), N stage (AJCC, 7th ed.), and bone metastasis were also taken into account when constructing the model. Previous studies have found that the applications of predictive nomograms in some malignancies had a better prognostic performance than the conventional staging systems.[12,13] Wang et al[12] constructed a nomogram that contained laboratory indices as well as demographic data from patients with intrahepatic cholangiocarcinoma following partial hepatectomy, and this nomogram was proven to predict OS more accurately than different staging systems. Wang et al[13] combined TNM stage with routinely available demographic data and developed a nomogram that performed better than models that used AJCC staging. Taken together, since these multiple factors can be used as a supplement to the staging system, the prognostic tool has more power to provide valuable information in clinical practice, which makes it possible to better stratify patients, and to offer much better evidence for guiding treatment.

Previous studies have constructed nomograms to assess OS in lung cancer.[21,24,25] Demographic and clinicopathologic data have been used for the construction of most nomograms. The nomograms constructed by Guo et al[26] may be valuable for the precise evaluation of patient prognosis and the development of further treatment against locally advanced NSCLC, achieving a *c*-index of 0.692 and an AUC of 0.742. In addition, Botticelli et al[27] have developed a nomogram for NSCLC patients treated with nivolumab, which can accurately drive treatment strategies with a *c*-index of 0.76. One study [28] constructed nomograms based on gene expression data or more

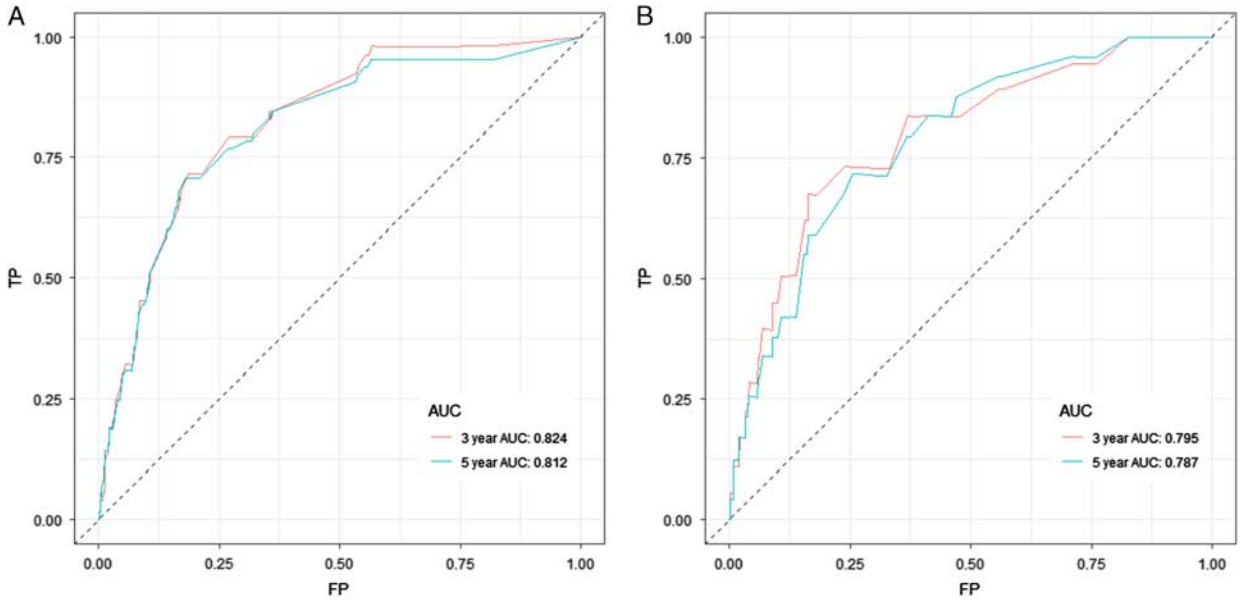

FIGURE 6. ROC curves of the nomogram. A, ROC curves for 3- and 5-year OS in the training cohort. B, ROC curves of 3- and 5-year OS in the validation cohort. AUC indicates area under the curve; FP, false positive; OS, overall survival; ROC, receiver operating characteristic; TP, true positive. full color online

complex information, not limited to clinical statistics. A tRNA-based prognostic model for NSCLC has been formulated and favorable results have been obtained, with a *c*-index of 0.814 and an AUC of 0.829 for cancer-specific survival.[28] In addition, Dong et al[29] integrated clinical data, DNA methylation and gene expression information into developing a trans-omics biomarker nomogram, which showed a superior predictive ability for early-stage lung adenocarcinoma, with a *c*-index of 0.81 and an AUC of 0.872. Compared with these prognostic indexes for lung cancer, this model has a good predictive capacity.

It is fair to say that the nomogram could be used for treatment decision making as well providing prognosis at the time of diagnosis. This is due to the fact that clinicians may find it easy to implement in the clinical setting because that variables used in this quantitative tool are easily-to-collect and inexpensive ones. What's more, this model is genuinely useful for doctors in daily practice to more precisely making treatment decision and enrollment onto clinical trials. Also, this illustrational model is incredibly perspicuous, making it easy for patients to understand their health condition and prognosis, contributing to barrier-free doctor-patient communication and good relationship, especially in recent days when violence against health workers has become an international concern.[30]

The present study, however, had several potential methodological disadvantages. First, the nomogram was developed based on a retrospective cohort, and thus the inherent biases could not be avoided. Further prospective clinical trials are needed for validation. Second, this study lacks external validations. Although 3 criteria were used for validation and favorable results were obtained from internal validations, external validations in another independent large-scale cohort could enhance the validity of the nomogram. Third, the 7th edition of the AJCC TNM staging system was used to establish the nomogram. Previous studies had a preference for the 8th edition,[3,4] but we failed to access that edition's information in SEER. Fourth, this study has only considered the OS and has not encompassed disease specific survival, which results in the fact that the OS would be impacted for patients with comorbid illnesses or specific treatment because of longer survival for typical carcinoid tumors compared with other lung cancers.[31] Considering more relative information about patients' complications and special treatment such as octreotide into further analysis is needed to effectively address this problem. Notwithstanding these limitations, this is, to the best of our knowledge, the first prognostic nomogram model for typical lung carcinoid tumors, and the key strengths of this nomogram are its inclusion of easily accessible information, high accuracy, and individuality in prognostic prediction.

To explore the predictive function of nomogram which was based on variables associated with response to therapy is without doubt an important issue for further in-depth research, particularly with the increasing utilization of targeted therapy, which has incredibly improved a great number of patients' survival.[32–34] The aim of our study is to figure out the impacts that demographics and clinicopathologic variables have on clinical outcome before using intervene, which is mainly from the prognostic perspective. More research is required to develop a deeper understanding of the function of the nomogram involved in the relationship between predictive variables and their related targetable driver mutations, since in this way the target population would be recognized and categorized much more easily, and therefore patients could receive expeditious treatment. Apart from that, a previous study has emphasized the importance of Ki-67 labeling index (Ki-67%) for stratifying pulmonary carcinoids into different grades with different diagnoses.[35] The expression of somatostatin receptors has also been found to be associated with prognosis in patients with pulmonary carcinoids.[36] Further studies taking Ki-67% and somatostatin receptors into account will need to be undertaken to construct more predictive nomograms. In addition, further research could also be conducted to determine whether our nomogram can be applicable to other patient cohorts.

Availability of Data and Material

The data sets generated during the current study are available from the corresponding author on reasonable request. Raw data from SEER database were listed in Supplemental Data Content 3 (http://links.lww.com/AJCO/A336); characteristics of patients with typical lung carcinoid tumors in the training cohort and validation cohort were listed in Supplemental Data Content 4 and 5 (http://links.lww.com/AJCO/A336); risk scores of patients in the training cohort and validation cohort were listed in Supplemental Data Content 6 and 7 (http://links.lww.com/AJCO/A336).

ACKNOWLEDGMENT

The authors thank SEER for providing open access to the database.

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