ORIGINAL RESEARCH

Establishment and Validation of a Survival Benefit Prediction Model for Non-small Cell Lung Cancer after Immunotherapy

Rui Duan, MM; Hao Li, MM; Jie Yang, BM; Yong Xin, PhD

ABSTRACT

Objective • This study aimed to analyze the prognosis of patients with non-small cell lung cancer (NSCLC) after receiving immunotherapy and construct a prediction model to evaluate the overall survival rate of patients.

Methods • This study was a retrospective study that collected data from 493 NSCLC patients who received immunotherapy for the first time. Survival data were analyzed using Cox regression models and the Kaplan-Meier method. The average age of patients was 56 years, and the data collection process included regular outpatient follow-up and observation of overall survival (OS) in the last 36 months.

Results • Multivariate analysis identified significant risk factors such as smoking history, age, T stage, and M stage on survival and disease progression. The model's performance indicators (C-index and AUC) and calibration curve verified the model's accuracy and predictive ability. In the training set, the AUCs of 3-year and 5-year survival were 0.761 and 0.763, respectively, and in the validation set, they were 0.739 and 0.761.

Conclusion • This study developed a prediction model for evaluating the survival of NSCLC patients after immunotherapy that integrates multiple influencing factors. This predictive model can be used as a tool to assess individual risks in NSCLC patients after immunotherapy, helping clinicians to develop more precise treatment and follow-up plans, potentially improving patient outcomes. (*Altern Ther Health Med.* 2024;30(10):483-489).

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INTRODUCTION

Lung cancer, also known as primary bronchopulmonary cancer, arises from the bronchial mucosa or alveolar cells and is the most prevalent and deadly malignant tumor.[1] According to global cancer statistics in 2020, lung cancer accounts for 18% of all cancer deaths worldwide and is the cancer with the highest fatality rate. In China, lung cancer has the highest incidence and mortality rates among men, and is also the cancer with the highest mortality rate among women. Lung cancer is mainly divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), of which NSCLC accounts for about 80%-85%, mainly including adenocarcinoma and squamous cell carcinoma, followed by adenosquamous carcinoma and large cell neuroendocrine carcinoma. It is worth noting that squamous cell carcinoma is more likely to be associated with lymph node metastasis and local invasion, while the primary tumor of adenocarcinoma grows slowly but may metastasize to early supraclavicular lymph nodes and distant organs. [2-5] Notably, squamous carcinoma is more associated with lymph node metastasis and local invasion. At the same time, adenocarcinoma tends to have a slower-growing primary tumor but may present with early supraclavicular lymph node and distant organ metastases.

According to GLOBOCAN estimates, a total of approximately 18.1 million new cancer cases were reported globally in 2018, of which approximately 2.09 million were lung cancer cases, accounting for 11.6% of all cancer cases. Lung cancer also caused approximately 1.76 million deaths, accounting for 18.4% of all cancer-related deaths, with both figures showing slow growth. Due to the lack of obvious clinical symptoms of early-stage lung cancer, less than 25% of patients are diagnosed early every year, and two-thirds of patients are already in an advanced incurable stage at the time of diagnosis. Despite advances in science, technology and medical care, including precision treatments such as targeted therapy and immunotherapy, the 5-year overall

survival rate of lung cancer patients is still less than 15%. Therefore, exploring prognostic factors in NSCLC patients, assessing the tumor microenvironment, predicting individual survival time, and selecting appropriate diagnostic and treatment strategies are crucial to improving patients' quality of life and prolonging survival.[6]

With the enhancement of public health screening awareness and the advancement of high-resolution CT imaging technology, more and more glass nodules in early stage lung cancer are being detected. Treatment of early-stage lung cancer usually involves thoracoscopic surgery, which generally results in long-term survival. However, most patients, especially in stages IIIB and IV, are not candidates for surgical intervention at the time of diagnosis. In contemporary lung cancer management, in addition to traditional surgery, chemotherapy, targeted therapy and radiotherapy, immunotherapy has become an effective treatment modality for advanced patients. The introduction of tyrosine kinase inhibitors and immunotherapy drugs has significantly changed the treatment landscape of lung adenocarcinoma and greatly improved patient prognosis. Nonetheless, predicting treatment outcomes remains a significant challengeThe American Cancer Society's 2017 data report indicates that NSCLC constitutes about 80%-85% of lung cancer cases, while SCLC accounts for 15%-20%.[7,8] National Cancer Institute statistics reveal that from 2007 to 2013, the 5-year overall survival rate for lung cancer was only 18%. Specifically, the 5-year survival rate for NSCLC without metastasis was around 55.6%, with regional lymph node metastasis at about 28.9%, and for cases with distant metastasis, it dropped to just 4.5%.[9]

Due to the absence of distinct clinical symptoms in early-stage lung cancer, less than 25% of patients are diagnosed early each year, with two-thirds presenting at an advanced, incurable stage at diagnosis. Despite advancements in science, technology, and medical care, including precision treatments like targeted therapy and immunotherapy, the 5-year overall survival rate for lung cancer patients remains below 15%. Consequently, exploring prognostic factors in NSCLC patients, evaluating tumor microenvironments, predicting individual survival durations, and selecting appropriate diagnostic and treatment strategies are crucial for improving patient quality of life and extending survival.

With increasing public awareness of health screenings and advancements in high-resolution CT imaging, the detection of early ground-glass nodules, indicative of early-stage lung cancer, has become more frequent. Treatment for early-stage lung cancer typically involves thoracoscopic surgery, which generally results in long-term survival.[10] However, a significant proportion of patients, particularly those in advanced stages IIIB and IV, are ineligible for surgical intervention at diagnosis.[11] In contemporary lung cancer management, alongside traditional surgical, chemotherapy, targeted therapy, and radiotherapy options, immunotherapy has emerged as an effective treatment for advanced-stage patients. The introduction of tyrosine kinase inhibitors and immunological agents has significantly altered the therapeutic landscape for lung adenocarcinoma, substantially improving patient prognosis. Nonetheless, predicting treatment outcomes remains a significant challenge.[12]

The treatment landscape for advanced lung adenocarcinoma has undergone a dramatic shift with the introduction of tyrosine kinase inhibitors in 2007 and immune checkpoint inhibitors (ICIs) in 2015.[12] Particularly in 2015, the focus of lung adenocarcinoma treatment transitioned from targeted therapies to immunotherapy.[13] Furthermore, our understanding of lung adenocarcinoma has expanded, recognizing numerous prognostic factors beyond TNM staging, including age, gender, ethnicity, and even psychosocial elements like marital status. Despite these advancements, current prognostic tools, including the still-utilized TNM staging, have not kept pace with the evolving understanding of tumor biology, diminishing their prognostic relevance.[13,14] Recently, columnar mapping has gained prominence for predicting various tumor-related events. By integrating molecular and clinical tumor features, columnar plots offer individualized event probabilities, reflecting both our advanced tumor knowledge and the ethos of personalized medicine. These plots, with their accessible interface, allow both clinicians and patients to quickly and accurately assess risks, making them increasingly favored over traditional TNM staging for clinical decision-making.

Recently, histogram plotting has become an important means of predicting various tumor-related events. By integrating molecular and clinical tumor characteristics, histograms provide the possibility for individualized event probabilities, reflecting our deeper understanding of oncology and the spirit of personalized medicine. These charts have an easy-to-access interface that allows clinicians and patients to quickly and accurately assess risk, making them increasingly preferred over traditional TNM staging for clinical decision-making. Furthermore, the study evaluates the application value of this model, which is designed to assist clinicians in assessing patient conditions and making informed treatment decisions. Therefore, this study performed a statistical analysis of non-small cell lung cancer (NSCLC) cases admitted to our hospital based on the basic clinical characteristics of the patients. The purpose of this study was to identify independent prognostic factors and establish a survival prediction model for NSCLC patients after immunotherapy. Furthermore, this study evaluates the applied value of this model, which is designed to assist clinicians in assessing patient status and making informed treatment decisions. This study aims to provide valuable reference for the clinical practice of NSCLC.

OBJECTS AND METHODS

Case selection

We conducted a retrospective analysis of the electronic medical records of NSCLC patients who underwent surgical treatment in our hospital from January 1, 2015 to December 31, 2019, and conducted a 3-year postoperative follow-up. Inclusion criteria included: (1) histologically or cytologically confirmed NSCLC; (2) first-time immunotherapy; (3)

complete electronic medical records, including regular follow-up and documented results. Exclusion criteria included: (1) non-NSCLC or unclear diagnosis; (2) insufficient information or no pathological results; (3) lack of follow-up data from the initial study and cases lost to follow-up.

Follow-up

The primary objective is to assess the status of NSCLC patients three years after receiving immunotherapy. Follow-up duration and outcomes were divided into overall survival (OS) and progression-free survival (PFS). Patient follow-up was conducted by telephone, hospital follow-up visits and email, initially every two months and then every three to six months. The endpoint of OS was defined as the occurrence of death, while PFS included recurrence, metastasis, or lung cancer-related death.

Quality control

Prior to retrospective data collection, expert consultation and staff training were conducted to ensure accuracy. Data entry was verified on closing day. For the collection of tracking information, we clearly define endpoints and collection dates. In addition, for patients who develop endpoints such as recurrence and metastasis, we clarify the methods and locations of confirmation to ensure comprehensive and accurate data collection.

Statistical analysis

We used the Kaplan-Meier method to analyze and plot survival curves. Considering the unique biological characteristics of tumors, TNM stage and pathological grade were treated as unordered categorical variables. Continuous variables such as age and tumor size were also grouped and converted into unordered categorical variables. We used the variance inflation factor (VIF) to assess multicollinearity. Univariate Cox hazard analysis was performed on all variables to identify statistically significant differences ($P < .05$, independent prognostic factors were clinically confirmed at $P < .1$). Multivariable Cox hazard analysis was then performed to identify independent prognostic factors.

RESULTS

Clinical and pathological characteristics of patients

In the primary cohort of our study, all 493 NSCLC patients who received immunotherapy during the study period met the inclusion criteria and were thus included. For validation, we selected a consecutive sample of 82 patients, representing 30% of the total, for analytical comparison. Table 1 presents the clinical and pathological characteristics of patients in both the modeling and validation groups. In the main cohort of this study, all 493 patients with NSCLC who received immunotherapy met the inclusion criteria. For verification, we continuously selected 82 patients, accounting for 30% of the total, for analysis and comparison. Table 1 shows the clinical and pathological characteristics of patients in the modeling group and validation group.

Table 1. Basic Clinical Characteristics of Patients

Group	Modeling Group			Validation group		
	Number of people		Proportion	Number of people		Proportion
Sex						
Male	248		31.1	42		28.9
Female	245		38.9	103		71.1
Year, age						
Median		56			55	
Range		25-77			28-75	
Somking						
Yes	369		16.3	106		73.1
No	124		83.7	39		26.9
Marital history						
Exist	332		67.3	96		66.2
Null	161		32.6	49		33.7
T stage						
T1a	32		6.4	10		6.8
T1b	141		28.6	41		28.2
T1c	72		14.6	22		15.1
T2a	83		16.8	23		15.8
T2b	64		12.9	18		12.4
T3	33		6.5	7		4.7
T4	68		13.7	24		16.5
N stage						
N0	379		76.8	117		80.6
N1	58		11.7	14		9.6
N2	56		11.3	14		9.6
Presence of distant metastases						
M0	387		78.4	105		73.2
M1	106		21.5	39		26.8
PD-L1						
Exist	412		83.23	8		9.7
Null	81		16.36	74		90.3
Immunotherapy						
Exist	313		85.3	117		78.6
Null	54		14.7	28		21.4
Lymphatic node transfer						
Exist	276		55.9	77		21.9
Null	217		44.1	68		78.1

Table 2. Multifactor Cox analysis of two groups

Group	Modeling Group			Validation group		
	HR	*P* value	95%CI	HR	*P* value	95%CI
Age≥50	1.3845	0.01	0.7415~2.585	3.9592	0.02	1.2297~12.747
Sex (male)	1.5634	0.06	1.1455~2.134	1.1301	0.07	0.6463~1.976
Marital status (no)	0.5947	0.20	0.2677~1.321	0.4697	0.30	0.1124~1.962
Stage_TT1b	2.989	0.04	1.0567~8.454	1.6428	0.04	0.3555~7.592
Stage_TT2b	2.3679	0.12	0.8035~6.979	1.3693	0.71	0.2758~6.799
Stage_TT1c	6.8515	0.00	2.426~19.35	3.3444	0.01	0.7137~15.67
Stage_TT2b	6.9411	0.00	2.4187~19.919	3.7519	0.02	0.7419~18.973
Stage_TT3	8.4546	0.02	1.5036~47.54	4.5647	0.04	0.6047~34.46
Stage_TT4	7.5226	0.00	2.5018~22.62	2.3035	0.01	0.32~16.58
Stage_NN1	0.7686	0.21	0.5102~1.158	0.9872	0.97	0.449~2.17
Stage_NN2	0.9939	0.98	0.6445~1.533	1.1195	0.80	0.4646~2.698
Stage_MM1	2.2189	0.00	1.6375~3.007	1.6455	0.01	0.933~2.902
Smoking	1.9552	0.08	0.9291~4.114	2.0796	0.29	0.5291~8.175
Lymphaticmetastasis	0.8157	0.58	0.3968~1.677	0.4572	0.24	0.1214~1.721

Independent prognostic factors in the modelling group and validation group

In constructing the multifactorial Cox model, all 493 patients in the modeling group were included, while the validation group comprised 30% of the total and was selected consecutively. Multifactorial Cox analysis was performed in the modeling group. Utilizing existing indicators and outcomes from univariate analysis, predictive models for survival status and disease progression following immunotherapy have been developed. Within these models, several risk factors for survival and disease progression in patients have been identified. These include a history of smoking, age of 50 years or older, advanced T stage, and advanced M stage. (refer to Table 2). When constructing the multifactor Cox model, all 493 patients in the modeling group were included, while the validation group accounted for 30% of the total and were selected consecutively. Multifactor Cox analysis was performed in the modeling

Figure 1. Survival nomogram of non-small cell lung cancer

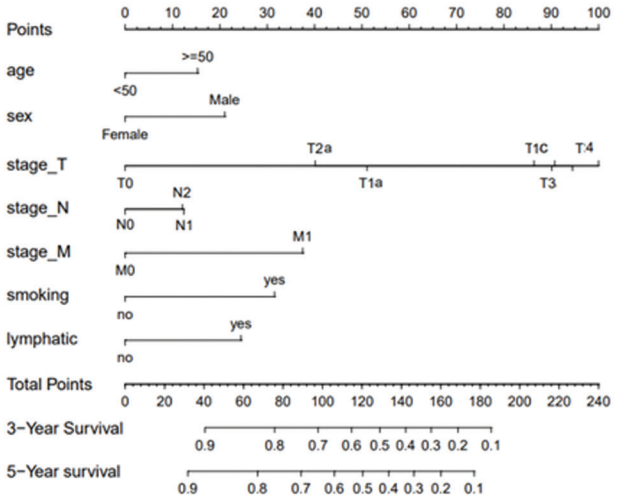
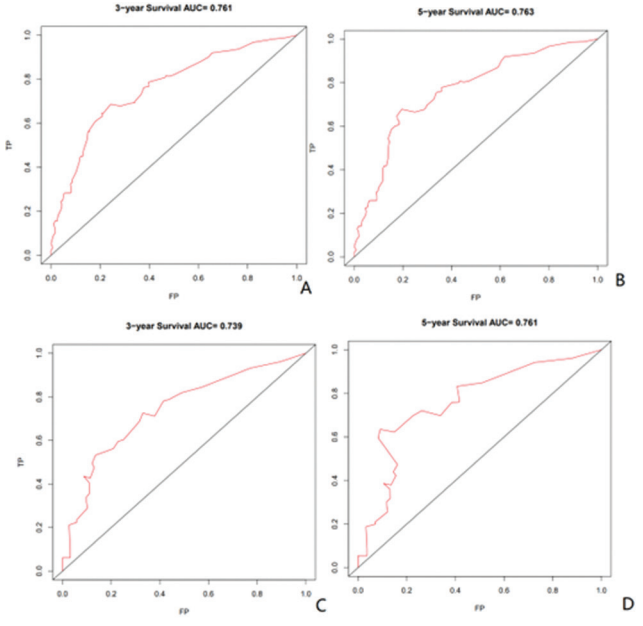


Figure 2. Receiver operating characteristic of 3-year and 5-year survival of patients with Nomogram model in modeling group and validation group.



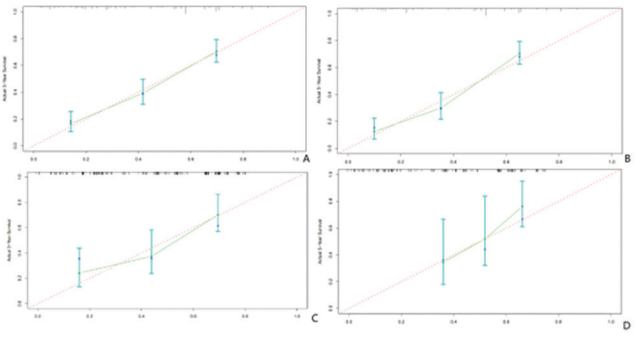
Abbreviations: TP, sensitivity; FP, 1-specificity

group. Predictive models for survival status and disease progression after immunotherapy were developed using existing indicators and results from univariate analyses. In these models, several risk factors affecting patient survival and disease progression were identified, including smoking history, age over 50 years, high T stage, and high M stage.

Visualization and validation of column charts

Using regression coefficients from the COX regression model, we constructed a probability line chart to predict the 3-year and 5-year outcomes for early-stage NSCLC patients after immunotherapy. This chart includes six variables: age at diagnosis, gender, smoking history, T stage, N stage, and M stage. For prognostic predictions, scores corresponding to these variables are summed to derive the total score. As demonstrated in Figure 1, the prognosis for an early-stage NSCLC patient is calculated by first determining the values for each variable. These values are scored on the integration line at the top of the chart, and the total score is obtained by adding the scores of all variables. This total score is then used to determine the probabilities of 3-year and 5-year survival, as indicated on the prediction line. For example, if an NSCLC patient receiving immunotherapy is male (22 points)+70 years old (16 points)+T2 (40 points)+N1 (12 points)+M0 (2 points)+smoking history (32 points)+lymph node metastasis (28 points)=192 points, the 3-year survival rate of the patient is 36%, and the 5-year recurrence-free survival rate is 28%.

Figure 3. Consistency test curves for 3-year and 5-year survival rates of patients in the modeling and validation groups



Using the regression coefficients of the COX regression model, we constructed a probability line plot to predict the 3- and 5-year outcomes of patients with early-stage NSCLC after immunotherapy. The graph includes six variables: age at diagnosis, gender, smoking history, T stage, N stage, and M stage. For prognostic prediction, the scores corresponding to these variables are summed to give a total score. As shown in Figure 1, the prognosis of early-stage NSCLC patients was calculated by first determining the value of each variable. These values are scored on a score line at the top of the chart, and a total score is then calculated by adding the scores for all variables. This total score is then used to determine the probability of 3- and 5-year survival, as shown on the prediction lines.

Cox model performance evaluation

The column chart's validation focused on assessing the model's accuracy and calibration, involving internal validation in the training set and external validation in the validation set. The C-index for the column chart was 0.7207 in the modeling group and 0.7059 in the validation group, indicating good accuracy. Furthermore, the model showed better authenticity in both groups, with 3-year and 5-year AUCs of 0.761 and 0.763, respectively, in the modeling group (Figures 2A, B), and 0.739 and 0.761 in the validation group (Figures 2C, D). Calibration curves for consistency testing in both the modeling (Figure 3A, B) and validation groups (Figure 3C) demonstrated a high concordance between predicted risks and actual prognoses for NSCLC patients.

Figure 4. Kaplan Meier curve for evaluating survival in non-small cell lung cancer patients at high and low risk

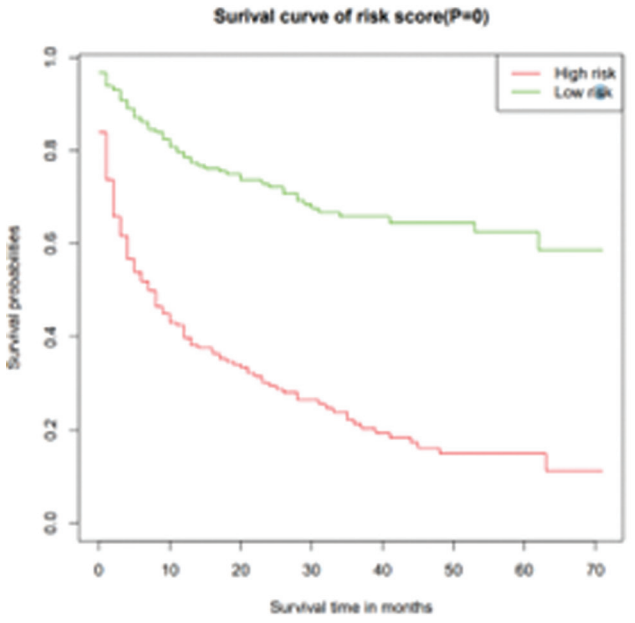
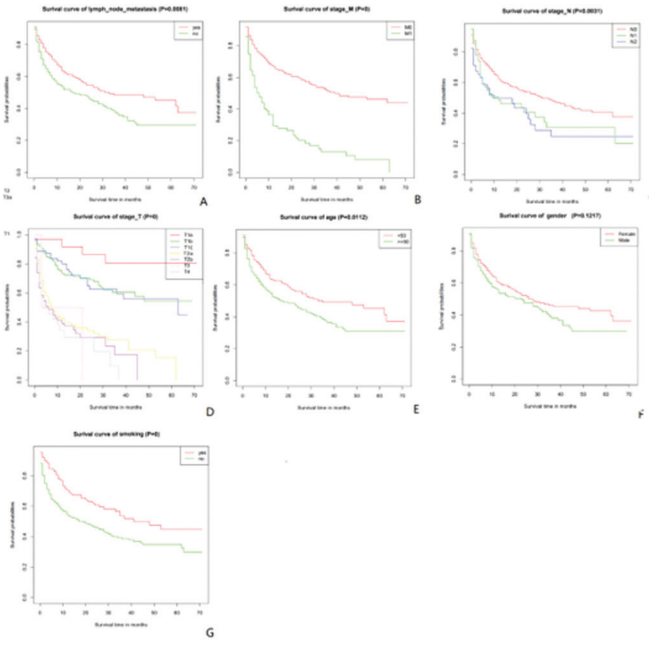


Figure 5. Kaplan Meier curves for different factors



Survival analysis

The average survival time of all included patients in this study was 71.261 months. The Kaplan Meier curve for the survival rate of high-risk and low-risk non-small cell lung cancer patients is shown in Figure 4. At high risk, the average survival time of non-small cell lung cancer patients is 71.217 months, with a survival rate of 12.14%. At low risk, the average survival time of non-small cell lung cancer patients was 71.305 months, with a survival rate of 59.67% ($P < .001$).

The KM survival curve based on different independent prognostic factors for all included cases is shown in Figure 5. The lower the degree of lymph node metastasis, the better the prognosis ($P < .001$, Figure 5A). The lower the T stage ($P < .001$, Figure 7B), N stage ($P = .0031$, Figure 5C), or M stage ($P < .001$, Figure 5D), the better the prognosis of the patient. The difference in age can also lead to different prognoses, with better prognosis for those under 50 years old ($P = .0112$, Figure 5E). In this study, we found that gender differences did not lead to different prognoses ($P = .1217$, Figure 5F). The survival rate of non-small cell lung cancer patients varies depending on whether they have a history of smoking ($P < .001$, Figure 5G).

DISCUSSION

Lung cancer is clinically divided into two major types: small-cell lung cancer and non-small cell lung cancer. Most non-small cell lung cancer in its early stage can be cured by radical surgery, with less recurrence. A multidisciplinary approach treats non-small cell lung cancer (NSCLC). The deterioration of non-small cell lung cancer is relatively slow, and the spread and metastasis are relatively late. If non-small cell lung cancer is in the early stage, it can be treated by surgery, chemotherapy, and radiotherapy, and the effect is better, and the patient can live longer. Small cell lung cancer (SCLC) accounts for about 20%. It is a neuroendocrine carcinoma, often accompanied by endocrine abnormalities or carcinoid syndrome, mostly located in the central part of the lung, with rapid growth and early metastasis. Most patients are very sensitive to initial chemotherapy or radiotherapy, but most patients quickly develop drug resistance. Small cell lung cancer was divided into bureau deadlines and widely, bureau within a small cell lung cancer emphasizes beginning as early as possible after chemotherapy combined with radiotherapy; Some patients with extensive stage can be treated with thoracic radiotherapy after chemotherapy. Compared with non-small cell lung cancer, small cell lung cancer has a higher degree of malignancy, rapid deterioration, and early metastasis.[15] This study focuses on the survival prediction of NSCLC patients treated with immunotherapy.

Lung cancer is divided into two major categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Most early-stage NSCLC can be treated with radical surgery, and the chance of recurrence is low. In contrast, SCLC is a neuroendocrine cancer that is often accompanied by endocrine abnormalities or carcinoid syndrome. It is mainly located in the central part of the lung, grows rapidly, and metastasizes early. Most SCLC patients are very sensitive to initial chemotherapy or radiotherapy, but most patients quickly develop resistance. Compared with NSCLC, SCLC is more malignant, deteriorates faster, and metastasizes early.

So far, the prognostic factors of NSCLC have not been fully determined, and further consensus is needed on the significance of certain factors on prognosis. We extracted data from NSCLC patients in our hospital from 2018 to 2019, analyzed independent factors affecting OS, and constructed a

column chart model based on statistical analysis results. In the COX model, age of diagnosis, T stage, N stage, and other factors are important influencing factors for survival status and disease progression, and lymph node metastasis is also a prognostic factor for NSCLC patients. Age growth is a recognized prognostic risk factor. This study divided patients into two groups based on the age of 50, with patients aged≥50 having poorer prognosis, consistent with Ricciuti et al.[12]. The reason for this is that elderly patients have poor physical fitness, often accompanied by multiple underlying diseases, and have a higher probability of competitive risk events. In addition, it may also be related to the lower tolerance of elderly patients to immunotherapy, leading to poorer treatment benefits. TNM staging is most commonly used to evaluate the prognosis of tumor patients, and the survival rate column chart constructed in this study also indicates that T staging and N staging have a significant proportion in prediction. Donnem et al.'s retrospective analysis showed that T staging divides tumor diameter into subgroups of 1, 2, 3, 4, and 5cm, and this fine staging standard can distinguish different prognostic outcomes.[16] The International Association for the Study of Lung Cancer proposes that compared to stage N0, the overall 5-year survival rate of N2/N3 patients can be reduced by 48.1% to 58.9%.[17]

This study confirmed that factors such as age at diagnosis, TNM stage, and lymph node metastasis are important prognostic factors for NSCLC. Increasing age is considered a prognostic risk factor, and older patients have a worse prognosis, which may be related to elderly patients' poorer physical condition, multiple underlying diseases, and lower tolerance to immunotherapy. TNM staging is the most commonly used in predicting the prognosis of tumor patients. The survival rate histogram constructed in this study also shows that T stage and N stage occupy an important proportion in prediction. Lymph node status and distant metastasis are important factors in evaluating the prognosis of cancer patients. Once lymph node metastasis or distant metastasis occurs, the patient's survival rate will be greatly reduced.

Lymph node status and distant metastasis are important factors in evaluating the prognosis of tumor patients. Once lymph node metastasis or distant metastasis occurs, the survival rate of patients will be greatly reduced. In a recent analytical study, the results showed that lymph node metastasis was independently associated with a decrease in CSS in AS (HR=2.34, 95%CI: 1.29-4.25, P = .01), ESS (HR=2.43, 95%CI: 1.99-2.98, P < .001), and LMS (HR=2.10, 95%CI: 1.75-2.52, P < .001).[18] In a foreign study, the survival rate of lymph node-negative patients (64.2%) was significantly higher than that of lymph node-positive patients (26%) (P < .001).[19] Ran et al.[20] also mentioned a correlation between lymph node involvement and poor prognosis in NSCLC. This study also confirms that lymph node status and distant metastasis affect the survival rate of NSCLC patients.[20] At present, the correlation between the total number of lymph nodes, positive rate of lymph nodes, and number of lymph nodes with the prognosis of malignant tumors has attracted attention. A large number of studies have confirmed its correlation with the prognosis of malignant tumor patients, and further verification of its role in evaluating the prognosis of NSCLC is needed in the future.

In this study, a Cox model was constructed to evaluate the survival and disease progression of NSCLC patients after immunotherapy. The Cox model constructed in this study demonstrated high prediction accuracy with C-index >0.71. To visualize the prediction results, we created a bar graph for overall survival (OS), and the 3- and 5-year calibration curves showed strong prediction performance. However, this study still has some limitations, including that information collection was mainly postoperative indicators, the study site was a single site, and the retrospective analysis was carried out despite the establishment of inclusion and exclusion criteria to avoid other potential factors that affect the efficacy of immunotherapy as much as possible. Subject selection bias cannot be completely avoided, and it is unclear whether nomograms produced from data obtained by a single institution in China are applicable to patients from Western backgrounds. Future work will involve collecting preoperative patient data, establishing a multicenter clinical cohort to enhance population representation, and performing external validation to improve the robustness of the model. Both models demonstrated high predictive accuracy, with a C-index >0.71. To present the predictions in a straightforward manner, a column-line graph for overall survival (OS) was created, and the 3- and 5-year calibration curves indicated strong predictive performance. However, this study still has some limitations: (1) The information collected is mainly postoperative indicators; (2) The study site was a single site; (3) Although the inclusion and exclusion criteria were established to avoid other potential factors affecting the efficacy of immunotherapy as much as possible, retrospective analysis still cannot completely avoid the selection bias of research subjects; (4) The nomogram was based on data obtained from a single institution in China, and whether the findings generalize to patients with Western backgrounds is unclear. Future work will involve gathering preoperative patient data and establishing a multi-center clinical cohort to enhance population representativeness. Additionally, external validation will be conducted to improve the model's robustness.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

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This study did not receive any funding in any form.

AUTHOR CONTRIBUTIONS

RD and YX designed the study, HL and JY collected the data, RD and HL performed the analysis and wrote the manuscript, RD and HL are co-first authors and contribute equally to this work. All authors read and approved the final manuscript.

ETHICAL COMPLIANCE

The ethics committee of Affiliated Hospital of Xuzhou Medical University approved this study.

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