Original Article

Clinical predictors of treatment efficacy and a prognostic nomogram in patients with lung adenocarcinoma receiving immune checkpoint inhibitors: a retrospective study

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Background: At present, there is no accurate biomarker for immune checkpoint inhibitors (ICIs). Since the efficacy of ICIs is associated with a variety of indicators, establishing a model to predict its efficacy is more clinically significant and in line with clinical needs.

Methods: We collected and retrospectively analyzed the relationship between immunotherapy efficacy and clinicopathologic features in lung adenocarcinoma patients treated with ICIs. Progression-free survival (PFS) and overall survival (OS) were analyzed. Univariate and multivariate Cox proportional hazards regression analyses were conducted to identify prognostic factors associated with PFS. Besides, a clinical prediction model was established based on the results of the multivariate Cox regression analyses to predict PFS.

Results: A total of 201 lung adenocarcinoma patients treated with ICIs were assessed. Univariate analysis showed that male gender [hazard ratio (HR) =0.521, 95% confidence interval (CI): 0.356–0.761, P=0.001], smoking (HR =0.595, 95% CI: 0.420–0.843, P=0.003), epidermal growth factor receptor (EGFR) wild type (HR =2.766, 95% CI: 1.719–4.452, P<0.001), Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation (HR =0.449, 95% CI: 0.271–0.743, P=0.001), positive programmed death ligand 1 (PD-L1) expression (HR =0.527, 95% CI: 0.336–0.825, P=0.004), early tumor node metastasis (TNM) stage (HR =0.581, 95% CI: 0.344–0.983, P=0.039), no liver metastasis (HR =1.801, 95% CI: 1.046–3.102, P=0.031), ICIs combined with chemotherapy (HR =0.560, 95% CI: 0.384–0.815, P=0.002), having immune-related adverse effects (HR =0.354, 95% CI: 0.228–0.511, P<0.001) and first-line immunotherapy (HR =0.596, 95% CI: 0.420–0.845, P=0.003) were significantly associated with better PFS in patients with lung adenocarcinoma receiving immunotherapy. Multivariate analysis showed that smoking status, KRAS mutation, PD-L1 expression, line of immunotherapy and immune-related adverse effects were independent prognostic factors affecting PFS. A clinical prediction model was established to predict the PFS of lung adenocarcinoma patients treated with ICIs. The model showed good predictive ability via C-index, calibration curve and receiver operating characteristic (ROC) curve validation.

Conclusions: The clinical prediction model developed in this study can be used to some extent to predict PFS after immunotherapy in lung adenocarcinoma patients. However, the model still needs to be validated in studies with large sample size.

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Keywords: Lung adenocarcinoma; immune checkpoint inhibitors (ICIs); clinical prediction model; nomogram; real-world study

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Introduction

Among the 36 cancers considered in the 2020 Global Cancer Statistics, lung cancer was the second most common type of cancer and the leading cause of cancer-related mortality worldwide (1). Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer, among which adenocarcinomas accounts for about 60% of all NSCLCs and are the most common subtype of NSCLC (2).

In 2015, the *New England Journal of Medicine* successively published the research results of the CheckMate-017/057 trials, which marked the official commencement of immunotherapy treatment in patients with NSCLC (3,4). One year later, with the amazing results of the Keynote-024 study, the first first-line treatment indication for advanced lung cancer was approved, creating a new pattern of immunotherapy for NSCLC (5). Since then, given the excellent results of the Keynote-042 and Keynote-189/407 studies, the indications of immunotherapy have been extended to programmed death ligand 1 (PD-L1) ≥1% and the whole population (6-8). Thereafter, immunotherapeutic drugs such as camrelizumab, sintilimab, tislelizumab, and penpulimab have been successively developed (9-11). Within the past 5 years, the application of immunotherapy has spread rapidly in clinics and has become the standard first-line treatment for some patients.

The popularity of immunotherapy has drastically changed the current treatment landscape for lung cancer patients. At present, immune checkpoint inhibitors (ICIs) have successfully transitioned from being a later-line therapy to a first-line and locally advanced consolidation treatment for NSCLC, and are evolving into neoadjuvant and adjuvant treatments for early lung cancer. At the same time, multiple drug-use modes for single-drug and combined treatments are being comprehensively developed. The strategy of combined immunotherapy further improves the efficacy of immunotherapy and enhances the treatment methods. Furthermore, it also expands the cohort of patients who benefit from immunotherapy, achieves full coverage for driver gene-negative patients, and initiates a new era of immunotherapy.

However, identifying the patient cohort that will benefit from immunotherapy remains a pressing problem to be addressed. Previous studies have explored the prediction of immunotherapy efficacy from multiple perspectives, such as drug-based score (12), lung immune prognostic index (LIPI) (13), smoking (14), liver metastasis (15), lactate dehydrogenase (LDH) (16,17), tumor mutational burden (TMB) expression (18), neutrophil-to-lymphocyte ratio (NLR) (19,20), modified lung immune predictive index (mLIPI) scores (21), and so on. Despite achieving some results, the existing literature does not completely solve the problem of predicting immunotherapy efficacy.

Programmed death ligand 1 tumor proportion score (PD-L1 TPS) is the most common clinical prognostic markers used to predict the efficacy of immunotherapy. However, existing studies have shown that the expression level of PD-L1 is not completely related to the prognosis of ICIs treatment, and the data between various clinical studies are inconsistent (8,22). Similarly, tissue tumor mutation burden (TMB) as a predictor of immunotherapy has its limitations, including the lack of standardization between the testing platforms used and the lack of a fixed TMB threshold, which requires more exploration (23). An existing study show that about 60% of patients with advanced NSCLC cannot benefit from immunotherapy (24). At present, the development of biomarkers for predicting the efficacy of ICIs in patients with advanced lung adenocarcinoma is limited, and there is a lack of prediction models. In addition, immunotherapy is different from the targeted therapy commonly used in the past. Its function involves complex tumor microenvironment, and there is no precise target. Therefore, we speculate that the prediction model under the combination of multiple factors is more promising to predict the efficacy of immunotherapy. Thus, it is necessary to develop a model with high clinical accessibility to help clinicians effectively identify potentially effective populations for ICIs treatment. The existing studies have also carried out some exploration on the prediction model of immunotherapy efficacy (25,26). Yuan

and his colleagues developed a nomogram to predict the prognosis of NSCLC patients treated with anti-PD-1 antibodies. His model was a retrospective study and lacked the inclusion of some important indicators, such as PD-L1 expression (25). Zeng and colleagues constructed a prognostic model for patients with NSCLC receiving ICIs in combination with chemotherapy, and their study included a total of 130 patients (26). This study included patients with lung adenocarcinoma and did not restrict the immunotherapy modalities. Thus, this study is more applicable to patients with lung adenocarcinoma. Although these existing studies have explored predictive models for immunotherapy efficacy, there are some common problems, such as small sample size, insufficient population concentration, lack of important indicators and other defects.

Therefore, this study retrospectively analyzed the survival data of 201 patients with lung adenocarcinoma who received immunotherapy in the real world to explore the correlation between clinicopathological characteristics and immunotherapy efficacy. We also sought to build an immunotherapy efficacy prediction model that is suitable for clinical use to provide greater data support for clinical decision-making. We present the following article in accordance with the TRIPOD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1270/rc).

Methods

Patients

This study was a single-center retrospective study. The medical records of lung adenocarcinoma patients who received ICIs [including anti-PD-L1 and anti-programmed cell death 1 (PD-1) therapy] treatment at Shanghai Chest Hospital between August 2017 and February 2021 were screened and reviewed.

The inclusion criteria were as follows: (I) lung adenocarcinoma patients diagnosed by histopathology or cytology; (II) patients who received ICIs; (III) those with measurable target lesions; and (IV) tumor node metastasis (TNM) stage assessed by chest computed tomography (CT), abdominal ultrasound, magnetic resonance imaging (MRI) of the brain, bone scanning, or by replacing some of the above tests with positron emission tomography (PET)-CT. The TNM status of patients was assessed according to the American Joint Committee on Cancer (AJCC) 8th edition staging system. Firstly, patients who had received immunotherapy were screened. Next, patients with lung adenocarcinoma with sufficient clinical data were selected. Finally, the patients were divided into groups according to the clinicopathological characteristics and treatment data and analyzed separately.

The exclusion criteria were as follows: (I) non-adenocarcinoma patients; (II) those with tumors of organs other than the lungs; (III) lung cancer in which the type of pathology was not specified; (IV) patients with insufficient survival data; (V) patients that did not receive regular treatment; (VI) those with other concurrent tumors; (VII) cases complicated by serious systemic diseases; and (VIII) patients who were lost to follow-up. This study was approved by the Institutional Review Board of Shanghai Chest Hospital (Shanghai, China, No. IS21127) and was carried out in accordance with the requirements of the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all the patients.

Data collection

Follow-up was conducted via hospital visit or telephone conversation. Major clinicopathological characteristics, including age, sex, smoking history, TNM stage, Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation status, tumor protein p53 (TP53) mutation status, tumor status, PD-L1 expression, liver metastases, brain metastases, tumor location, adverse effects (AEs), line of immunotherapy, and immunotherapy modalities were collected. Data that were not available were recorded as missing data (NA, not available). Gene mutation was detected by the amplification refractory mutation system (ARMS) or next-generation sequencing (NGS) technology. PD-L1 expression was analyzed via immunohistochemistry assay in tumor tissue with 22C3, E1L3N, or SP142 antibodies (PD-L1 expression ≥1% was considered positive).

Treatment

All lung adenocarcinoma patients included in this study had received at least one cycle of immunotherapy. The immunotherapeutic drugs involved in this study included nivolumab, pembrolizumab, tislelizumab, sintilimab, camerelizumab, atezolizumab, and durvalumab, and the doses and usage of drugs administered are shown in Table S1. Treatment was continued until disease progression, intolerable toxicity, or death. Progression

assessment was conducted every 6–8 weeks until disease progression. The clinical follow-up examination items mainly included physical examination, imaging examination (such as chest CT, abdominal ultrasound, brain-enhanced MRI, bone scan or PET-CT instead of some of the above examinations), and routine laboratory examination (such as blood routine examination, liver function, renal function, tumor indicators, thyroid function, myocardial injury biomarkers).

Therapeutic response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Progression-free survival (PFS) was defined as the date from the initiation of immunotherapy until the date of progression or last follow-up visit (June 1, 2021). Overall survival (OS) was defined as the time from the start of immunotherapy to the date of death or last follow-up visit. The primary endpoint of this study was PFS, and the secondary endpoints were OS and objective response rate (ORR). The median follow-up time for the entire study cohort was 10.9 months.

Construction and verification of a prognostic nomogram

Variables that were statistically different were screened out by univariate analysis of PFS, and then a Cox regression model was constructed for multivariate analysis for those variables that were significant in the univariate analysis. Following univariate and multivariate analyses, all of the identified independent prognostic parameters were utilized to develop a prognostic nomogram for predicting the 3-month, 6-month, 1-year, and 2-year PFS outcomes of lung adenocarcinoma patients using the rms package in R version 4.1.1 (https://www.rdocumentation.org/packages/rms/versions/4.1-1). Next, the models were internally validated via the bootstrap method. The predictive power of the nomogram was quantitatively assessed by the C-index and the area under the curve (AUC). The C-index value ranges from 0.5–1.0, with 0.5 indicating a random probability and 1.0 indicating a perfectly correct prediction of the outcome using the model.

Statistical analysis

The patients' demographic, clinicopathological, and prognostic data were analyzed. Categorical variables were compared using Fisher's exact or chi-square test. Univariate survival analyses were conducted using the Kaplan-Meier method, and data were compared using the log-rank test. Subsequently, positive variables and important clinical variables that may affect prognosis were further analyzed using multivariate Cox proportional hazards regression models. The hazard ratio (HR) and corresponding 95% confidence interval (CI) were calculated using the Cox regression model. All variables included in the nomogram model were evaluated by the variance inflation factor (VIF); VIF >2.0 was interpreted as indicating multicollinearity. Analyses were carried out using SPSS 24.0 software (IBM, Armonk, NY, USA). A two-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

According to the inclusion and exclusion criteria, 201 eligible lung adenocarcinoma patients who received immunotherapy were enrolled. Among these patients, 101 received first-line immunotherapy, while the remaining 100 cases received second-line and above immunotherapy. The patient selection steps are shown in *Figure 1*, and the characteristics of the entire patient cohort treated with immunotherapy are summarized in *Table 1*.

The immunotherapy modalities involved in this study included immune monotherapy (n=63, 31.3%), immunotherapy combined with chemotherapy (n=117, 58.2%), immunotherapy combined with targeted therapy (n=2, 1.0%), immunotherapy combined with chemotherapy and bevacizumab (n=9, 4.5%), immunotherapy combined with bevacizumab (n=5, 2.5%), and immunotherapy combined with anlotinib (n=5, 2.5%).

Efficacy and survival

Univariate and multivariate analyses for PFS

Univariate analysis of the 201 lung adenocarcinoma patients who received immunotherapy showed that clinical factors such as male gender (median PFS of 9.7 *vs.* 5.1 months, P=0.001), smoker (median PFS of 11.6 *vs.* 5.9 months, P=0.003), epidermal growth factor receptor (EGFR) wild type (median PFS of 9.8 *vs.* 2.4 months, P<0.001), KRAS mutation (median PFS of 16.8 *vs.* 7.6 months, P=0.001), earlier TNM stage (median PFS of 15.9 *vs.* 7.4 months, P=0.039), PD-L1 positive (median PFS of 9.0 *vs.* 4.9 months, P=0.004), no liver metastasis (median PFS of 8.6 *vs.* 4.0 months, P=0.031), immune combined chemotherapy (median PFS of 10.2 *vs.* 3.5 months,

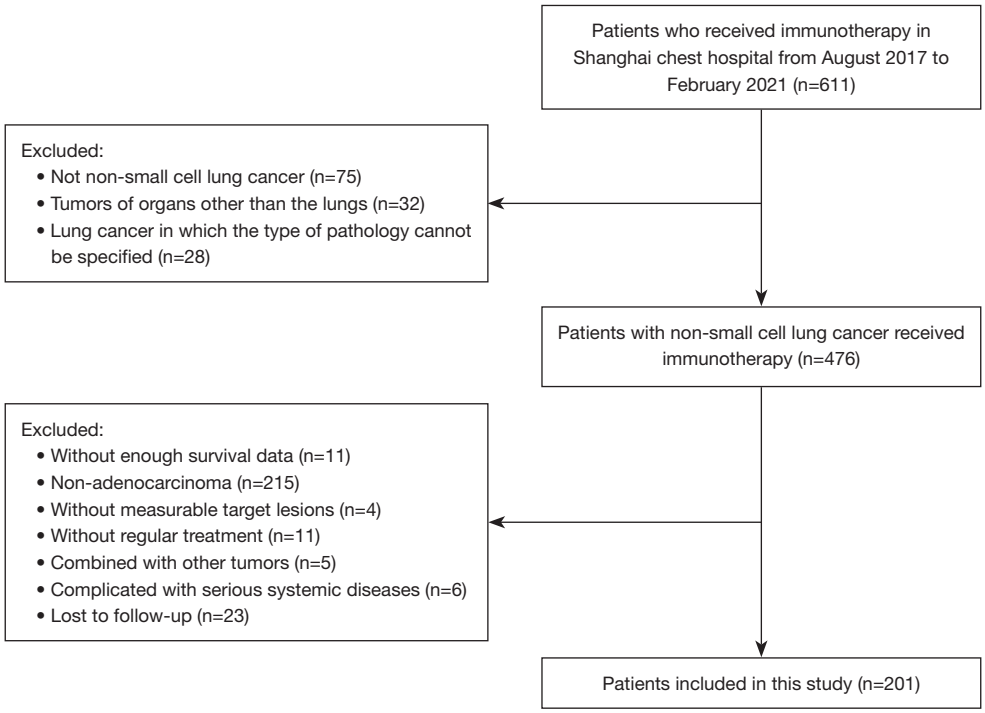


Figure 1 Patient selection flow diagram.

P=0.002), adverse effects (median PFS of patients with AE *vs.* without AE: 13.5 *vs.* 1.8 months, P<0.001), and first-line of immunotherapy (median PFS of 10.4 *vs.* 5.9 months, P=0.003) were significantly associated with improved PFS, compared with female gender, never-smoker, EGFR mutation, KRAS negative, poor TNM stage, PD-L1 negative, liver metastasis, immunotherapy alone, and patients without adverse effects. The univariate analyses of PFS outcomes are shown in *Table 2*.

For multivariate analysis of the entire cohort, Cox proportional hazard multivariable modeling was performed on the variables of those with significant associations confirmed by univariate analysis (sex, smoking status, EGFR mutation, KRAS mutation, PD-L1, TNM stage, liver metastases, immunotherapy modalities, adverse effects and line of immunotherapy) to predict each outcome separately. The results demonstrated a significant PFS benefit for lung adenocarcinoma patients treated with immunotherapy exhibiting the following clinical parameters: smoker (P=0.011), KRAS mutation (P=0.006), first-line of immunotherapy (P=0.009), AEs (P=0.014) (*Figure 2*). While the patients with PD-L1 positive (PD-L1 TPS ≥1%) had a significantly better trend of PFS than those with PD-L1 negative (PD-L1 TPS <1%) (P=0.052), which was speculated to be false negative due to small sample size and more missing values (*Figure 2*).

Multivariate analysis of lung adenocarcinoma patients receiving first-line immunotherapy showed that age (P=0.003), sex (P=0.001), tumor status (P=0.015), KRAS mutation (P=0.022), PD-L1 expression (P=0.006), and brain metastases (P=0.027) were independent prognostic factors for PFS (Figure S1A). In addition, multivariate analysis of lung adenocarcinoma patients receiving immunotherapy as second-line and above found that smoking status (P=0.033), EGFR mutation (P=0.003), TP53 mutation (P=0.020), PD-L1 expression (P=0.032), and immunotherapy modalities (P<0.001) are independent prognostic factors that affect PFS (Figure S1B).

Univariate and multivariate analyses for OS

Univariate analysis found that among lung adenocarcinoma patients receiving immunotherapy, those who were EGFR negative (median OS of 27.7 *vs.* 10.9 months, P<0.001), PD-L1 positive (median OS of not reached *vs.* 11.7 months, P=0.001), had a TNM stage of IIIA–IIIC (median OS of not reached *vs.* 20.5 months, P=0.002), received immunotherapy combined with chemotherapy (median OS of 26.9 *vs.* 15.0 months, P=0.004), and had adverse effects (median OS

Table 1 Demographic characteristics of 201 patients treated with immunotherapy

Characteristics	Total
Median age, years [range]	64 [32–84]
Sex	
Male/female	154 (76.6%)/47 (23.4%)
Smoking status	
Smoker/never-smoker	117 (58.2%)/84 (41.8%)
EGFR mutation status	
Yes/no/NA	28 (13.9%)/162 (80.6%)/11 (5.5%)
KRAS mutation	
Yes/no/NA	47 (23.4%)/95 (47.3%)/59 (29.4%)
TP53 mutation	
Yes/no/NA	70 (34.8%)/44 (21.9%)/87 (43.3%)
Tumor status	
Recurrent/primary	59 (29.4%)/142 (70.6%)
TNM stage	
IIIA–IIIC/IV	30 (14.9%)/171 (85.1%)
PD-L1	
Negative/positive/NA	40 (19.9%)/83 (41.3%)/78 (38.8%)
Liver metastases	
Yes/no	19 (9.5%)/182 (90.5%)
Brain metastases	
Yes/no	69 (34.3%)/132 (65.7%)
Location	
Central/peripheral/NA	40 (19.9%)/121 (60.2%)/40 (19.9%)
Adverse effects	
Yes/no/NA	87 (43.3%)/47 (23.4%)/67 (33.3%)
Immunotherapy modalities	
Immuno+ chemo*/ immunotherapy alone/ other**	117 (58.2%)/63 (31.3%)/21 (10.4%)
Treatment line	
First-line/second-line and above	101 (50.2%)/100 (49.8%)

*, immunotherapy combined with chemotherapy; **, other combination modalities refer to combinations other than immunotherapy combined with chemotherapy, including the combination of bevacizumab, anlotinib, and EGFR-TKIs. EGFR, epidermal growth factor receptor; NA, not available; KRAS, Kirsten rat sarcoma viral oncogene homolog; TP53, tumor protein p53; TNM stage, tumor node metastasis stage; PD-L1, programmed cell death-ligand 1; TKIs, tyrosine kinase inhibitors.

of not reached *vs.* 9.3 months, P<0.001) had significantly longer OS (*Table 2*). In addition, univariate analysis of lung adenocarcinoma patients receiving first-line immunotherapy showed that PD-L1 positive patients had significantly better OS than PD-L1 negative patients (median OS of not reached *vs.* 13.2 months, HR =0.439, 95% CI: 0.203–0.949, P=0.031, *Figure 3A*), and stage IIIA–IIIC patients had significantly longer OS than stage IV patients (median OS of not reached *vs.* 22.4 months, HR =0.244, 95% CI: 0.074–0.803, P=0.012, *Figure 3B*). Meanwhile, a statistically insignificant trend was observed between patients with and without adverse effects (median OS of not reached *vs.* 18.8 months, HR =0.431, 95% CI: 0.178–1.045, P=0.055, Figure S2).

The results of univariate analysis for OS in lung adenocarcinoma patients with second-line and above immunotherapy showed that EGFR wild-type (27.7 *vs.* 10.9 months, HR =0.393, 95% CI: 0.217–0.712, P=0.001, *Figure 4A*), PD-L1 positive (not reached *vs.* 7.6 months, HR =0.381, 95% CI: 0.168–0.866, P=0.017, *Figure 4B*), immunotherapy combined with chemotherapy (26.9 *vs.* 13.5 months, HR =0.514, 95% CI: 0.274–0.964, P=0.035, *Figure 4C*), and adverse reactions (not reached *vs.* 8.5 months, HR =0.210, 95% CI: 0.104–0.423, P<0.001, *Figure 4D*) were significantly correlated with improved OS.

Among lung adenocarcinoma patients who received first-line immunotherapy, multivariate analysis showed that patients younger than 60 years old and PD-L1 positive were significantly associated with longer OS (*Figure 5A*). Moreover, multivariate analysis of patients receiving second-line and above immunotherapy found that patients younger than 60 years old, male, non-smoking, EGFR wild type, and patients with adverse effects were significantly associated with improved OS (*Figure 5B*).

Best response outcomes

The best response outcome results for patients with different clinical characteristic factors are shown in *Table 3*. The best response outcomes were statistically different in terms of sex (P=0.037), smoking status (P=0.031), EGFR mutation status (P<0.001), KRAS mutation (P<0.001), PD-L1 expression (P=0.001), line of immunotherapy (P<0.001), immunotherapy modalities (P=0.022), and adverse effects (P<0.001).

Nomogram construction and validation of PFS

According to the Cox regression results of PFS in the entire

Table 2 Univariate analyses of clinical characteristics on progression-free survival and overall survival outcomes

Variables	Univariate analysis on PFS		Univariate analysis on OS	
	Hazard ratio	P value	Hazard ratio	P value
Age (years)				
<60	1.016 (95% CI, 0.706–1.462)	0.933	0.638 (95% CI, 0.388–1.047)	0.072
≥60	1		1	
Sex				
Male	0.521 (95% CI, 0.356–0.761)	0.001	0.868 (95% CI, 0.533–1.414)	0.569
Female	1		1	
Tumor status				
Recurrent	1.078 (95% CI, 0.740–1.570)	0.695	1.073 (95% CI, 0.675–1.707)	0.765
Primary	1		1	
Smoking status				
Smoker	0.595 (95% CI, 0.420–0.843)	0.003	0.826 (95% CI, 0.538–1.269)	0.382
Never-smoker	1		1	
EGFR mutation				
Yes	2.766 (95% CI, 1.719–4.452)	<0.001	2.698 (95% CI, 1.585–4.591)	<0.001
NA	1.627 (95% CI, 0.783–3.365)	0.183	3.071 (95% CI, 1.457–6.471)	0.002
No	1		1	
TP53 mutation				
Yes	0.929 (95% CI, 0.578–1.492)	0.758	1.014 (95% CI, 0.535–1.925)	0.965
NA	1.069 (95% CI, 0.680–1.681)	0.770	1.515 (95% CI, 0.852–2.692)	0.154
No	1		1	
KRAS mutation				
Yes	0.449 (95% CI, 0.271–0.743)	0.001	0.788 (95% CI, 0.432–1.440)	0.438
NA	0.919 (95% CI, 0.622–1.358)	0.668	1.220 (95% CI, 0.759–1.962)	0.410
No	1		1	
PD-L1				
Positive	0.527 (95% CI, 0.336–0.825)	0.004	0.414 (95%CI, 0.236–0.725)	0.001
NA	0.534 (95% CI, 0.342–0.834)	0.007	0.616 (95% CI, 0.368–1.031)	0.062
Negative	1		1	
TNM stage				
IIIA–IIIC	0.581 (95% CI, 0.344–0.983)	0.039	0.212 (95% CI, 0.077–0.578)	0.002
IV	1		1	
Liver metastases				
Yes	1.801 (95% CI, 1.046–3.102)	0.031	1.670 (95% CI, 0.879–3.173)	0.113
No	1		1	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Univariate analysis on PFS		Univariate analysis on OS	
	Hazard ratio	P value	Hazard ratio	P value
Brain metastases				
Yes	1.271 (95% CI, 0.889–1.818)	0.186	1.252 (95% CI, 0.807–1.942)	0.315
No	1		1	
Location				
Central	0.929 (95% CI, 0.596–1.449)	0.745	0.887 (95% CI, 0.499–1.579)	0.684
NA	1.025 (95% CI, 0.648–1.619)	0.916	1.222 (95% CI, 0.712–2.096)	0.466
Peripheral	1		1	
Immunotherapy modalities				
Immuno + chemo*	0.560 (95% CI, 0.384–0.815)	0.002	0.513 (95% CI, 0.322–0.818)	0.004
Other combinations**	0.832 (95% CI, 0.463–1.495)	0.535	1.093 (95% CI, 0.566–2.111)	0.790
Immunotherapy alone	1		1	
Adverse effects				
Yes	0.354 (95% CI, 0.228–0.551)	<0.001	0.284 (95% CI, 0.165–0.487)	<0.001
NA	0.551 (95% CI, 0.353–0.860)	0.007	0.588 (95% CI, 0.354–0.976)	0.037
No	1		1	
Line of immunotherapy				
First-line	0.596 (95% CI, 0.420–0.845)	0.003	0.655 (95% CI, 0.421–1.020)	0.059
Second-line and above	1		1	

*, immunotherapy combined with chemotherapy; **, other combination modalities refer to combinations other than immunotherapy combined with chemotherapy, including the combination of bevacizumab, anlotinib, and EGFR-TKIs. PFS, progression-free survival; OS, overall survival; CI, confidence interval; EGFR, epidermal growth factor receptor; NA, not available; TP53, tumor protein p53; KRAS, Kirsten rat sarcoma viral oncogene homolog; TNM stage, tumor node metastasis stage; PD-L1, programmed cell death-ligand 1.

cohort, our model contained the following factors: KRAS mutation, smoking status, PD-L1, lines of immunotherapy and adverse effects. We constructed a nomogram for PFS in lung adenocarcinoma patients who received immunotherapy according to the variables screened (*Figure 6A*). When using the nomogram to predict the PFS of patients, it is necessary to calculate the scores of each variable and then add the scores of all variables to obtain the total scores of patients. The percentage corresponding to the total score is the predicted probability of reaching PFS in 3 months, 6 months, 1 year, and 2 years.

The VIF values were all <2, indicating that no collinearity existed between the variables. The C-index value was 0.714 (95% CI: 0.692–0.736). The calibration curves of the nomogram showed relatively high consistencies between the predicted and observed survival probability in lung adenocarcinoma patients treated with immunotherapy (*Figure 6B-6E*). The area under the ROC curve (AUC) was 0.779 (95% CI: 0.692–0.867) for 3-month PFS, 0.760 (95% CI: 0.675–0.846) for 6-month PFS, 0.802 (95% CI: 0.717–0.888) for 1-year PFS and 0.689 (95% CI: 0.543–0.831) for 2-year PFS, indicating that this prognostic model performed well as a predictor of PFS (*Figure 6F*). Therefore, the nomogram for the PFS of lung adenocarcinoma patients receiving immunotherapy showed considerable predictive and calibrating abilities.

Discussion

As the most common pathological type of lung cancer, lung

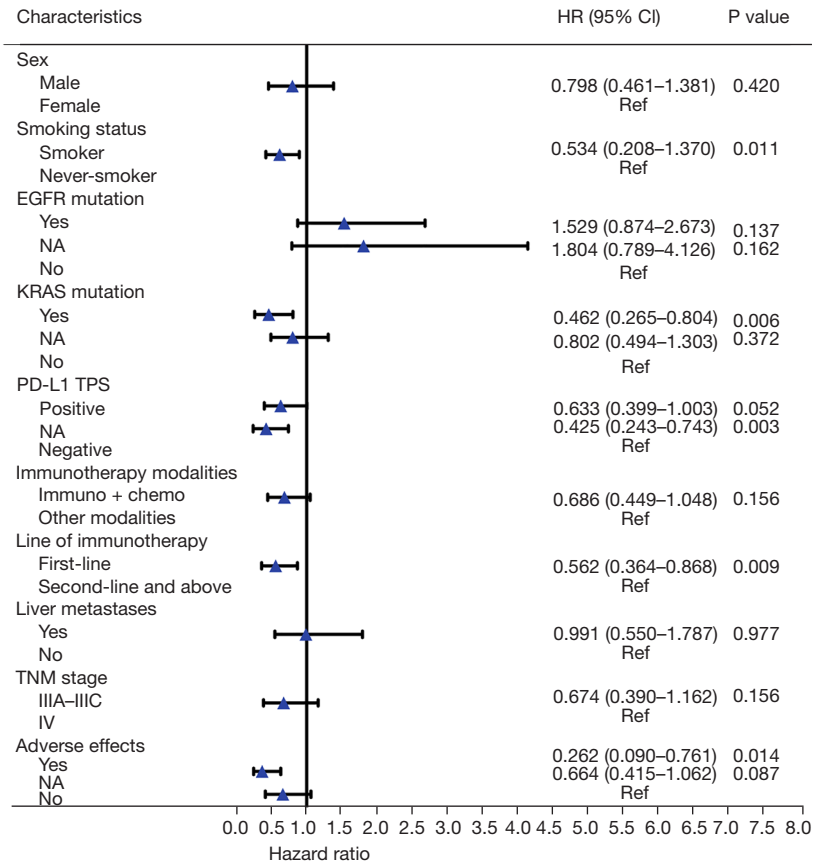


Figure 2 Forest plot of the Cox proportional hazard multivariable modeling of progression-free survival for lung adenocarcinoma patients who received immunotherapy included in this study. HR, hazard ratios; 95% CI, 95% confidence interval; Ref, reference; EGFR, epidermal growth factor receptor; NA, not available; KRAS, Kirsten rat sarcoma viral oncogene homolog; PD-L1, programmed death receptor ligand 1; immuno + chemo, immunotherapy plus chemotherapy; TNM stage, tumor-node-metastasis stage.

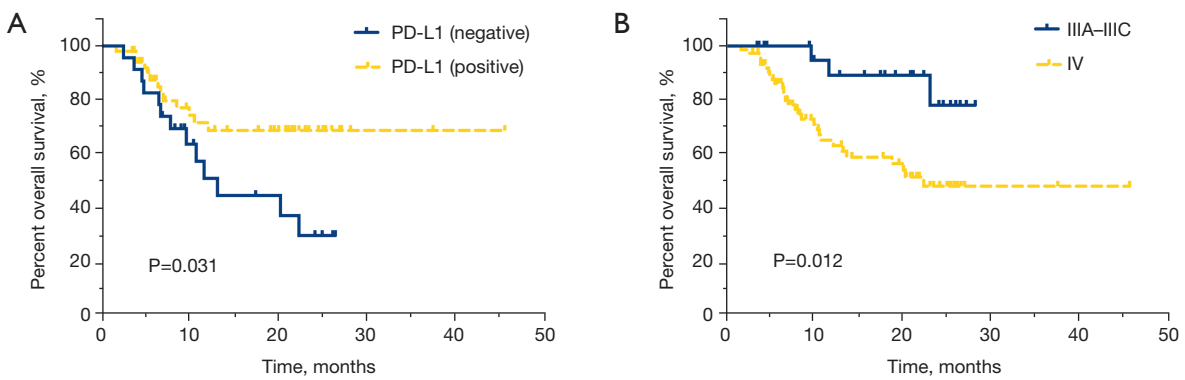


Figure 3 OS of lung adenocarcinoma patients receiving first-line immunotherapy. (A) PD-L1 positive patients showed a significantly longer OS than PD-L1 negative patients. (B) Stage IIIA–IIIC patients had significantly longer OS than stage IV patients. PD-L1, programmed death receptor ligand 1; OS, overall survival.

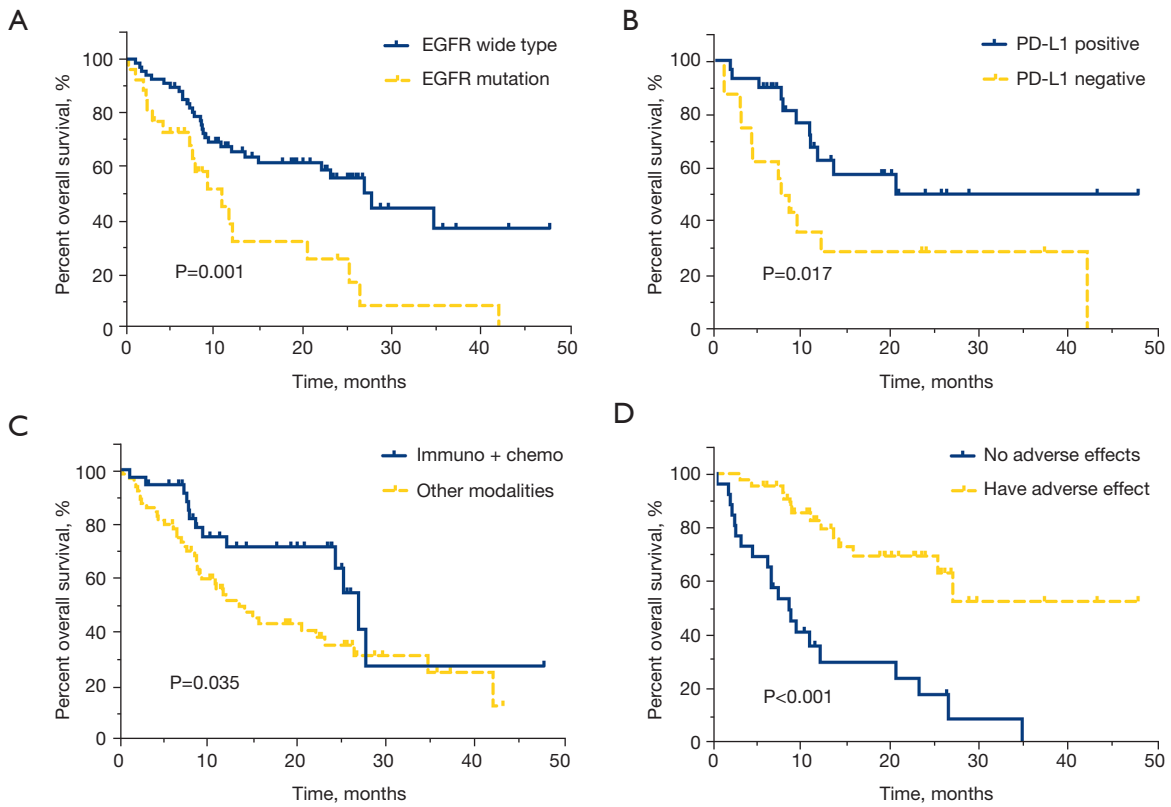


Figure 4 The OS survival curve for patients treated with second-line and above immunotherapy. (A) Overall survival was significantly improved in patients who were EGFR wild type, (B) PD-L1 positive, (C) received immune combined chemotherapy, and (D) had adverse reactions. EGFR, epidermal growth factor receptor; PD-L1, programmed death receptor ligand 1; immuno + chemo, immunotherapy plus chemotherapy; OS, overall survival.

adenocarcinoma seriously affects the health of patients. For lung adenocarcinoma diagnosed in the early stage, complete remission can be achieved through surgery. However, most patients are already at advanced stages at the time of diagnosis, and the 5-year survival rate is less than 20%. Previously, chemotherapy was the most commonly used treatment for patients with advanced lung adenocarcinoma. For lung adenocarcinoma patients with driver-oncogene mutations, such as EGFR and anaplastic lymphoma kinase (ALK) mutations, targeted therapy has greatly improved their outcomes. In recent years, with the rapid development of biomedical technology, numerous immunotherapeutic drugs have been approved for clinical treatment after a series of clinical studies, which has not only restored hope for patients with lung adenocarcinoma but also greatly changed the current lung cancer treatment landscape. However, despite the increasing popularity of immunotherapy in clinical practice, the efficacy of immunotherapy is inconsistent, with some patients receiving a long-term survival benefit, while others are not sensitive to immunotherapy. At present, identifying the potential beneficiaries of immunotherapy is an important clinical problem that remains to be solved.

In this study, the PFS and OS of lung adenocarcinoma patients treated with anti-PD-1/PD-L1 ICIs were statistically analyzed to explore the prognostic differences of lung adenocarcinoma patients with different clinicopathological characteristics after anti-PD-1/PD-L1 ICIs treatment. In addition, a clinical prediction model was established to predict the PFS of lung adenocarcinoma patients treated with ICIs, with the aim of providing a reference for clinical treatment decision-making.

Previous studies on lung cancer have proposed some factors that potentially affect the prognosis of patients with lung adenocarcinoma treated with immunotherapy, such as PD-L1 expression, tumor mutational burden

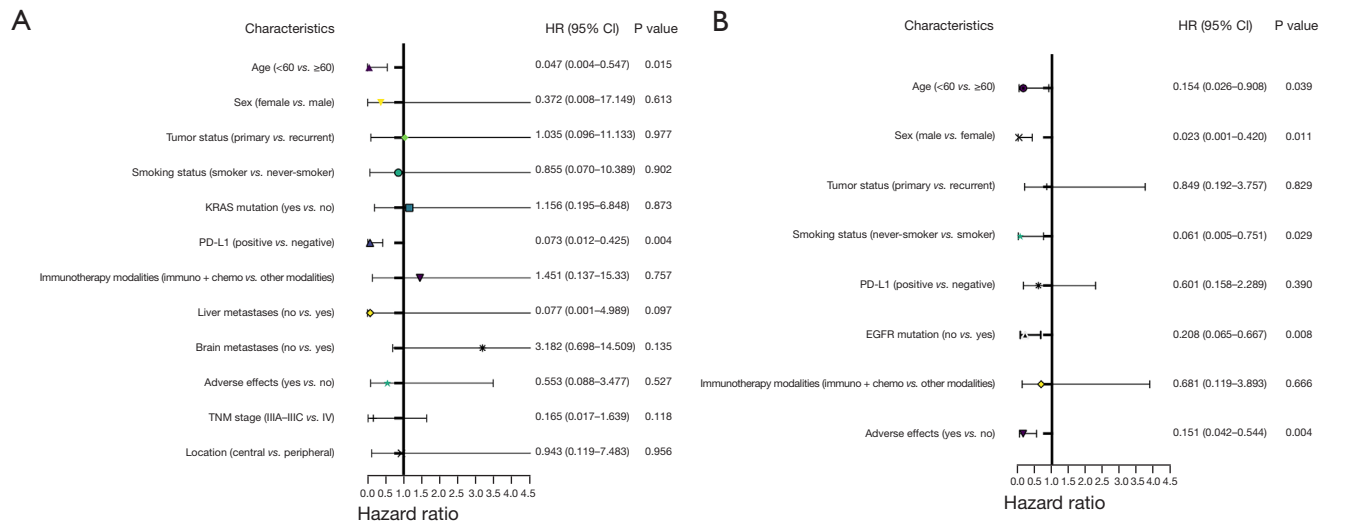


Figure 5 Forest plot of the Cox proportional hazard multivariable modeling of overall survival. (A) Multivariate analysis of overall survival in patients with lung adenocarcinoma who received immunotherapy in the first-line. (B) Multivariate analysis of overall survival in patients with lung adenocarcinoma who received immunotherapy in the second-line and above. HR, hazard ratios; 95% CI, 95% confidence interval; KRAS, Kirsten rat sarcoma viral oncogene homolog; PD-L1, programmed death receptor ligand 1; immuno + chemo, immunotherapy plus chemotherapy; TNM stage, tumor-node-metastasis stage; EGFR, epidermal growth factor receptor.

status, smoking status, driver gene mutation status, and so on (14,27-29). These factors were fully considered in our present study. Gainor *et al.* reported that the degree of smoking in patients is correlated with immunotherapy efficacy. Their study found that never and light smokers had relatively shorter PFS and duration of overall response (DOR) compared to heavy smokers, although the difference was not statistically significant (14). This is consistent with our findings; statistical analysis in the present study showed that PFS was markedly longer in smoking patients with lung adenocarcinoma receiving immunotherapy compared to non-smokers.

In addition, previous studies have explored the relationship between different driver gene mutations and immunotherapy efficacy. Liu *et al.* confirmed that NSCLC patients with KRAS mutations have notable immunotherapy clinical benefits (30). Furthermore, the clinical study conducted by Skoulidis *et al.* found that the change of liver kinase B1/serine-threonine kinase 11 (STK11/LKB1) is the most common genomic driver of primary resistance to PD-1 inhibitors in lung adenocarcinoma patients with KRAS mutations (31). In this study, due to the relatively small number of patients enrolled, we did not conduct a subgroup analysis of the specific subtypes of KRAS mutation. Notably, patients with KRAS mutations in this study achieved surprising survival outcomes after immunotherapy.

Previously, the AMG510 clinical study, which included 59 NSCLC patients with KRAS p.G12C mutation, reported a median PFS of 6.3 months (range, 0.0+ to 14.9 months) after receiving the KRAS p.G12C inhibitor, Sotorasib, with an ORR of 32.2% and the disease control rate (DCR) of 88.1% (32). In our study, 14 patients with KRAS p.G12C mutation who received immunotherapy were screened, and the results showed that the mean PFS was 17.649 months [range, 11.607 to 23.690 months; since only five patients (35.7%) suffered disease progression before the last follow-up, the median PFS could not be calculated], the ORR was 57.1%, and the DCR was 100.0%. This result suggests that immunotherapy is a good clinical option for patients with KRAS G12C mutations. However, only 14 patients with KRAS p.G12C mutation were included in this study, and thus, a statistical analysis could not be conducted, as a larger patient population is needed for verification.

In addition, the results of our study showed that patients with TP53 mutations achieved a better OS after received second-line and above immunotherapy. However, a study conducted by Sun *et al.* found that not all types of TP53 mutations are the same in predicting the efficacy of lung adenocarcinoma patients treated with ICIs. Their study

Table 3 Best response outcomes of different clinical characteristic factors

Variables	Number	CR	PR	SD	PD	NA	ORR	DCR	P value
Age (years)									0.445
<60	69	1	20	32	19	0	30.43%	76.81%	
≥60	132	0	37	68	26	1	28.03%	79.55%	
Sex									0.037
Male	154	1	51	72	29	1	33.77%	80.52%	
Female	47	0	6	28	13	0	12.77%	72.34%	
Tumor status									0.097
Recurrent	59	0	11	35	12	1	18.64%	77.97%	
Primary	142	1	46	65	30	0	33.10%	78.87%	
Smoking status									0.031
Smoker	117	0	40	58	19	0	34.19%	83.76%	
Never-smoker	84	1	17	42	23	1	21.43%	71.43%	
EGFR mutation									<0.001
Yes	28	0	1	13	14	0	3.57%	50.00%	
No	162	1	53	81	26	1	33.33%	83.33%	
TP53 mutation									0.372
Yes	70	0	23	33	14	0	32.86%	80.00%	
No	44	1	10	25	8	0	25.00%	81.82%	
KRAS mutation									<0.001
Yes	47	0	25	17	4	1	53.19%	89.36%	
No	95	1	17	55	22	0	18.95%	76.84%	
PD-L1									0.001
Positive	83	1	31	35	16	0	38.55%	80.72%	
Negative	40	0	3	23	14	0	7.50%	65.00%	
TNM stage									0.052
IIIA–IIIC	30	0	11	18	1	0	36.67%	96.67%	
IV	171	1	46	82	41	1	27.49%	75.44%	
Liver metastases									0.325
Yes	19	0	3	9	7	0	15.79%	63.16%	
No	182	1	54	91	35	1	30.22%	80.22%	
Brain metastases									0.609
Yes	69	0	18	37	13	1	26.09%	79.71%	
No	132	1	39	63	29	0	30.30%	78.03%	

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Number	CR	PR	SD	PD	NA	ORR	DCR	P value
Location									0.490
Central	38	0	15	16	7	0	39.47%	81.58%	
Peripheral	121	1	30	63	26	1	25.62%	77.69%	
Line of immunotherapy									<0.001
First-line	101	1	42	42	16	0	42.6%	84.2%	
Second-line and above	100	0	15	58	26	1	15.0%	73.0%	
Immunotherapy modalities									0.022
Immuno+chemo*	117	1	39	62	15	0	34.19%	87.18%	
Other combinations**	21	0	4	11	6	0	19.05%	71.43%	
Immunotherapy alone	63	0	14	27	21	1	22.22%	65.08%	
Adverse effects									<0.001
One AE	68	1	26	37	3	1	39.71%	94.12%	
Two or more AEs	18	0	4	10	4	0	22.22%	77.78%	
No	47	0	5	18	24	0	10.64%	48.94%	

*, immunotherapy combined with chemotherapy; **, other combination modalities refer to combinations other than immunotherapy combined with chemotherapy, including the combination of bevacizumab, anlotinib, and EGFR-TKIs. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available; ORR, objective response rate; DCR, disease control rate; EGFR, epidermal growth factor receptor; TP53, tumor protein p53; KRAS, Kirsten rat sarcoma viral oncogene homolog; TNM stage, tumor node metastasis stage; PD-L1, programmed cell death-ligand 1; AEs, adverse effects.

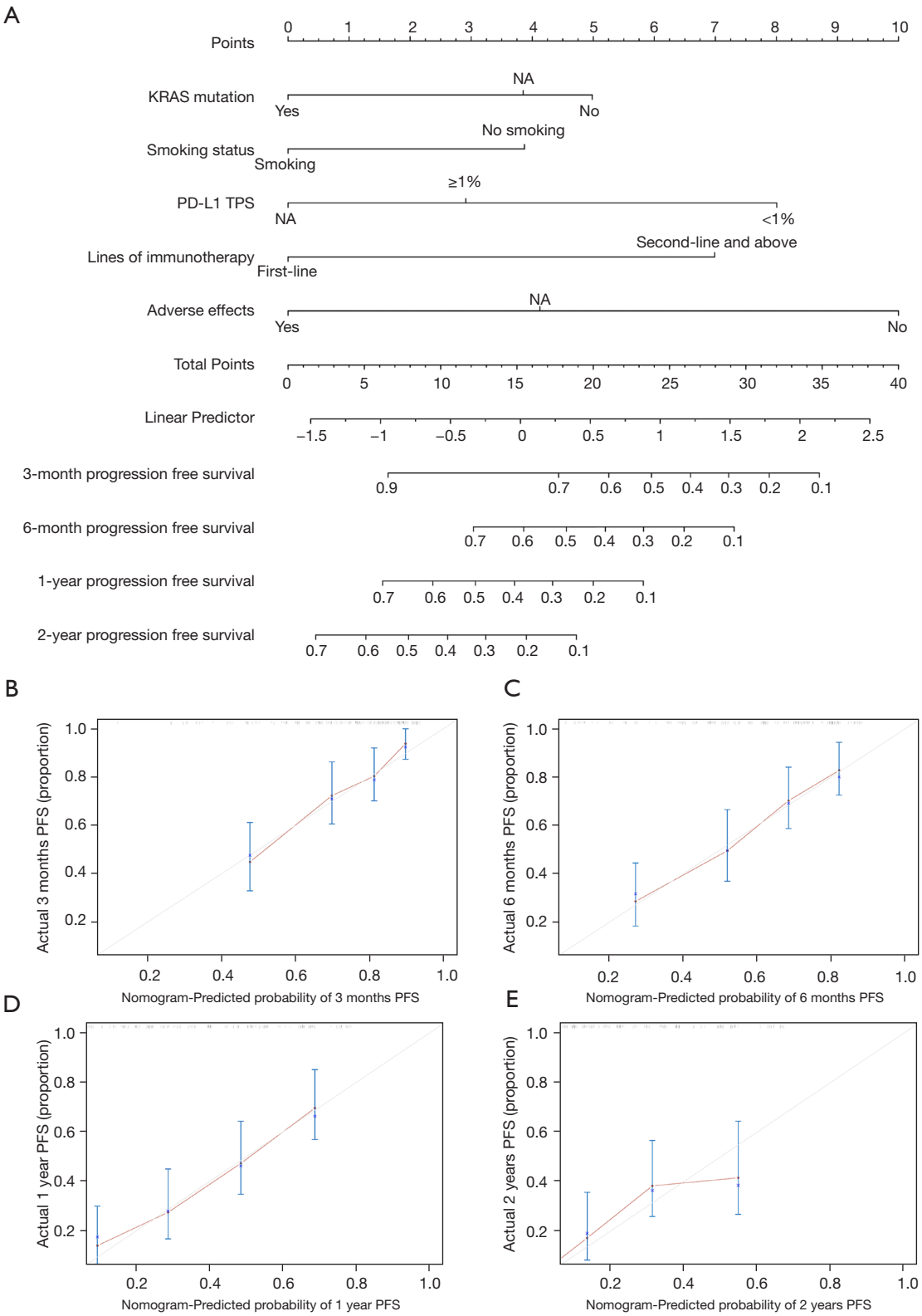
showed that patients with TP53 missense mutations benefited more from anti-PD-L1/PD-1 treatment compared to those with nonsense mutations. However, all patients with either missense or nonsense TP53 mutations responded well to nivolumab plus ipilimumab therapy (33).

Some previous studies have attempted to predict the efficacy of immunotherapy and identify the cohort of patient who would benefit from immunotherapy. Several papers have sought to identify biomarkers that can predict immunotherapy efficacy, such as TMB levels (18), titin (TTN) mutations (34), beta-2-microglobuli (B2M) gene expression (35), EPH receptor A5 (EPHA5) mutations (36), and thymocyte selection-associated high mobility group box (TOX) expression (37). A 17-immune-related genes prognostic model has also been constructed to predict the survival rate and response to ICIs therapy in patients with lung adenocarcinoma (38). Most of these studies have focused on molecular markers, gene regulation, and the immune microenvironment. There is a currently lack of real-world data about how to better predict the efficacy of immunotherapy in clinical practice. Therefore, a prognostic model was constructed in the present study, which aims to determine the ideal patient population for immunotherapy based on the analysis of real-world clinical data and further improve the accuracy of clinicians seeking to identify the beneficiaries of immunotherapy based on existing evidence-based medicine.

However, this study also has some limitations that should be noted. Firstly, the major limitation of this study was its retrospective design. Secondly, the total number of patients enrolled in this study was relatively small. Furthermore, when verifying the predictive model, the simple resampling method was adopted for internal verification due to the small sample size, and thus, the expansion of the model still needs to be verified externally with large samples.

Conclusions

In this study, we found that lung adenocarcinoma patients who were smoker, had KRAS mutations, were treated with first-line immunotherapy and had immune-related adverse reactions were more likely to have a survival benefit



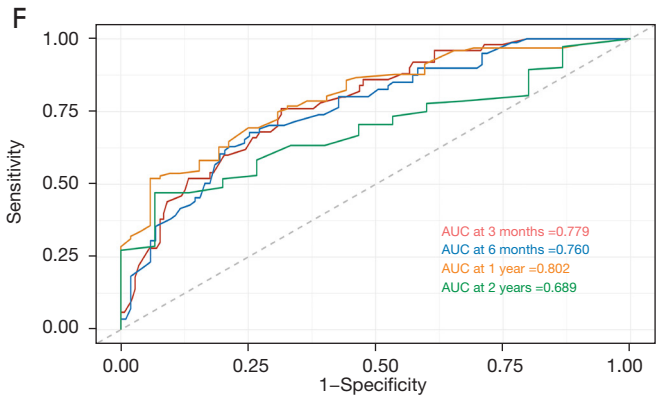


Figure 6 A nomogram for progression-free survival prediction of lung adenocarcinoma patients receiving immunotherapy was constructed. (A) The variables included in this nomogram refer to the Cox regression results of PFS. To use the nomogram, the score for each variable should be calculated based on the clinicopathological features and treatment of the patient and then added up to obtain the total score. Then, based on the total score, draw a vertical line down the total points axis to the survival axes to determine the probability of progression-free survival at 3 months, 6 months, 1 year, and 2 years. (B-E) Calibration curves of the 3 months, 6 months, 1 year, and 2 years PFS for lung adenocarcinoma patients receiving immunotherapy. The nomogram-predicted probability of PFS is plotted on the x-axis; actual PFS is plotted on the y-axis. (F) ROC curves of the nomogram to predict the sensitivity and specificity of 3-month, 6-month, 1-year and 2-year PFS. The AUC of the probability of PFS at 3 months, 6 months, 1 year and 2 years in the patients treated with immunotherapy. KRAS, Kirsten rat sarcoma viral oncogene homolog; PD-L1 TPS, programmed death receptor ligand 1 tumor proportion score; NA, not available; PFS, progression-free survival; AUC, area under the curve; ROC, receiver operating characteristic.

after ICI treatment. Also, the nomogram in this study can be used to some extent to predict the prognosis of lung adenocarcinoma patients after receiving immunotherapy.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1270/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1270/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1270/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Review Board of Shanghai Chest Hospital (Shanghai, China, No. IS21127) and was carried out in accordance with the requirements of the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all the patients before taking part.

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Supplementary

Table S1 Immunotherapy administration methods and doses

ICI drugs	Dose and usage
Nivolumab	3 mg/kg, 2W
Pembrolizumab	200 mg, 3W
Tislelizumab	200 mg, 3W
Sintilimab	200 mg, 3W
Camerelizumab	200 mg, 3W
Atezolizumab	1200 mg, 3W
Durvalumab	10 mg/kg, 2W or 20 mg/kg, 3W

ICI, immune checkpoint inhibitor; W, week.

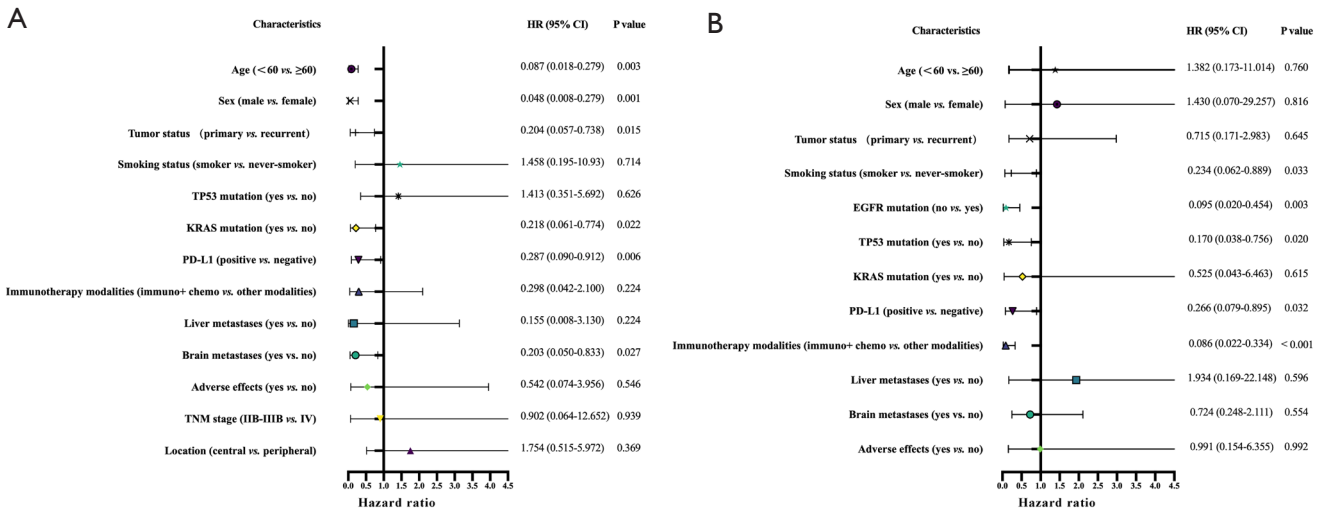

Figure S1 Forest plot of the Cox proportional hazard multivariable modeling of progression-free survival. (A) Multivariate analysis of progression-free survival in lung adenocarcinoma patients receiving first-line immunotherapy. (B) Multivariate analysis of progression-free survival in lung adenocarcinoma patients receiving second-line and above immunotherapy.

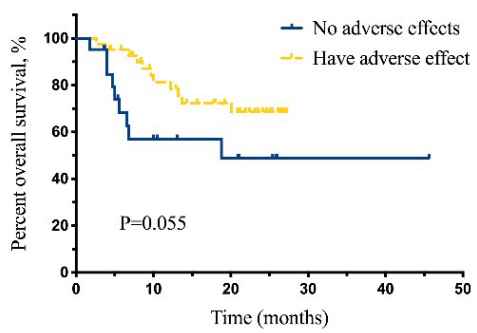

Figure S2 Overall survival of lung adenocarcinoma patients with and without adverse effects receiving first-line immunotherapy.

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