A nomogram model of postoperative prognosis for metastatic lung adenocarcinoma
A study based on the SEER database

Xiaowei Tie, MD[a] , Lianlian Chen, MD[a], Xiaomin Li, MD[a], Wenjuan Zha, MD[a], Yangchen Liu, MD[a],*

Abstract

We have observed that patients with metastatic lung adenocarcinoma can obtain survival benefits from surgical resection of the primary tumor. A model was developed to evaluate the prognosis of patients. The patients with metastatic lung adenocarcinoma were identified in the Surveillance, Epidemiology, and End Results database and divided into surgery group and non-surgical group. Through Kaplan–Meier analysis, the survival rate of the non-surgical group was found to be significantly lower no matter before or after propensity score matching. One thousand one hundred and seventy surgical patients were divided into a training group and a verification group. In the training group, univariate and multivariate Cox models were used to explore the prognostic factors, and logistic regression was used to establish a nomogram based on significant predictors. In total, 12,228 patients with metastatic lung adenocarcinoma were recognized; primary tumor surgery accounted for 9.5%. After propensity score matching, the median survival time of 2 groups was significantly different. For the training group, univariate and multivariate COX analysis was conducted, and a nomogram was constructed. Acceptable agreement has been achieved between the predicted and observed survival rates, and the nomogram can divide patients with metastatic lung adenocarcinoma into different risk groups and predict their prognostic survival rate.

Abbreviations: AJCC = American Joint Committee on Cancer, AUC = the area under the curve, LUAD = lung adenocarcinoma, OS = overall survival, PSM = Propensity score matching, SEER = Surveillance, Epidemiology, and End Results database

Keywords: metastatic lung adenocarcinoma, nomogram, SEER, surgery

1. Introduction

The development of cancer is usually driven by the accumulation of changes in genome structure and function caused by exposure to various carcinogens.[1] In the process of gene replication, errors occur, which are influenced by chemical, physical and biological factors, resulting in gene sequence changes.[2,3] This series of changes evolved through natural selection, mutated and heritable, and eventually led to cancer.

Lung cancer is a most commonly found malignant tumor and it's the main cause of deaths related to cancer for men and women worldwide.[4] Lung adenocarcinoma (LUAD) is a common pathological subtype of lung cancer, accounting for nearly 40% of lung cancer cases.[5] Its 5-year relative survival rate is only 5%, about 57% patients suffer from advanced stage and metastatic diseases.[6,7] Metastatic LUAD is a heterogeneous disease. The survival of patients with that disease is closely related to physical conditions, including age, gender, behavioral status and TN stage, pathological or genotypic characteristics, metastatic organ types, metastatic site number, treatment situation, etc. For those patients, chemotherapy, targeted therapy and immunotherapy are the preferred treatments.[2,8–10]

The resection of the primary tumor is usually not considered in the conventional treatment of patients with metastatic LUAD.[11] The focus of treatment for such patients is to control disease progression and improve patient survival and prognosis, rather than giving radical surgical treatment. The eighth version of the TNM staging system came into effect in the United States in 2018, distinguishing between single and multiple extrathoracic metastase, suggesting that in addition to systemic treatment, patients with oligometastasis can also receive more active local treatments and may survive for a long time. At present, studies have shown that for those patients who are with non-small cell lung cancer, surgical intervention on no matter the primary or metastatic tumor site can both improve the survival rate to certain degrees,[11,12] but few people have conducted individual studies on metastatic LUAD. Therefore, we are the first to study whether surgery can benefit patients with metastatic LUAD.

A nomogram is a chart that simplifies a statistical prediction model containing a large number of complex factors into a simple numerical model to predict the probability of an event. Therefore, it is very popular to use a nomogram in the prognosis of cancer. Studies have shown that such easy-to-use survival prediction tool can help to provide better medical care for those patients who are with liver cancer, gastric cancer, and small cell lung cancer.[13–15] As far as we know, there is no similar nomogram yet for the postoperative prognosis prediction of patients with metastatic LUAD.

This study aims to gather relevant data of patients with metastatic LUAD from the Surveillance, Epidemiology, and End Results (SEER) database, to determine the prognostic factors affecting patients with metastatic LUAD through statistical analysis, and establish and verify a new nomogram model of postoperative prognosis for metastatic LUAD metastasis. A reliable and efficient nomogram model will help identify patients of high risk and develop proper treatment plans for patients with metastatic LUAD.

2. Methods

2.1. Patient

We carried out a population-based retrospective study with data collected from the SEER national database. The inclusion and exclusion criteria adopted in the study is as follows. Inclusion criteria: Patients that have been diagnosed with metastatic LUAD from 2010 to 2015 (histologically confirmed). LUAD being the first primary malignant tumor. Exclusion criteria: Unable to obtain information such as age, gender, race, primary site, tumor grade, surgery, radiotherapy, chemotherapy, metastatic information, survival time and current survival status. In total, 12,228 patients with metastatic LUAD who did or didn't undergo thoracic local surgery were identified, of which 1170 patients received surgery and 11,058 patients did not. General flowchart of this study is shown in the Figure 1.

2.2. Research variables and end points

The research variables are mainly divided into clinical pathology and follow-up variables, including gender, age, race, tumor grade, TN stages determined referring to American Joint Committee on Cancer (AJCC), primary site, bone metastasis, liver metastasis, brain metastasis, lung metastasis, primary cancer surgery, chemotherapy, radiotherapy, survival status and survival time, etc. The definition of overall survival (OS) is the time between diagnosis and death.

2.3. Statistical analysis

The 1170 selected patients were randomly divided at a ratio of 7:3 through a digital method into 2 sets, 1 being a training set and the other being a validation set. A descriptive analysis was performed to include the clinicopathological and demographic characteristics of the patients from the 2 sets. Meanwhile, Kaplan–Meier analysis was adopted to calculate the median survival time of each subgroup, training data was adopted to build a nomogram, and clinicopathological variables were statistically analyzed, including age, gender, race, primary tumor location, tumor grade, lateral position, T description, N description, treatment strategy, in order to select the prognostic factors of metastatic LUAD. The predictive factors and the weights of them were estimated by Multivariate Cox regression analysis, and univariate with statistical significance (P < .05) was covered in the multivariate analysis. According to the results obtained from the Cox proportional hazards model, the "rms" and "survival" packages of R software package 3.3.3 were used to incorporate the variables with statistical significance (P < .05) in the nomogram.

The methods used to evaluate this nomogram model on its predictive performance are as follows. To begin with, based on the constructed Cox regression model, the risk score was obtained for every patient from the training set. Secondly, the area under the curve (AUC) of ROC, calibration chart and decision curve were obtained through regression analysis, and the discriminating ability and accuracy of the nomogram were
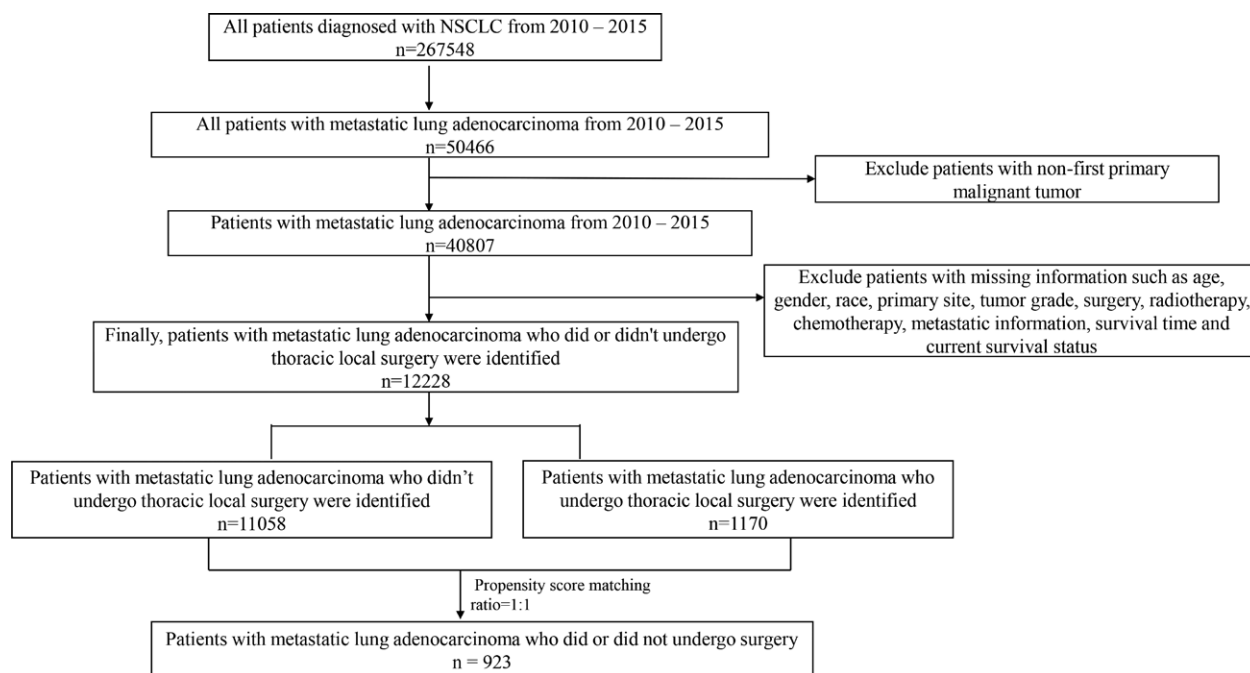

Figure 1. General flowchart of this study.

evaluated respectively. Finally, the patients from training set were classified as 3 groups through the 3-quantile stratification of their risk scores, and the Kaplan–Meier survival curve was drawn based on their risk score levels.

Log-rank test, along with Kaplan–Meier method, was used to compare the survival time. Univariate and multivariate Cox regression analysis were applied to determine independent prognostic variables related to OS. In order to eliminate the significant differences in baseline covariates and inherent selection bias, propensity score matching (PSM) analysis was conducted on the patients who underwent surgery and those who did not. PSM is a tool to reduce the selection bias in non-randomized studies to achieve balanced variables between treatment groups. By that method, we set a 1:1 ratio to reduce bias. Student's t test was adopted for the comparison of continuous variables, and Chi-square test and Fisher's exact test were adopted for the comparison of categorical variables. In all analyses, statistical significance was considered valid when a P value is <.05. R version 3.6.1, IBM SPSS Statistics software version 25 was adopted to perform all statistical analyses.

3. Results

3.1. Patient characteristics before and after PSM

From 2010 to 2015, 267,548 lung cancer patients in total were identified in the SEER database, and 12,228 patients with metastatic LUAD met the criteria. Among the eligible patients, 1170 (9.5%) received surgical treatment of the primary tumor site (Fig. 1). Just as Table 1 showed the statistical comparison between the surgical group and the non-surgical group (χ^2 test). The first 2 groups of patients before PSM had significant differences in gender, age, race, TN stages, tumor size, lesion laterality, degree of differentiation, radiotherapy, liver metastasis, brain metastasis, lung metastasis, and bone metastasis, among whom, surgical intervention is related to patients with older age, larger tumors, and higher N stage. That indicated that the baseline characteristics of the 2 groups (the surgical group and the non-surgical group) were imbalanced, and the PSM analysis was carried out to reduce the effect of confounding covariates from the clinical characteristics of patients. Variables affecting treatment outcome were considered in the 1:1 PSM, including gender, age, race, TN stages, tumor size, laterality, degree of differentiation, radiotherapy, lung metastasis, liver metastasis, bone metastasis, and brain metastasis. After the 1:1 PSM, 923 patients with metastatic LUAD who did or did not undergo surgery at the primary site were included in the statistical comparison (χ^2 test). Baseline characteristics, including gender, race, T stages, N stages, tumor size, laterality, degree of differentiation, radiotherapy, lung metastasis, liver metastasis, bone metastasis, and brain metastasis were all balanced (P > .05), with details as shown in Table 2.

3.2. Primary tumor resection's effect on the survival outcome of patients with metastatic LUAD

Before PSM, for the surgical group and the non-surgical group, Kaplan–Meier analysis showed that patients who underwent primary tumor resection had a longer OS: the median survival time of patients who had primary tumor resection was 20 months, while that of the patients who did not undergo surgery was only 6 months, P < .001 (Fig. 2A). After PSM, similar results were obtained (20 months vs. 10 months, P < .001) as showed in Figure 2B. To further study the function of surgery in patients with advanced LUAD, the patients with metastatic LUAD were further divided into surgery, radiotherapy and chemotherapy combination group, surgery and chemotherapy combination group, surgery and radiotherapy combination group, surgery group, radiotherapy and chemotherapy group,

Table 1

Baseline characteristics before PSM, showing the statistical comparison between the surgical group and the non-surgical group (χ^2 test).

Variables	All patients (N = 12,228)	Surgery to primary site (N = 1170)	Non-surgery to primary site (N = 11,058)	P value
Age(years)				.000
<66	5075	639	5066	
65 to 73	3078	301	2777	
>73	3445	230	3215	
Race				.012
Black	1621	123	1498	
White	9283	923	8360	
Other	1324	124	1200	
Sex				.000
Female	6064	639	5425	
Male	6164	531	5633	
Tumor site				.128
Upper	7190	654	6536	
Middle	544	62	482	
Lower	3398	339	3059	
Other	1096	115	981	
Grade				.000
Grade I-II	4989	625	4364	
Grade III-IV	7239	545	6694	
Laterality				.094
Left	4977	503	4474	
Right	7251	667	6584	
T stage				.000
T1/T2	4822	537	4285	
T3/T4	7406	633	6773	
N Stage				.000
N0	4822	537	4285	
N1-3	7406	633	6773	
Tumor size (mm)				.000
<38	4835	772	4063	
38 to 58	3696	240	3456	
>58	3697	158	3539	
Radiation				.000
No	6348	717	5631	
Yes	5880	453	5427	
Chemotherapy				.484
No	4275	441	4284	
Yes	7350	729	6774	
Bone				.000
No	7631	986	6645	
Yes	4597	184	4413	
Brain				.003
No	8340	839	7465	
Yes	3924	331	3593	
Liver				.000
No	10,635	1116	9519	
Yes	1593	54	1539	
Lung				.000
No	8274	852	7422	
Yes	3954	318	3636	

PSM = propensity score matching.

radiotherapy group and chemotherapy group as showed in Figure 3. From the Kaplan–Meier analysis it can be found that the median survival times of patients in surgery and chemoradiation combination group (24 months; 95% CI 0.480–0.529), surgery and chemotherapy combination group(27 months, 95% CI 0.456–0.561), and surgery group (16 months; 95% CI 0.453–0.565) are better than radiotherapy and chemotherapy combination group (10 months; 95% CI 0.468–0.502), radiotherapy group (2months; 95% CI 0.480–0.529) and chemotherapy group(12 months; 95% CI 0.493–0.529), but the outcome of surgery combined with radiotherapy group was

Table 2

Baseline characteristics after PSM, showing the statistical comparison between the surgical group and the non-surgical group (χ² test).

Variables	All patients (N = 1846)	Surgery to primary site (N = 923)	Non-surgery to primary site (N = 923)	P value
Age(years)				.192
<66	989	481	508	
65 to 73	439	236	203	
>73	418	206	212	
Race				.818
Black	188	98	90	
White	1461	726	735	
Other	197	99	98	
Sex				.327
Female	995	508	487	
Male	851	415	436	
Tumor site				.183
Upper	1086	526	560	
Middle	78	47	31	
Lower	524	268	256	
Other	158	82	76	
Grade				.963
Grade I to II	915	457	458	
Grade III to IV	931	466	465	
Laterality				.925
Left	782	390	392	
Right	1064	533	531	
T stage				.456
T1/T2	866	425	441	
T3/T4	980	498	482	
N Stage				.420
N0	749	383	366	
N1-3	1097	540	557	
Tumor size(mm)				.387
<38	1101	548	553	
38 to 58	455	220	235	
>58	290	155	135	
Radiation				.146
No	1039	535	504	
Yes	807	388	419	
Chemotherapy				.484
No	647	325	322	
Yes	1199	598	601	
Bone				.723
No	1490	742	748	
Yes	356	181	175	
Brain				.099
No	1259	646	613	
Yes	587	277	310	
Liver				.678
No	1748	872	876	
Yes	98	51	47	
Lung				.958
No	1361	681	680	
Yes	485	242	243	

PSM = propensity score matching.

not good(8 months; 95% CI 0.418–0.599). However, we still have reason to believe that for patients with metastatic LUAD, receiving primary mass resection can bring survival benefits as showed in Figure 3.

3.3. Screening of prognostic risk factors for postoperative patients with metastatic LUAD and establishment of nomogram

In the training group, the univariate and multivariate cox analysis results of prognostic factors for metastatic LUAD are shown in the Table 3. In the univariate analyses, statistically significant predictive factors of metastatic LUAD included age at diagnosis ($P < .001$), gender ($P = .003$), lymph node metastasis ($P < .001$), tumor size ($P < .001$), race ($P < .001$), degree of differentiation ($P = .014$), presence or absence of chemotherapy ($P < .001$) and presence or absence of bone metastasis ($P < .001$). The significant factors of the univariate analyses are brought into multivariate cox analysis. Age ($P < .001$), gender ($P = .003$), lymph node metastasis ($P < .001$), tumor size ($P = .001$), race ($P < .05$), degree of differentiation ($P = .028$), presence or absence of chemotherapy ($P < .001$) or presence or absence of bone metastasis ($P < .001$) were related to the survival and prognosis of patients.

A nomogram that integrates the above prognostic factors (Fig. 4) was constructed using the training cohort. The nomogram shows that the N stage contributes the most to the prognosis, followed by the size of the mass and age. According to the matching score for each factor, a prognostic nomogram was obtained. The 1-, 2-, and 3-year AUC values of the nomogram in the training set are 0.709, 0.688, and 0.691, respectively, and the 1-, 2-, and 3-year AUC values in the validation set are 0.726, 0.697, and 0.691, respectively, which is showed in Figures 5B and 6B. The risk scoring system was further compared with a single clinical indicator as shown in (Figs. 5C–E and 6C–E), showed certain advantages. The 1-, 2-, and 3-year OS calibration curves showed that acceptable agreement has been achieved between the predicted and actual survival rates of the 2 groups of patients (Figs. 7A–C and 8A–C). According to the decision curve, for patients with metastatic LUAD who can be operated, using the nomogram to predict the profit probability of operation provides greater net profit than the strategy of "all surgical treatments" or "non-surgical treatments" (Figs. 7D–F and 8D–F).

3.4. Risk stratification

The total scores of each patient in the training set were added up, and the patients were classified as high-, medium- and low-risk with the optimal cutoff values being determined by X-tile software: low risk (less than or equal to 319), intermediate risk (320–361), and high risk (more than 361). Each risk group represents a different prognosis. As shown in Figure 5A, in the training group, the median OS of the 3 risk groups were 37.00 months (95% CI 0.460–0.566), 17.00 months (95% CI 0.446–0.562), and 5.00 months (95% CI 0.424–0.610). Similarly, as shown in the Figure 6A, in the verification group, the median OS of the 3 risk groups were 36.00 months (95% CI 0.429–0.595), 17.00 months (95% CI 0.424–0.600), and 5.00 months (95% CI 0.370–0.630).

4. Discussion

We realized that many models have been constructed for the prognosis prediction of NSCLC patients, including: survival rate after resection, N2 pathological diseases, selection of suitable candidates after surgery,[16–18] however, LUAD being an important type of NSCLC, there are few studies about the postoperative prognosis of patients who are diagnosed with metastatic LUAD.

From what we've learnt, our nomogram is the first postoperative nomogram of metastatic LUAD on the basis of a population-based cohort study that's also large and diverse, with information obtained from the SEER database. The nomogram is able to predict patients' prognosis easily, make individuals aware of the advantages of certain medical treatments, and divide patients into various risk subgroups, making it potentially helpful and informative for clinical decision-making. When it comes to the high-risk population diagnosed by the nomogram designed by us, close attention should be paid to
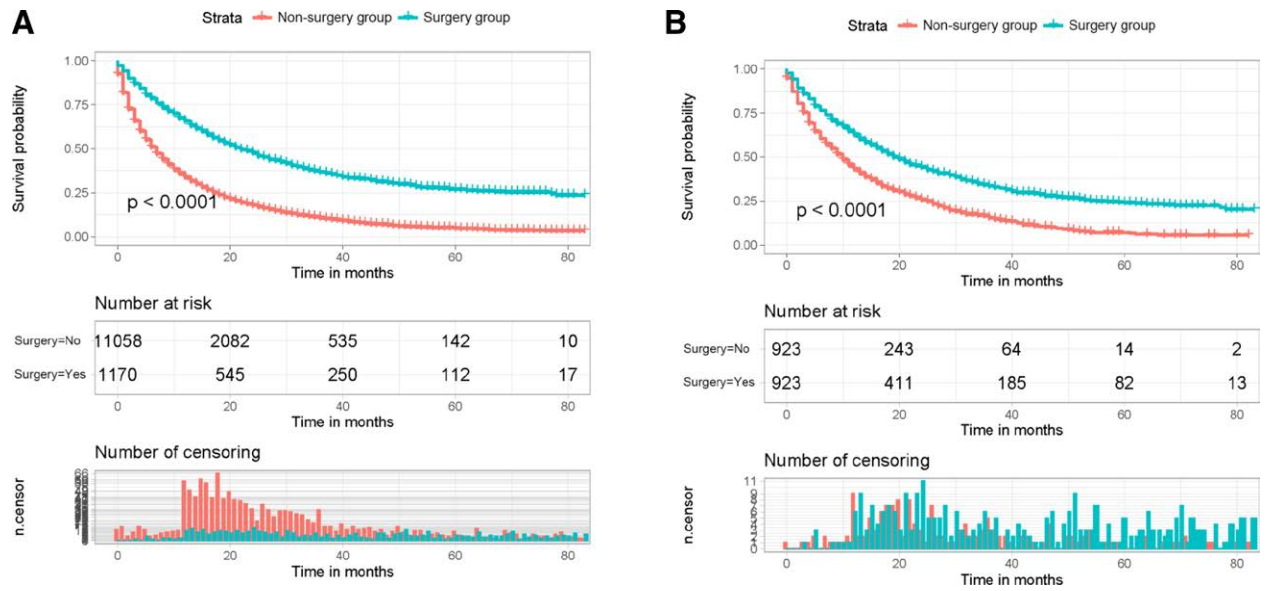
Figure 2. Kaplan–Meier plot of metastatic lung adenocarcinoma patients according to treatment. (A) OS of metastatic LUAD before PSM. (B) OS of metastatic lung adenocarcinoma after PSM. LUAD = lung adenocarcinoma, OS = overall survival, PSM = propensity score matching.
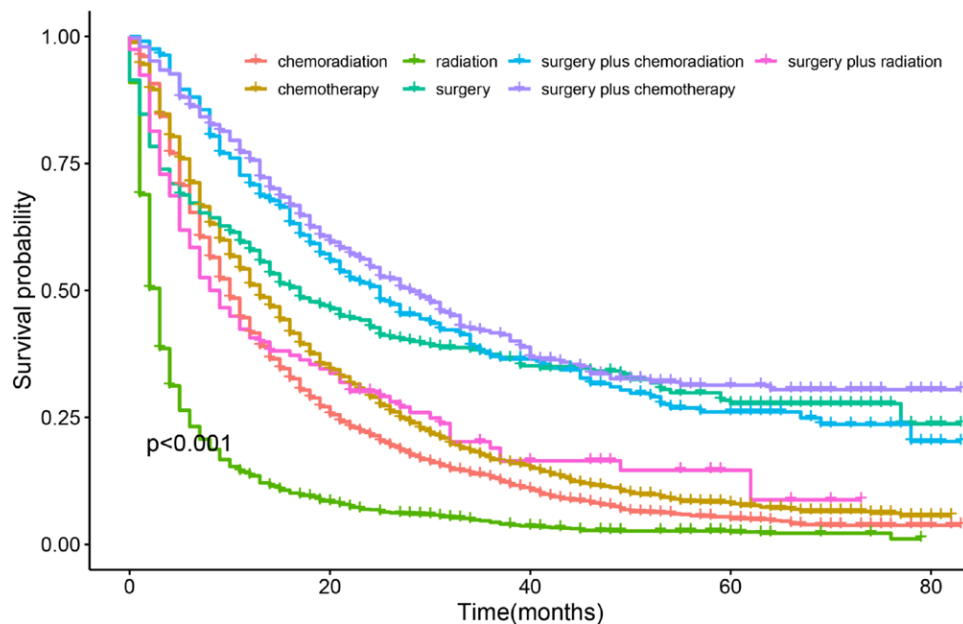

Figure 3. Kaplan–Meier plot of metastatic LUAD patients according to different treatment modalities. LUAD = lung adenocarcinoma.

reduce the follow-up time, and adjustment should be made in time according to the changes in the patient's tumor condition. More palliative care can also be delivered, such as psychological or emotional support, encouraging them to join in clinical trials of anti-cancer drugs. In addition, these tools can be helpful to clinical trial designers in obtaining more equivalent baselines between different study groups. We should also realize that 34.6% of the US population[19] is covered in the SEER database, which ensures that our nomogram is representative and also means that our nomogram has potential universality, acceptable recognition capabilities and good prediction accuracy.

Through analysis, it was first confirmed that patients with partially metastatic LUAD can obtain survival benefits from local mass resection. Second, a visual nomogram was created based on the logistic regression selection model for predicting

the postoperative prognosis of patients who are diagnosed with metastatic LUAD. Finally, both internal and external verifications have proved that our model is useful and stable.

Given the good response of patients to systemic treatments such as targeted therapy and immunotherapy, primary cancer surgery may be seen as part of multimodal therapy. Enough tissue can be gained from surgery to make detailed genetic and molecular typing of lung cancer possible.[20] It can also reduce the burden of tumors on patients, ease or eliminate complications brought by tumors, and better the quality of patient's life. First, the patients who did and did not undergo surgery were collected and matched based on baseline characteristics to eliminate selection bias. Second, the median OS time of the surgical group and the non-surgical group was calculated, and the OS of the surgery group was found to be still longer (20 months vs. 10 months, $P < .001$), which preliminarily confirmed that surgery

Table 3

Univariate and multivariate Cox proportional hazards regression analysis of clinical risk factors in the training group.

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Age(years)				
<66		.000		.000
65 to 73	1.394 (1.137, 1.708)	.001	1.465 (1.190, 1.802)	.000
>73	1.896 (1.526, 2.355)	.000	1.807 (1.44, 2.261)	.000
Race				
Black		.002		.005
White	0.591 (0.395, 0.883)	.010	1.618 (0.413, 0.927)	.020
Other	1.070 (0.815, 1.405)	.626	1.075 (0.816, 1.415)	.608
Sex	1.294 (1.091, 1.536)	.003	1.306 (1.098, 1.553)	.003
Tumor site				
Upper		.069		
Middle	1.048 (0.696, 1.577)	.824		
Lower	1.256 (1.037,1.522)	.020		
Other	1.307 (0.974, 1.753)	.074		
Laterality	1.028 (0.965, 1.221)	.755		
T stage				
T1		.190		
T2	1.086 (0.830, 1.421)	.549		
T3	1.313 (0.999, 1.724)	.051		
T4	1.194 (0.910, 1.567)	.200		
N Stage				
N1		.000		.000
N2	1.210 (0.925, 1.582)	.164	1.346 (1.018, 1.779)	.037
N3	1.341 (1.104, 1.629)	.003	1.443 (1.175, 1.774)	.000
N4	2.005 (1.423, 2.824)	.000	2.092 (1.451, 3.017)	.000
Grade	1.239 (1.044, 1.470)	.014	1.219 (1.022, 1.454)	.028
Tumor size				
<38		.000		.001
38 to 58	0.948 (0.761, 1.181)	.631	0.903 (0.721, 1.132)	.378
>58	1.622 (1.276, 2.061)	.000	1.541 (1.204, 1.973)	.001
Radiation	1.155 (0.972, 1.373)	.102		
Chemotherapy	0.653 (0.548, 0.778)	.000	0.645 (0.533, 0.780)	.000
Bone	1.541 (1.237, 1.920)	.000	1.536 (1.222, 1.931)	.000
Brain	0.961 (0.795, 1.163)	.685		
Liver	1.400 (0.963, 2.036)	.078		
Lung	0.908 (0.746, 1.105)	.334		

can benefit patients with metastatic LUAD. In order to further explore the impact of other treatment methods on surgery, we divided patients into surgery, radiotherapy and chemotherapy combination group, surgery and chemotherapy combination group, surgery and radiotherapy combination group, surgery group, radiotherapy and chemotherapy group, chemotherapy group, and radiotherapy group. Survival analysis showed that the median survival time of the surgery, radiotherapy and chemotherapy combination group, surgery and chemotherapy combination group, and surgery group were longer than that of the non-surgical group. However, surgery and radiotherapy combination did not show a significant survival benefit. Based on the above analysis, we have reason to believe that surgery can provide survival benefits for patients with metastatic LUAD.

Elizabeth A. David and her colleagues developed SSS (a scoring system) to predict surgical treatment options for patients with advanced NSCLC, where AJCC metastasis status, AJCC lymph node status, and age are the strongest predictors for selecting SSS patients for surgery.[21] We created a visual nomogram based on the logistic regression selection model for the postoperative prognosis prediction for patients with metastatic LUAD, in which chemotherapy, bone metastasis, N stage, tumor size, tumor grade, gender, age, etc. were included. It was found that N stage has the greatest impact on the score, followed by bone metastasis, mass size, and age. Zhang et al. proved that compared with squamous cell carcinoma, the bone or brain recurrence rate[22] is higher for adenocarcinoma. Yoshino et al. reported that bone metastasis is a significant disadvantage in the post-recurrence survival of

patients who underwent stage I-III NSCLC resection.[23] Shimada et al. confirmed that bone metastasis (P = .001) and liver metastasis (P < .001) were significantly and independently related to the deterioration of post-recurrence survival.[24] Similarly, we believe that the prognosis of patients with bone metastasis may be worse after surgery. Therefore, bone metastasis was also considered as a nomogram indicator. As mentioned earlier, for lung cancer patients undergoing primary tumor surgery, fewer lymph node infiltrations, no bone metastases, smaller tumor lesions, and younger age all contribute to a better prognosis. Those facts show that for patients with metastatic LUAD, their own conditions are very important for surgery, of which the reason might be that the difficulty of surgery is relatively low, and the life expectancy is long. Subsequently, the 1-, 2-, and 3-year OS calibration curves of the experimental group and the validation group showed that acceptable agreement has been achieved between the predicted and actual survival rates of the 2 groups of patients. The decision curve verifies that our risk scoring system is superior to other clinical factors. To further evaluate whether our scoring system can successfully distinguish patients with metastatic LUAD, we ranked the patients and defined them accordingly as high-, medium-, and low-risk. It was found that our prognostic model successfully distinguished the survival status of patients after surgery.

This study is with a few limitations. To begin with, it is a retrospective study, so selection bias is unavoidable. Secondly, it needs to be recognized that many variables can affect the prognosis of patients with metastatic LUAD, including the patient's own condition, postoperative immunotherapy, and targeted
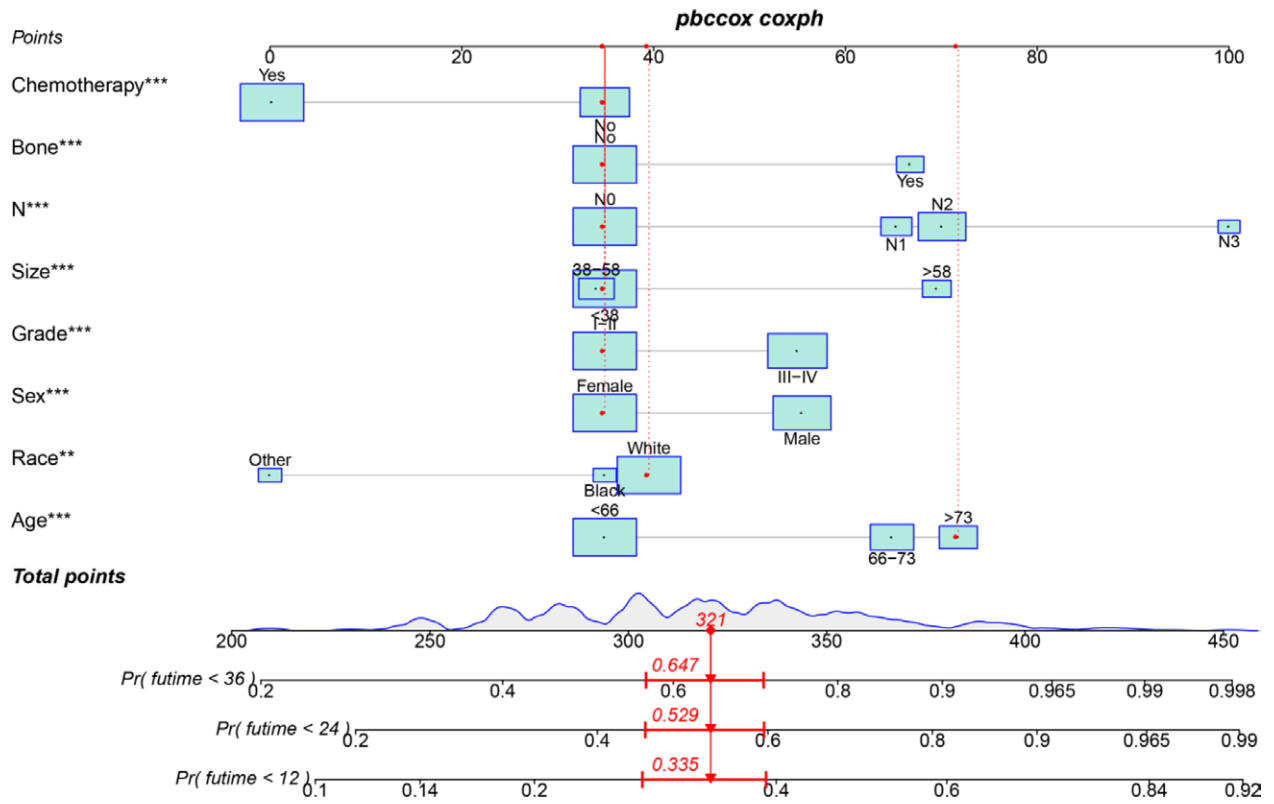
Figure 4. Nomogram for predicting OS of metastatic LUAD patients. LUAD = lung adenocarcinoma, OS = overall survival.
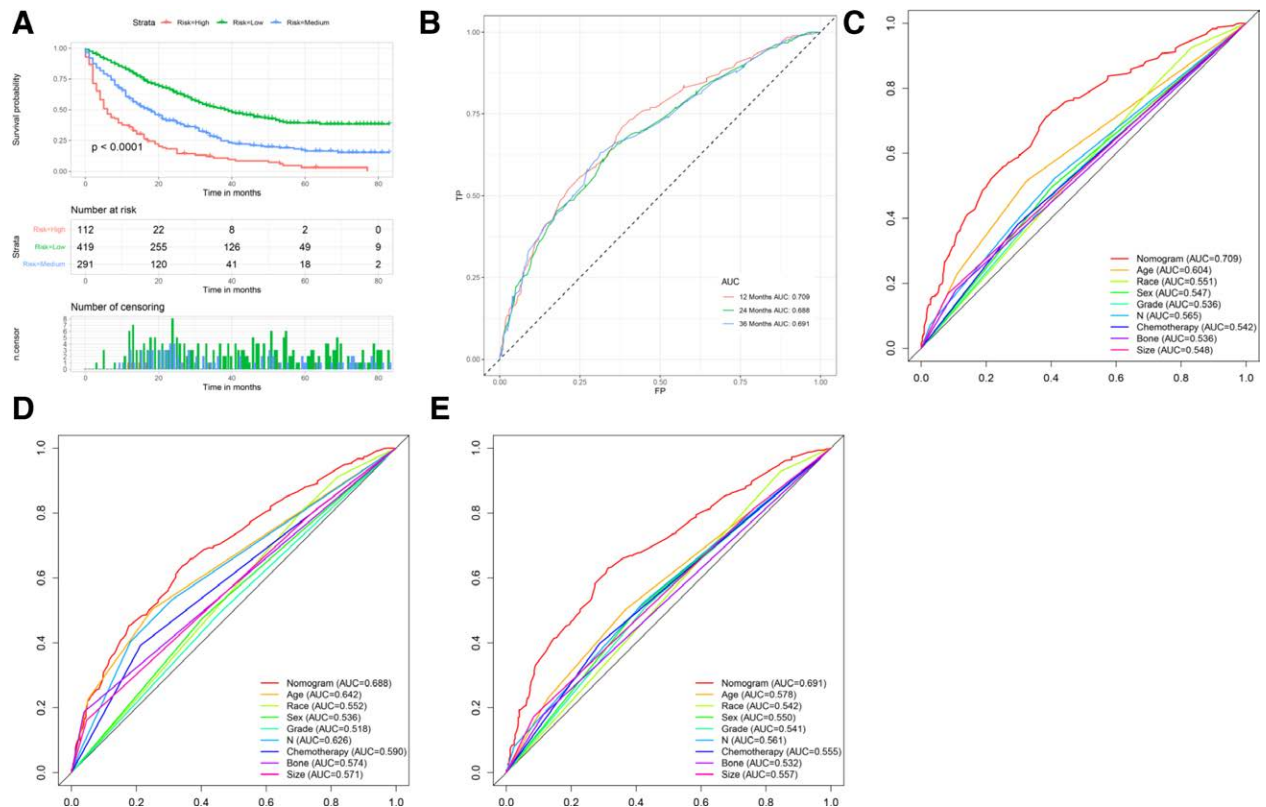

Figure 5. (A). Kaplan–Meier curves result in the training group. (B). The AUC values for the prediction of 1, 2, 3-year survival rate of metastatic LUAD in the training group. (C–E). The AUC values of the risk factors for 1, 2, 3-year survival rate in the training group. AUC = the area under the curve, LUAD = lung adenocarcinoma.
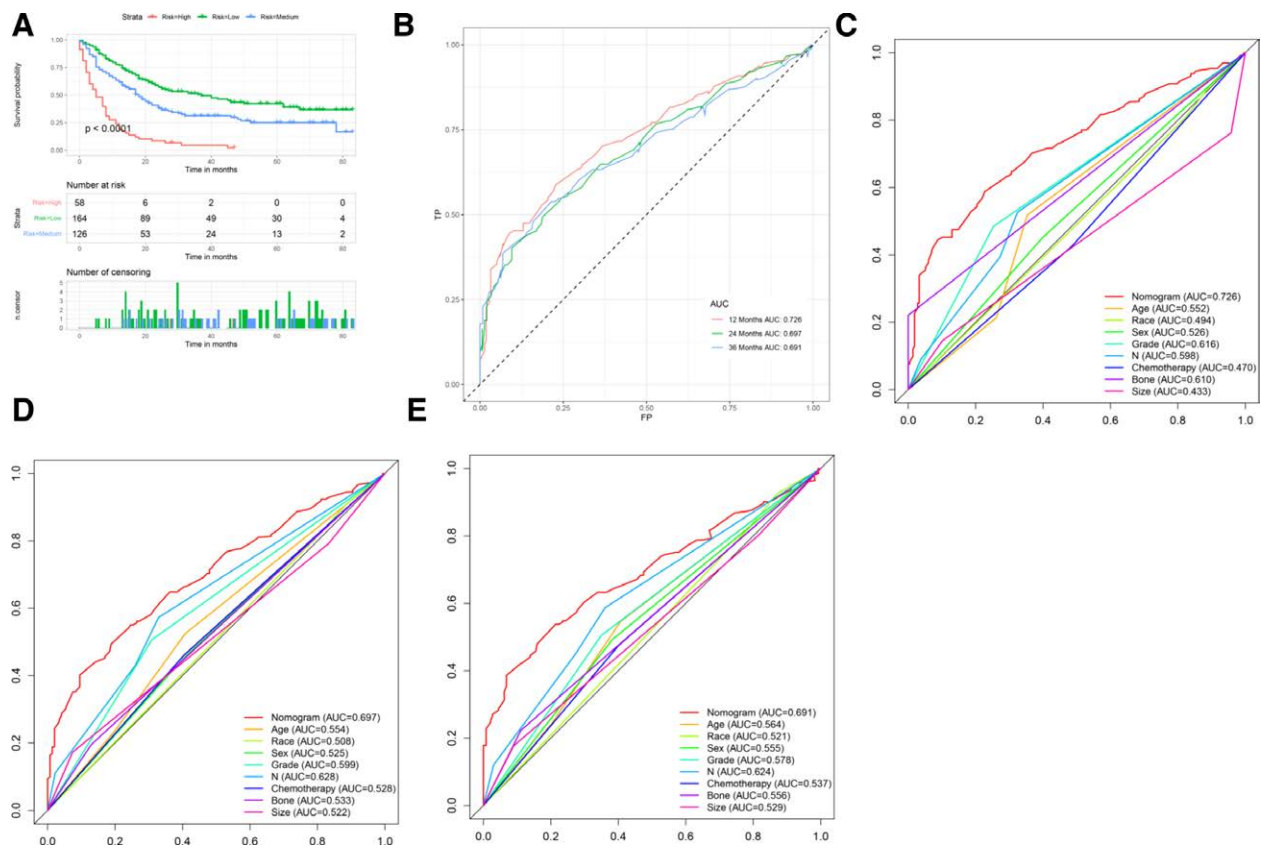
Figure 6. (A). Kaplan–Meier curves result in the verification group. (B). The AUC values for the prediction of 1, 2, 3-year survival rate of metastatic LUAD in the verification group, (C–E). The AUC values of the risk factors for 1, 2, 3-year survival rate in the verification group. AUC = the area under the curve, LUAD = lung adenocarcinoma.
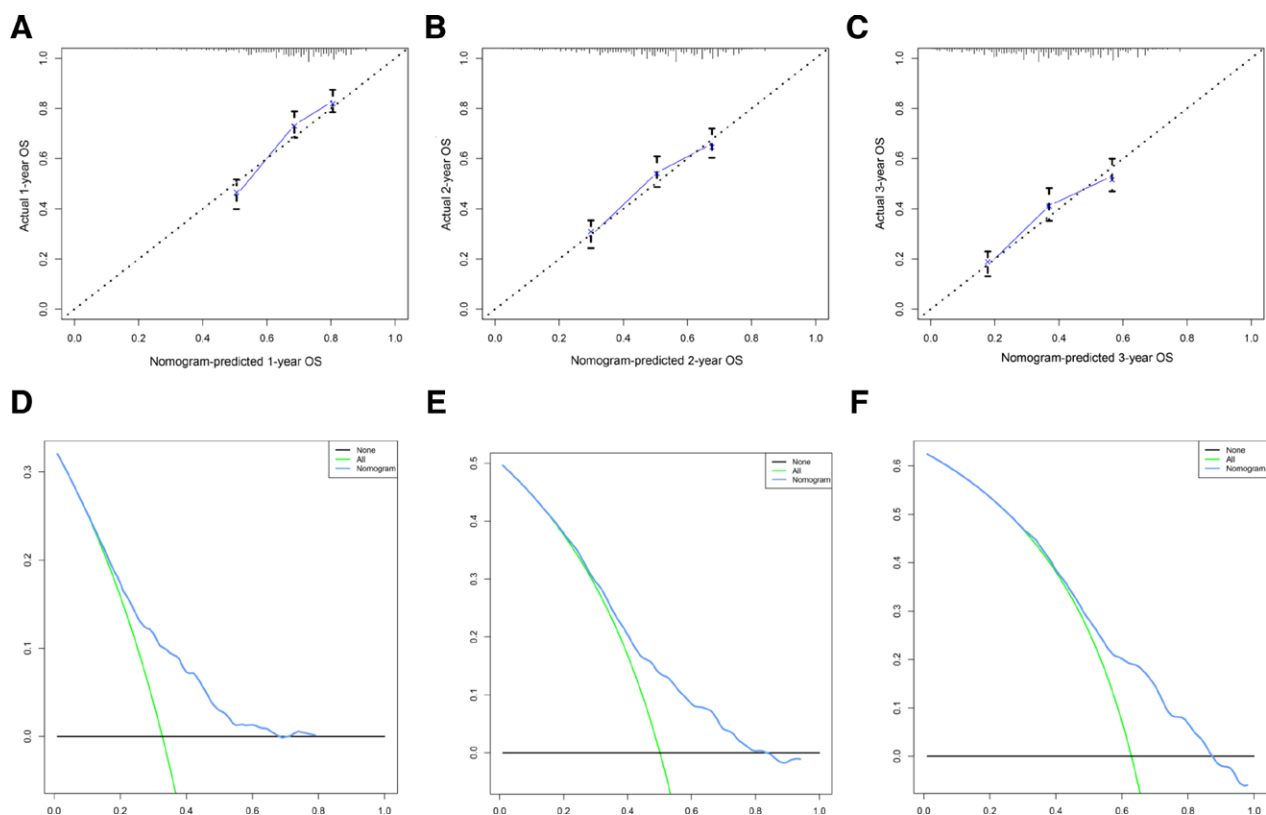

Figure 7. The calibration curve and DCA curve analysis to evaluate the accuracy of the nomogram at 1, 3 and 5 years, respectively. (A–C) The calibration curve analysis of the nomogram compared for 1, 3, and 5 years in the training group. (D–F) DCA curve analysis of the nomogram compared for 1, 3, and 5 years in the training group.
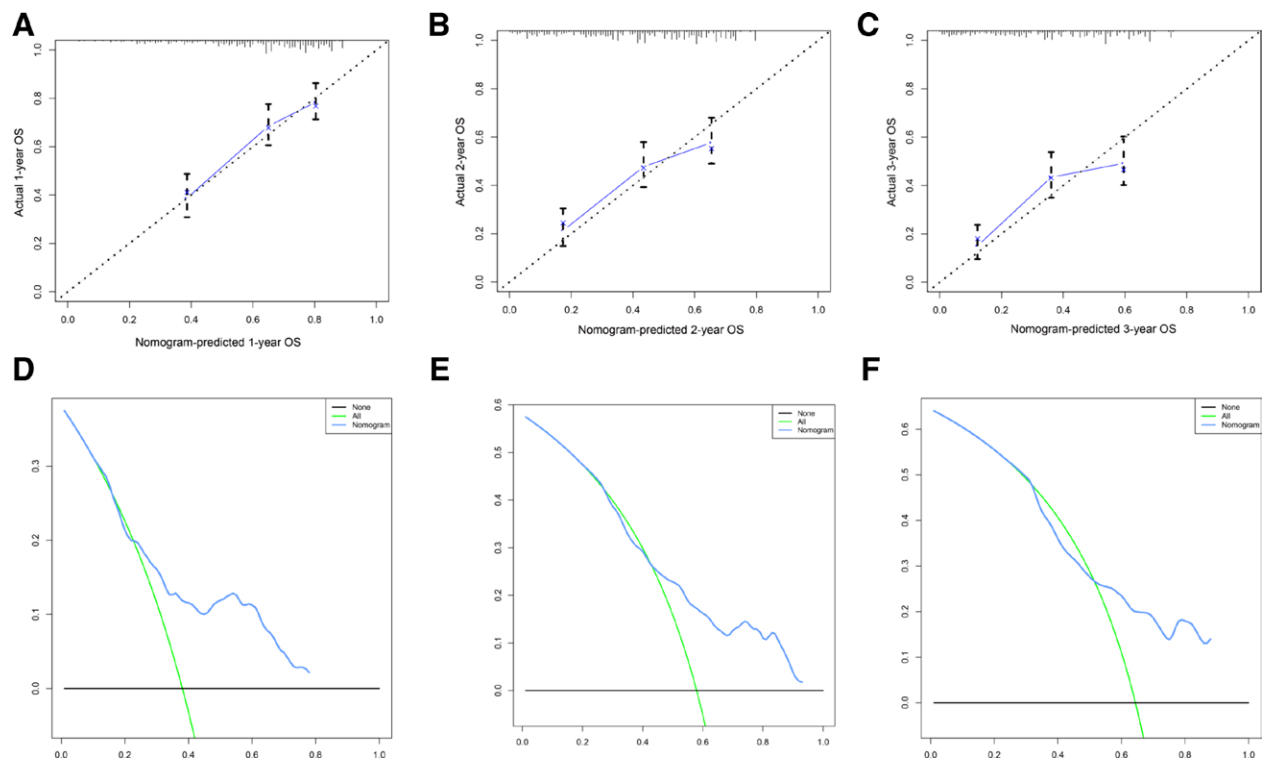
Figure 8. The calibration curve and DCA curve analysis to evaluate the accuracy of the nomogram at 1, 3 and 5 years, respectively. (A–C) The calibration curve analysis of the nomogram compared for 1, 3, and 5 years in the verification group. (D–F) DCA curve analysis of the nomogram compared for 1, 3, and 5 years in the verification group.

therapy, which could not be obtained from the SEER database. Meanwhile, our research also has certain advantages. First of all, as far as we know, our study is 1 of the few studies currently using the nomogram model in the prognosis prediction for patients who are diagnosed with metastatic LUAD. Secondly, the study collected a large-scale population of subjects to establish the nomogram, and conducted internal and external verification, so that the nomogram model is of high reliability.

Author contributions

Conceptualization: Yangchen Liu.
Data curation: Lianlian Chen.
Formal analysis: Lianlian Chen.
Methodology: Xiaomin Li.
Software: Xiaowei Tie, Xiaomin Li, Wenjuan Zha.
Supervision: Wenjuan Zha.
Validation: Xiaomin Li.
Writing – original draft: Xiaowei Tie.
Writing – review & editing: Yangchen Liu.

References

[1] Neto RAM, Santos CBR, Henriques SVC, et al. Novel chalcones derivatives with potential antineoplastic activity investigated by docking and molecular dynamics simulations. J Biomol Struct Dyn. 2022;40:2204–16.

[2] Galucio NCDR, Moysés DA, Pina JRS, et al. Antiproliferative, genotoxic activities and quantification of extracts and cucurbitacin B obtained from Luffa operculata (L.) Cogn. Arabian J Chem. 2022;15.

[3] Castro ALG, Cruz JN, Sodré DF, et al. Evaluation of the genotoxicity and mutagenicity of isoeleutherin and eleutherin isolated from Eleutherine plicata herb. using bioassays and in silico approaches. Arabian J Chem. 2021;14:103084.

[4] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA. 2021;71:209–49.

[5] Imielinski M, Berger AH, Hammerman PS, et al. Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing. Cell. 2012;150:1107–20.

[6] Zeng X, Liu Q, Yang Y, et al. Placenta-specific protein 8 promotes the proliferation of lung adenocarcinoma PC-9 cells and their tolerance to an epidermal growth factor receptor tyrosine kinase inhibitor by activating the ERK signaling pathway. Oncol Lett. 2019;18:5621–7.

[7] Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA. 2019;69:363–85.

[8] Rego CMA, Francisco AF, Boeno CN, et al. Inflammasome NLRP3 activation induced by Convulxin, a C-type lectin-like isolated from Crotalus durissus terrificus snake venom. Sci Rep. 2022;12:4706.

[9] Giustini NP, Jeong AR, Buturla J, et al. Advances in treatment of locally advanced or metastatic non-small cell lung cancer: targeted therapy. Clin Chest Med. 2020;41:223–35.

[10] Martinez P, Peters S, Stammers T, et al. Immunotherapy for the first-line treatment of patients with metastatic non-small cell lung cancer. Clin Cancer Res. 2019;25:2691–8.

[11] Abdel-Rahman O. Outcomes of surgery as part of the management of metastatic non-small-cell lung cancer: a surveillance, epidemiology and end results database analysis. Cancer Invest. 2018;36:238–45.

[12] Liu K, Zheng D, Xu G, et al. Local thoracic therapy improve prognosis for stage IV non-small cell lung cancer patients combined with chemotherapy: a surveillance, epidemiology, and end results database analysis. PLoS One. 2017;12:e0187350.

[13] Kim SY, Yoon MJ, Park YI, et al. Nomograms predicting survival of patients with unresectable or metastatic gastric cancer who receive combination cytotoxic chemotherapy as first-line treatment. Gastric Cancer. 2018;21:453–63.

[14] Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol. 2013;31:1188–95.

[15] Liang W, Zhang L, Jiang G, et al. Development and validation of a nomogram for predicting survival in patients with rex`sected non-small-cell lung cancer. J Clin Oncol. 2015;33:861–9.

[16] Birim O, Kappetein AP, Waleboer M, et al. Long-term survival after non-small cell lung cancer surgery: development and validation of

a prognostic model with a preoperative and postoperative mode. J Thorac Cardiovasc Surg. 2006;132:491–8.

[17] Farjah F, Lou F, Sima C, et al. A prediction model for pathologic N2 disease in lung cancer patients with a negative mediastinum by positron emission tomography. J Thoracic Oncol. 2013;8:1170–80.

[18] Zhang Y, Sun Y, Xiang J, et al. A clinicopathologic prediction model for postoperative recurrence in stage Ia non-small cell lung cancer. J Thorac Cardiovasc Surg. 2014;148:1193–9.

[19] Scosyrev E, Messing J, Noyes K, et al. Surveillance epidemiology and end results (SEER) program and population-based research in urologic oncology: an overview. Urol Oncol. 2012;30:126–32.

[20] David EA, Clark JM, Cooke DT, et al. The role of thoracic surgery in the therapeutic management of metastatic non-small cell lung cancer. J Thoracic Oncol. 2017;12:1636–45.

[21] David EA, Andersen SW, Beckett LA, et al. A model to predict the use of surgical resection for advanced-stage non-small cell lung cancer patients. Ann Thorac Surg. 2017;104:1665–72.

[22] Zhang Y, Zheng D, Xie J, et al. Development and validation of web-based nomograms to precisely predict conditional risk of site-specific recurrence for patients with completely resected non-small cell lung cancer: a multiinstitutional study. Chest. 2018;154:501–11.

[23] Yoshino I, Yohena T, Kitajima M, et al. Survival of non-small cell lung cancer patients with postoperative recurrence at distant organs. Annal Thoracic Cardiovascular Surg. 2001;7:204–9.

[24] Shimada Y, Saji H, Yoshida K, et al. Prognostic factors and the significance of treatment after recurrence in completely resected stage I non-small cell lung cancer. Chest. 2013;143:1626–34.