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*Original Article*

# Efficacy and adverse reaction risk factors of immunotherapy in advanced non-small cell lung cancer: a retrospective study

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**Abstract:** Objective: To evaluate the clinical efficacy of programmed cell death 1 (PD-1) inhibitors and identify risk factors for immune-related adverse reactions (irAEs) in patients with advanced non-small cell lung cancer (NSCLC). Methods: A retrospective analysis was performed on data from 224 advanced NSCLC patients treated at the First Affiliated Hospital of Kunming Medical University between January 2021 and December 2022. The patients were divided into two groups based on the presence of adverse reactions after treatment: the irAE group (n = 117) and the non-irAE group (n = 107). General clinical data and treatment-related indicators were compared between the two groups, and the clinical therapeutic effect and incidence of adverse events were statistically evaluated. Finally, the influencing factors of immune-related adverse reactions in the patients were analyzed, and a corresponding prediction model was established. Results: The median survival time of the 224 patients was 23.5 months, with 1-year and 3-year survival rates of 88.5% and 32.1%, respectively. A total of 117 patients (accounting for 53.3%) experienced treatment-related adverse reactions, including fatigue, nausea, rash, and pruritus. Univariate and multivariate analyses indicated that smoking history, number of treatment cycles, and concurrent targeted therapy (TKI) were independent risk factors for immunotherapy-related adverse reactions in advanced NSCLC patients. The area under the curve (AUC) of the prediction model constructed based on the above factors was 0.768. Conclusion: Patients with advanced NSCLC receiving immune checkpoint inhibitors (ICIs) have a high incidence of irAEs, which are associated with their baseline patient characteristics. Smoking history, number of treatment cycles, and concurrent targeted therapy were identified as independent contributors.

**Keywords:** Advanced non-small cell lung cancer, immunotherapy, programmed death receptor-1, adverse reactions, influencing factors

## Introduction

Advanced non-small cell lung cancer (NSCLC) is one of the most common malignancies in clinical practice, accounting for approximately 80%-85% of all lung cancer cases. The disease is often asymptomatic in early stages, and most patients are diagnosed at an advanced stage, precluding resection and resulting in a poor prognosis [1, 2]. Recent clinical data indicate that the 5-year survival rate of patients with advanced NSCLC is less than 15%. Although conventional radiotherapy and chemotherapy can control tumor progression and prolong survival to some extent, they have limitations, including low tumor specificity, substantial toxicity, and a high risk of drug resistance, which seriously affect patients' treatment compliance and quality of life [3, 4]. With the rapid advancement of tumor immunotherapy, programmed cell death-1 (PD-1) inhibitors have become a cornerstone in the treatment of advanced NSCLC. By relieving tumor-induced immunosuppression and activating autologous immune cells to kill tumor cells, PD-1 inhibitors have significantly improved the survival and prognosis of patients with advanced disease [5, 6]. Currently, PD-1 inhibitors are widely used in first-line, second-line, and third-line treatment of advanced NSCLC. However, considerable interpatient heterogeneity exists. While some patients show limited responses, approximate-

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ly half experience treatment-related toxicities of varying severity, including fatigue, nausea, and rash. Severe cases may require treatment interruption or even become life-threatening, thereby limiting the clinical utility of these agents [7, 8].

Most previous studies on PD-1 inhibitors in advanced NSCLC have focused on efficacy, with less attention to irAE patterns and risk factors. Although several studies have reported risk factors for irAEs, most are restricted to univariate analyses or underpowered exploratory studies. Key influencing factors remain unclear, and reliable, validated predictive models to guide clinical intervention are lacking [9]. In contrast to many previous studies, the potential added value of this study lies in the following aspects: (1) it is based on real-world clinical data from Southwest China, reflecting the treatment characteristics of the local population; (2) it simultaneously analyzes both efficacy and adverse reaction outcomes, providing a more comprehensive clinical reference; (3) it constructs a simple predictive model based on three readily available clinical indicators (smoking history, number of treatment cycles, and concurrent targeted therapy), facilitating clinical application. Elucidating risk factors for PD-1 inhibitor-related irAEs and establishing a validated predictive model is clinically significant for early identification of high-risk patients, development of targeted interventions, reduction of adverse reactions, and improvement of both treatment safety and efficacy.

## General information and methods

### *General information*

A retrospective analysis was performed on the clinical data of 224 patients diagnosed with advanced non-small cell lung cancer who were admitted to the Oncology Department of the First Affiliated Hospital of Kunming Medical University from January 2021 to December 2022. All patients had pathologically or cytologically confirmed advanced NSCLC (Stage IIIB and IV) through histopathological or cytological examination and received treatment with programmed death receptor-1 (PD-1) inhibitors. Based on the occurrence of immune-related adverse reactions after treatment, all patients were divided into the irAE group (n = 117) and the non-irAE group (n = 107). This study has been approved by the First Affiliated Hospital of Kunming Medical University ethics committee (Ethical Approval No.: L-2026-263).

### *Inclusion criteria*

1. Aged between 18 and 75 years old; 2. Patients diagnosed with advanced non-small cell lung cancer (Stage IIIB, IV) by histopathological or cytological examination, according to the “Chinese Society of Clinical Oncology (CSCO) guidelines for the Diagnosis and Treatment of Non-small Cell Lung Cancer (2021 Edition)” [10]; 3. All patients received monotherapy or combination therapy with PD-1 inhibitors (such as pembrolizumab, nivolumab); 4. Patients receiving first-line systemic therapy; 5. Before treatment, indicators including liver and kidney function, blood routine, and coagulation function were basically normal, without severe organ dysfunction; 6. Patients with complete clinical data, treatment records and follow-up data; 7. Patients who had not received other immunotherapy, chemo-radiotherapy or targeted therapy in the past month. Patients received various treatment regimens, including PD-1 monotherapy, PD-1 plus chemotherapy, and PD-1 plus targeted therapy. Due to the limited sample size, subgroup analysis according to treatment regimen was not performed. Future studies with larger sample sizes are needed to assess whether the predictive value of identified risk factors varies across different treatment regimens

### *Exclusion criteria*

1. Previous severe mental illness (such as severe depression, schizophrenia) or neurological diseases (such as cerebral hemorrhage, cerebral infarction sequelae); 2. Patients with other malignant tumor history; 3. Patients who have used glucocorticoids and immunomodulators in the past 1 month; 4. Severe infection, active pulmonary tuberculosis, autoimmune diseases (such as rheumatoid arthritis, systemic lupus erythematosus); 5. Pregnant or lactating women; 6. Incomplete information; 7. Heart, liver and kidney important organ dysfunction; 8. KPS score < 60 points, or unable to tolerate the study assessments.

### *Data collection*

Data were collected from the hospital’h electronic medical record system, treatment logs,

and follow-up records, supplemented by standardized scale assessments. The specific collection contents are as follows: 1. General information: including patients' gender, age, height, weight, smoking history (defined as ≥ eficigarette/day for 1 year), drinking history, tumor pathological type (adenocarcinoma, squamous cell carcinoma, other types), tumor stage (stage IIIB, stage IV), previous treatment history (whether or not received radiotherapy and chemotherapy), combined with underlying diseases (e.g., hypertension, diabetes, coronary heart disease). 2. Lung cancer treatment-related indicators: including the type of PD-1 inhibitor, treatment cycle, treatment plan, dosage and frequency of administration. 3. Adverse reactions and follow-up: The occurrence of adverse reactions in patients was recorded, including type, time of occurrence, severity (according to CTCAE 5.0 standard classification), treatment and outcome.

*Observation indicators*

*Main observation indexes:* Treatment response was assessed per RECIST 1.1 and categorized as complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD). Median survival time, and 1- and 3-year survival rates were calculated [11].

*Adverse reactions:* The number and incidence of treatment-related adverse reactions in all patients were counted, and the main types and severity of adverse reactions were identified.

*Influencing factors of adverse reactions to chemotherapy related indicators:* Including smoking history, PD-1 inhibitor treatment cycle, whether combined with targeted therapy, age, gender, tumor pathological type, tumor stage, etc. Secondary observation indicators: Pre- and post-treatment changes were assessed in both groups for quality of life (assessed by the EORTC QLQ-C30 scale, covering physical, role, emotional, cognitive, and social functioning domains) and for serum levels of CEA, SCC, and NSE [12].

*Data statistics*

SPSS 26.0 was used for data analysis. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared using the independent samples t-test. Non-normally distributed data were expressed as median (quartiles) [M (Q1, Q3)] and compared using the Mann-Whitney U test (non-parametric test). Categorical variables were expressed as [n (%)] and compared using the $\chi^2$ test or Fisher's exact test, as appropriate.

Univariate analysis was performed to identify factors associated with PD-1 inhibitor-related adverse reactions. Variables with $P < 0.10$ in univariate analysis were entered into a multivariate logistic regression model (entry threshold set at $P < 0.10$ to avoid excluding potential predictors). Forward stepwise selection was used for variable selection, with entry criteria set at $P < 0.05$ and removal criteria at $P > 0.10$.

Receiver operating characteristic (ROC) curves were used to evaluate the discriminative ability of the prediction model, and the area under the curve (AUC) was calculated with its 95% confidence interval (CI). To assess the risk of overfitting, 10-fold cross-validation was performed, and the cross-validated AUC was reported. Kaplan-Meier survival curves were generated to describe the overall survival of the entire cohort; no log-rank comparison was performed as the curve represents the entire study population. $P < 0.05$ was considered statistically significant unless otherwise specified.

## Results

*Survival and adverse reactions of patients in this group*

The median overall survival was 23.5 ± 3.0 months, with 1- and 3-year survival rates of 88.5% and 32.1%, respectively. During the treatment period, a total of 117 patients (53.3%) had treatment-related adverse reactions, among which fatigue (30.4%), nausea (23.2%), rash (20.1%), pruritus (17.0%) were common. In addition, diarrhea, hypothyroidism and immune pneumonia also accounted for a certain proportion. The specific results are shown in **Tables 1**, **2** and **Figure 1**.

*Baseline characteristics of patients with and without irAEs*

A total of 224 patients with advanced non-small cell lung cancer were enrolled and divided into an irAE group (n = 117) and a non-irAE

**Table 1.** Patient survival and treatment-related adverse reactions

| Parameter | Value |
|---|---|
| Overall survival | |
| Median survival time (months) | 23.5 |
| 1-year survival rate [%] | 88.5 |
| 3-year survival rate [%] | 32.1 |
| Treatment-related adverse reactions | |
| The total number of cases [n (%)] | 117 (53.3) |
| Fatigue [n (%)] | 68 (30.4) |
| Nausea [n (%)] | 52 (23.2) |
| Rash [n (%)] | 45 (20.1) |
| Pruritus [n (%)] | 38 (17.0) |
| Diarrhea [n (%)] | 31 (13.8) |
| Hypothyroidism [n (%)] | 24 (10.7) |
| Immune pneumonia [n (%)] | 12 (5.4) |
| Other [n (%)] | 28 (12.5) |

group (n = 107) based on the occurrence of immune-related adverse events after treatment. Baseline data comparisons are shown in **Table 1**.

No significant differences were observed between the two groups in age, gender, pathological type, clinical stage, PD-L1 expression level, or treatment plan (all P > 0.05), indicating balanced and comparable baseline data.

Further analysis revealed that the irAE group had significantly higher proportions of patients with a history of smoking (61.5% vs. 44.9%, P = 0.016), immune checkpoint inhibitor therapy cycles > 4 cycles (67.5% vs. 51.4%, P = 0.009), and combined targeted therapy (35.9% vs. 22.4%, P = 0.027). Univariate and multivariate analyses confirmed these three factors as independent risk factors for immunotherapy-related adverse reactions (**Table 3**).

*Comparison of serological data between groups*

As summarized in **Table 3**, pre-treatment serological comparisons revealed no statistically significant differences between the irAE group and the non-irAE group across all assessed parameters, including liver function parameters (alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin), renal function parameters (blood urea nitrogen, serum creatinine, estimated glomerular filtration rate), lung cancer-associated biomarkers (carcinoembryonic antigen, cytokeratin 19 fragment, neuron-specific enolase), and the composite inflammatory marker neutrophil-to-lymphocyte ratio (NLR) (all P > 0.05). These results suggest that the two groups were generally comparable in baseline serological profiles, indicating that no pre-treatment serological parameter could serve as a predictor for immunotherapy-related adverse events in this cohort (**Table 4**).

*Comparison of treatment efficacy between groups*

Clinical efficacy comparisons are shown in **Table 5**. In the irAE group, the objective response rate (ORR) was 42.7% and the disease control rate (DCR) was 76.1%. In the non-irAE group, the ORR was 57.0% and the DCR was 85.0%. Both differences were statistically significant (both P < 0.05), indicating that patients without adverse reactions had significantly higher response rates than those with adverse reactions.

*Multivariate analysis of adverse reactions in patients with advanced non-small cell lung cancer receiving Immune checkpoint inhibitor therapy*

Variables with significant differences in univariate analysis (smoking history, immune checkpoint inhibitor therapy cycle, combined targeted therapy) were entered into a multivariate logistic regression model to identify independent risk factors for immunotherapy-related adverse reactions in advanced non-small cell lung cancer. The results demonstrated that smoking history (OR = 2.156, 95% CI: 1.284-3.621, P = 0.004), > 4 cycles of immune checkpoint inhibitor therapy (OR = 2.438, 95% CI: 1.456-4.082, P = 0.001), and combined targeted therapy (OR = 1.982, 95% CI: 1.156-3.398, P = 0.013) were independent risk factors for immunotherapy-related adverse reactions (**Tables 6** and **7**).

*Establishment of adverse reaction model in patients with advanced non-small cell lung cancer receiving Immune checkpoint inhibitor therapy*

The results of this study showed that the combination of smoking history, Immune check-

**Table 2.** Number at risk for overall survival

| Time (months) | 0 | 6 | 12 | 18 | 24 | 30 | 36 |
|---|---|---|---|---|---|---|---|
| Number at risk | 224 | 210 | 198 | 175 | 140 | 95 | 72 |
| Deaths | 0 | 14 | 12 | 23 | 35 | 45 | 23 |

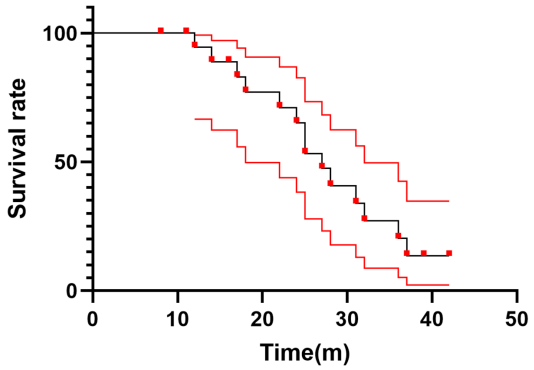



**Figure 1.** Kaplan-Meier survival curve of the entire study cohort (N = 224). The curve shows overall survival for the entire cohort (N = 224); no log-rank test was applied.

point inhibitor therapy cycle, and targeted therapy was used to establish an adverse reaction model curve for patients with advanced non-small cell lung cancer receiving Immune checkpoint inhibitor therapy. The AUC of the model curve was 0.768, 95% CI was 0.614, 0.923, and the Hosmer-Lemeshow test chi-square value was 9.565, P = 0.297, the model was stable, as shown in **Figure 2**. In this study, the accuracy of the prediction model was verified by the calibration curve. As shown in **Figure 3**, when compared with the observed probabilities, the probability distribution predicted by the model is very close to the diagonal, indicating a high degree of agreement between the predicted and actual values. The $R^2$ of goodness-of-fit test was 0.707, indicating that the model explained 70.7% of the observed variation, confirming its good calibration accuracy. These results show that the prediction model established in this study not only has clinical identification ability, but also is accurate and reliable, and the predicted risk is highly consistent with the actual risk.

*Comparison of quality of life between the two groups of patients*

No significant differences were observed in quality-of-life scores between the two groups before treatment (all P > 0.05), indicating comparability. After treatment, the irAE group had significantly lower scores than the non-irAE group in physiological function (68.2 ± 9.1 vs. 78.5 ± 7.6), role function (64.5 ± 9.8 vs. 75.2 ± 8.4), emotional function (61.3 ± 10.5 vs. 72.8 ± 9.1), cognitive function (66.8 ± 9.2 vs. 75.6 ± 8.0), social function (62.5 ± 10.1 vs. 73.4 ± 8.7), and overall health status (64.2 ± 9.5 vs. 76.8 ± 7.9), with statistically significant differences (all P < 0.001). These results suggest that patients with immunotherapy-related adverse reactions experienced a marked decline in quality of life. Therefore, close monitoring and timely intervention of adverse reactions are essential in clinical practice to improve patient quality of life (**Table 8**).

*Association between number of irAE types and treatment response*

Patients in the irAE group were further divided into a mild group (1-2 types, n = 68) and a severe group (≥ 3 types, n = 49) based on the number of adverse reaction types. Treatment efficacy comparisons between the two groups are shown in **Table 9**.

The mild group had significantly higher objective response rate (48.5% vs. 34.7%) and disease control rate (82.4% vs. 67.3%) than the severe group, with statistically significant differences (both P < 0.05). These findings indicate that a greater number of adverse reactions is associated with reduced treatment benefit.

*Comparison of serum CEA, SCC, and NSE levels before and after treatment between the adverse event group and the non-irAE group in advanced NSCLC patients receiving PD-1 inhibitors*

No significant differences were observed in baseline CEA, SCC, or NSE levels between the two groups (all P > 0.05). After treatment, the adverse event group had significantly lower levels of CEA (12.8 ± 6.2 vs. 28.5 ± 11.4 ng/mL), SCC (2.6 ± 1.1 vs. 5.2 ± 2.0 ng/mL), and NSE (9.5 ± 3.4 vs. 15.6 ± 5.1 ng/mL) than the non-irAE group (all P < 0.05). Additionally, both

**Table 3.** Comparison of baseline data between the reaction and non-irAE groups

| | IrAE group (n = 117) | Non-irAE group (n = 107) | Statistic | *P* value |
|---|---|---|---|---|
| General information | | | | |
| Age (years) | 62.4 ± 8.7 | 61.9 ± 9.1 | 0.422 | 0.673 |
| Gender [n (%)] | | | 0.227 | 0.634 |
| Male | 68 (58.1) | 60 (56.1) | | |
| Female | 49 (41.9) | 47 (43.9) | | |
| Smoking history [n (%)] | | | 5.824 | 0.016 |
| Yes | 72 (61.5) | 48 (44.9) | | |
| No | 45 (38.5) | 59 (55.1) | | |
| Pathological type [n (%)] | | | 0.305 | 0.581 |
| Adenocarcinoma | 78 (66.7) | 69 (64.5) | | |
| Squamous carcinoma | 39 (33.3) | 38 (35.5) | | |
| Clinical stage [n (%)] | | | 0.079 | 0.779 |
| Stage III | 45 (38.5) | 40 (37.4) | | |
| Stage IV | 72 (61.5) | 67 (62.6) | | |
| PD-L1 expression level [n (%)] | | | 0.062 | 0.969 |
| < 1% | 25 (21.4) | 23 (21.5) | | |
| 1-49% | 48 (41.0) | 45 (42.1) | | |
| ≥ 50% | 44 (37.6) | 39 (36.4) | | |
| Treatment plan [n (%)] | | | 0.008 | 0.929 |
| PD-1 inhibitor monotherapy | 58 (49.6) | 53 (49.5) | | |
| PD-1 inhibitor combined with chemotherapy | 59 (50.4) | 54 (50.5) | | |
| Immune checkpoint inhibitor treatment cycle [n (%)] | | | 6.731 | 0.009 |
| ≤ 4 cycles | 38 (32.5) | 52 (48.6) | | |
| > 4 cycles | 79 (67.5) | 55 (51.4) | | |
| Combined with targeted therapy [n (%)] | | | 4.892 | 0.027 |
| Yes | 42 (35.9) | 24 (22.4) | | |
| No | 75 (64.1) | 83 (77.6) | | |

**Table 4.** Comparison of baseline serological parameters between the two groups

| Parameters | IrAE group (n = 117) | Non-irAE group (n = 107) | Statistic | *P* value |
|---|---|---|---|---|
| Liver function | | | | |
| Alanine aminotransferase (U/L) | 28.6 ± 10.2 | 27.9 ± 9.8 | 0.524 | 0.601 |
| Aspartate aminotransferase (U/L) | 26.8 ± 9.5 | 26.1 ± 9.1 | 0.563 | 0.574 |
| Total bilirubin (μmol/L) | 12.4 ± 4.2 | 12.1 ± 4.0 | 0.548 | 0.584 |
| Direct bilirubin (μmol/L) | 4.2 ± 1.5 | 4.0 ± 1.4 | 1.025 | 0.306 |
| Renal function | | | | |
| Blood urea nitrogen (mmol/L) | 5.3 ± 1.4 | 5.1 ± 1.3 | 1.109 | 0.268 |
| Serum creatinine (μmol/L) | 68.5 ± 15.2 | 66.8 ± 14.6 | 0.849 | 0.397 |
| Estimated glomerular filtration rate (mL/min/1.73 $m^2$) | 92.4 ± 12.5 | 94.1 ± 13.0 | 0.987 | 0.325 |
| Lung cancer markers | | | | |
| Carcinoembryonic antigen (ng/mL) | 15.8 ± 8.6 | 14.9 ± 8.1 | 0.802 | 0.423 |
| Cytokeratin 19 fragment (ng/mL) | 8.6 ± 4.2 | 8.2 ± 3.9 | 0.735 | 0.463 |
| Neuron specific enolase (ng/mL) | 18.5 ± 7.8 | 17.9 ± 7.4 | 0.587 | 0.558 |
| Inflammatory composite marker | | | | |
| Neutrophil-to-lymphocyte ratio (NLR) | 2.6 ± 1.2 | 2.4 ± 1.1 | 1.245 | 0.214 |

**Table 5.** Comparison of treatment response between irAE and non-irAE groups [n (%)]

| Groups | CR | PR | SD | PD | ORR | DCR |
|---|---|---|---|---|---|---|
| irAE group | 5 (4.3) | 45 (38.5) | 39 (33.3) | 28 (23.9) | 50 (42.7) | 89 (76.1) |
| Non-irAE group | 8 (7.5) | 53 (49.5) | 30 (28.0) | 16 (15.0) | 61 (57.0) | 91 (85.0) |
| $\chi^2$ value | | | | | 4.621 | 3.892 |
| *P* value | | | | | 0.032 | 0.048 |

**Table 6.** Variable assignment table

| Variables | Definition |
|---|---|
| Dependent variable | |
| Adverse reactions related to immunotherapy | 0 = not happening, 1 = happening |
| Independent variable | |
| Smoking history | 0 = none, 1 = have |
| Immune checkpoint inhibitor treatment cycle | 0 = ≤ 4 cycles, 1 = > 4 cycles |
| Combined targeted therapy | 0 = No, 1 = Yes |

**Table 7.** Multivariate logistic regression analysis of immunotherapy-related adverse reactions

| Variables | β coefficient | SE | Wald $\chi^2$ | OR value | 95% CI | *P* value |
|---|---|---|---|---|---|---|
| Smoking history (yes vs. no) | 0.768 | 0.265 | 8.403 | 2.156 | 1.284-3.621 | 0.004 |
| Immune checkpoint inhibitor therapy cycle (> 4 cycles vs. ≤ 4 cycles) | 0.891 | 0.262 | 11.556 | 2.438 | 1.456-4.082 | 0.001 |
| Combined with targeted therapy (yes vs. no) | 0.684 | 0.276 | 6.136 | 1.982 | 1.156-3.398 | 0.013 |
| Intercept | -1.452 | 0.318 | 20.852 | 0.234 | - | < 0.001 |

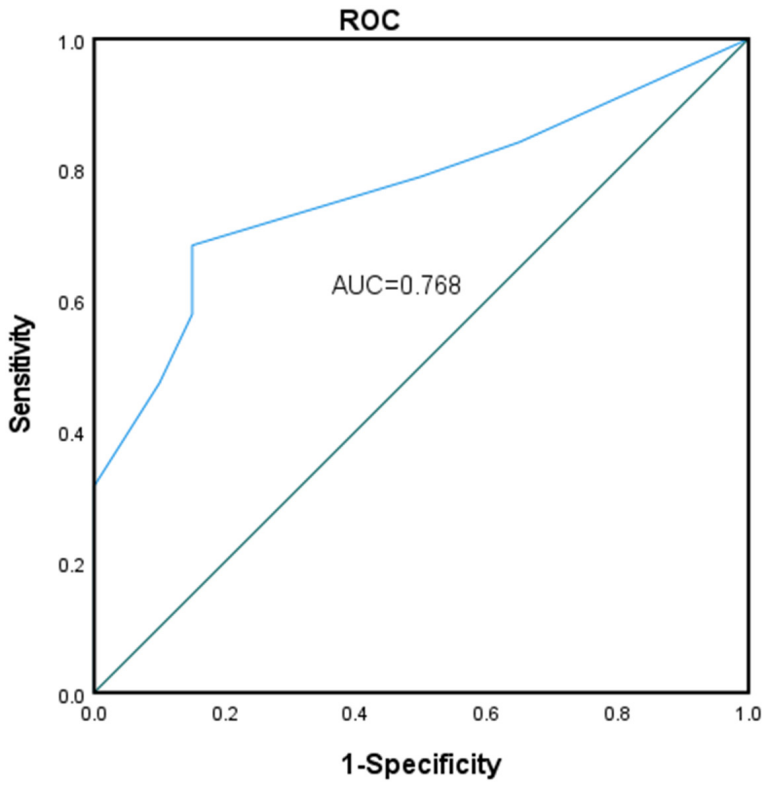



**Figure 2.** ROC curve for the prediction model of irAEs.

groups exhibited significant reductions in all tumor markers after treatment compared with baseline (all P < 0.001) (**Table 10**).

## Discussion

In recent years, ICIs have provided long-term survival benefits owing to their distinct antitumor mechanisms. They have become the core regimen for first-line and post-line treatment of advanced non-small cell lung cancer and are widely used in clinical practice [13, 14]. However, with the popularization of immunotherapy, immune-related adverse reactions have gradually become a problem that cannot be ignored in clinical practice. These irAEs can involve multiple organ systems, compromising treat-

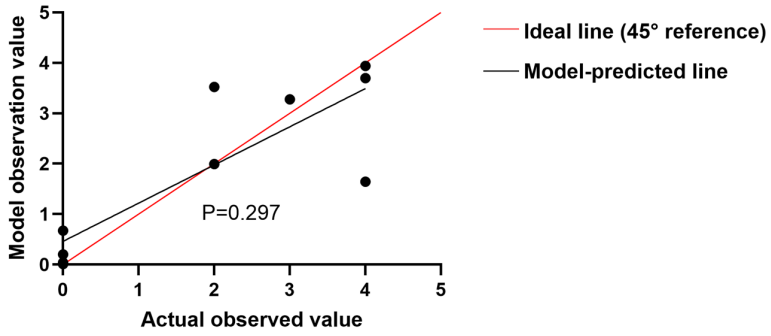



**Figure 3.** Calibration curve for the irAE types and treatment response.

ment adherence, leading to treatment interruptions, serious organ damage, and potentially life-threatening complications. At the same time, it will directly affect the overall treatment effect and the long-term quality of life of patients [15-17]. At present, the pathogenesis of immune-related adverse reactions has not been fully clarified. It is known that it is related to many factors such as excessive activation of the body's immune system, imbalance of immune tolerance, and antigen cross-reaction. Exploring independent risk factors for adverse reactions and constructing accurate risk prediction models have important clinical value for early screening, individualized intervention, and optimization of treatment management in high-risk populations.

The overall survival in our cohort was broadly consistent with the results of previous clinical studies at home and abroad, which confirmed the effective anti-tumor effect of immunotherapy in advanced non-small cell lung cancer, which could effectively prolong the survival cycle of patients and improve the long-term survival outcome [18]. The total incidence of adverse reactions during treatment was 53.3%. Mild to moderate adverse reactions such as fatigue, nausea, rash, and pruritus were the most common, and the incidence of diarrhea, hypothyroidism, and immune pneumonia was relatively low. The overall adverse reaction spectrum was consistent with the common adverse reaction characteristics of immune checkpoint inhibitors [19, 20].

Previous studies have found that the occurrence of immune-related adverse reactions is not a random event, but is closely related to the patient's own and treatment-related factors [21]. In this study, univariate and multivariate Logistic regression analysis confirmed that smoking history, ICI therapy cycle > 4 cycles, combined with targeted therapy were independent risk factors for immunotherapy-related adverse reactions in patients with advanced non-small cell lung cancer. The specific mechanism analysis is as follows. First, smoking history significantly increased the risk of irAEs. Chronic tobacco exposure damages the respiratory mucosal barrier and disrupts the local immune microenvironment. At the same time, it will affect the proliferation and activation of immune cells, leading to the dysfunction of immune cells such as T lymphocytes and macrophages, and breaking the balance of immune tolerance. On the basis of activating systemic anti-tumor immunity by immunotherapy, immune cells are over-activated and unbalancedly regulated, which is more likely to cause immune attack on normal tissues and organs, and then induce various immune-related adverse reactions. At the same time, long-term smoking also aggravates the body's oxidative stress response, further amplifies immune inflammatory damage, and increases the probability of adverse reactions. This result is also consistent with previous studies on risk factors related to tumor immunotherapy [22]. Second, the long treatment cycle of Immune checkpoint inhibitor agents is an important variable risk factor. The mechanism of action of immune checkpoint inhibitors is to continuously block the Immune checkpoint inhibitor pathway and activate the anti-tumor immune response. With the prolongation of the treatment cycle, drug exposure accumulates over time, leading to sustained immune activation and progressive disruption of immune homeostasis, so that the immune cells are over-activated and the immune inflammatory response continues to amplify, which will not only increase the risk of adverse reactions, but also increase the severity of adverse reactions. Third, the combination of targeted therapy will further increase the risk of adverse reactions. When immunotherapy and targeted therapy are combined, the mechanism of action of the two drugs is different. Although they can enhance the anti-tumor syn-

**Table 8.** Comparison of quality-of-life scores between the two groups (EORTC QLQ-C30) (points, $\bar{x} \pm s$)

| Domain | Pre-treatment | | | Post-treatment | | |
|---|---|---|---|---|---|---|
| | IrAE group (n = 117) | Non-irAE group (n = 107) | p v. | IrAE group (n = 117) | Non-irAE group (n = 107) | *P* value |
| Physical Functioning | 72.5 ± 8.6 | 73.1 ± 8.2 | 0.588 | 68.2 ± 9.1 | 78.5 ± 7.6 | < 0.001 |
| Role Functioning | 68.3 ± 9.4 | 69.0 ± 8.9 | 0.567 | 64.5 ± 9.8 | 75.2 ± 8.4 | < 0.001 |
| Emotional Functioning | 65.8 ± 10.2 | 66.5 ± 9.7 | 0.599 | 61.3 ± 10.5 | 72.8 ± 9.1 | < 0.001 |
| Cognitive Functioning | 70.2 ± 8.9 | 70.9 ± 8.5 | 0.546 | 66.8 ± 9.2 | 75.6 ± 8.0 | < 0.001 |
| Social Functioning | 66.5 ± 9.8 | 67.2 ± 9.3 | 0.579 | 62.5 ± 10.1 | 73.4 ± 8.7 | < 0.001 |
| GlobalHealth Status | 68.0 ± 8.5 | 68.7 ± 8.1 | 0.525 | 64.2 ± 9.5 | 76.8 ± 7.9 | < 0.001 |

**Table 9.** Comparison of treatment efficacy between patients with different numbers of adverse reactions [n (%)]

| Group | CR | PR | SD | PD | ORR | DCR |
|---|---|---|---|---|---|---|
| Mild group (n = 68) | 4 (5.9) | 29 (42.6) | 23 (33.8) | 12 (17.6) | 33 (48.5) | 56 (82.4) |
| Severe group (n = 49) | 1 (2.0) | 16 (32.7) | 16 (32.7) | 16 (32.7) | 17 (34.7) | 33 (67.3) |
| $\chi^2$ value | | | | | 4.213 | 4.867 |
| *P* value | | | | | 0.040 | 0.027 |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

**Table 10.** Comparison of tumor marker levels before and after treatment between the two groups (xe ± s)

| Indicator | Group | N | Pre-treatment | Post-treatment | Within-group comparison (*P* value) |
|---|---|---|---|---|---|
| CEA (ng/mL) | Adverse event group | 117 | 45.6 ± 18.3 | 12.8 ± 6.2† | < 0.001 |
| | Non-irAE group | 107 | 46.2 ± 19.1 | 28.5 ± 11.4 | < 0.001 |
| | Inter-group comparison (*P* value) | | > 0.05 | < 0.05 | |
| SCC (ng/mL) | Adverse event group | 117 | 8.4 ± 3.2 | 2.6 ± 1.1† | < 0.001 |
| | Non-irAE group | 107 | 8.1 ± 3.0 | 5.2 ± 2.0 | < 0.001 |
| | Inter-group comparison (*P* value) | | > 0.05 | < 0.05 | |
| NSE (ng/mL) | Adverse event group | 117 | 22.8 ± 7.6 | 9.5 ± 3.4† | < 0.001 |
| | Non-irAE group | 107 | 21.9 ± 7.2 | 15.6 ± 5.1 | < 0.001 |
| | Inter-group comparison (*P* value) | | > 0.05 | < 0.05 | |

Note: †P < 0.05 vs. the non-irAE group after treatment.

ergistic effect, they will also increase the metabolic burden of organs at the same time. Both drugs may induce immune disorders and inflammatory reactions in the body. The combination of the two drugs will produce a superposition effect, further exacerbating the immune imbalance, supporting previous research results [23, 24].

Previous studies have shown that irAEs may influence both treatment outcomes and quality of life [25]. In this study, it was found that the objective response rate (ORR) and disease control rate (DCR) were significantly higher in patients without irAEs than those with irAEs. The reason is that on the one hand, immune-related adverse reactions will lead to a decrease in the patient's physical tolerance, fatigue, gastrointestinal discomfort and other symptoms, forcing the clinical reduction of drug dose, interruption or even termination of treatment, which directly affects the integrity of the anti-tumor treatment course and reduces the overall treatment effect. On the other hand, the immune system of patients with adverse reactions is seriously disordered, and the immune system cannot accurately focus on tumor cells, resulting in a decrease in the effi-

ciency of anti-tumor immune response, which in turn affects the anti-tumor effect of immunotherapy. At the same time, this study compared the quality of life of the two groups of patients and found that the scores of physiological function, role function and emotional function of the patients in the irAE group after treatment were significantly lower than those in the non-irAE group, which fully indicated that immune-related adverse reactions would reduce the quality of life of patients from physiological, psychological and social functions. In clinical practice, we should not only pay attention to the anti-tumor effect, but also pay attention to the prevention and control of adverse reactions, taking into account the survival time and quality of life of patients [26, 27].

Previous studies have confirmed that the baseline data of patients can be used to establish an early prediction model of adverse reactions. In this study, a risk prediction model was constructed based on the above three independent risk factors. The model fitting degree was good, and the calibration curve also confirmed that the model prediction probability was highly consistent with the actual occurrence probability, indicating that the prediction model had good identification ability and calibration accuracy. It can be used for early clinical screening of high-risk patients with adverse reactions, and provide a quantitative basis for clinical development of individualized treatment plans and targeted interventions, which is consistent with previous research conclusions [28, 29].

Several limitations should be acknowledged. First, this was a single-center retrospective study with a modest sample size (n = 224) and no external validation, which may limit generalizability. Second, we did not measure direct inflammatory or immune biomarkers (e.g., cytokines, lymphocyte subsets, autoantibodies), relying on NLR as an indirect surrogate, which may not fully reflect immune status. Third, this study did not stratify adverse reactions by severity grade (grade 1-2 vs. grade ≥ 3) or by timing of onset (early vs. late). Therefore, we were unable to test the hypothesis that early mild adverse reactions serve as a biomarker of treatment efficacy. The current analysis only compared patients with and without adverse reactions, which does not allow for conclusions regarding the relationship between mild/early toxicities and clinical outcomes. Fourth, our prediction model underwent only internal validation; given the limited sample size, there is a potential risk of overfitting, and its performance in external populations remains unknown. Fifth, we were unable to fully adjust for potential confounders such as concomitant medications (e.g., corticosteroids, antibiotics), prior lines of therapy, and Eastern Cooperative Oncology Group performance status (ECOG PS), which may influence both adverse event occurrence and treatment outcomes. Sixth, the study included heterogeneous treatment regimens (PD-1 monotherapy, PD-1 plus chemotherapy, PD-1 plus targeted therapy) without stratification by regimen type, which may introduce variability in irAE profiles across subgroups. Seventh, while we identified independent risk factors for adverse reactions, we did not propose specific clinical protocols (e.g., monitoring frequency or preemptive thresholds) for high-risk patients, as these require further validation in prospective studies. To address these limitations, future multi-center, large-scale prospective studies should: (1) incorporate comprehensive panels of immune biomarkers to enable mechanistic insights; (2) adopt severity-stratified analyses of irAEs and regimen-stratified analyses to account for treatment heterogeneity; (3) conduct external validation of predictive models in independent cohorts; (4) systematically control for relevant confounders including concomitant medications and performance status; and (5) develop actionable clinical protocols, including risk-stratified monitoring schedules and evidence-based preemptive intervention thresholds, to facilitate translation into clinical practice.

## Conclusion

Immunotherapy can effectively prolong survival in patients with advanced non-small cell lung cancer, albeit with a high incidence of treatment-related adverse reactions. In this single-center analysis, smoking history, immunotherapy duration > 4 cycles, and concurrent targeted therapy were identified as independent risk factors for immune-related adverse reactions. A predictive model incorporating these three factors demonstrated good discriminative ability and calibration accuracy within the study cohort, providing a reference for early screening of high-risk patients and individualized treatment planning in clinical practice. Regarding the irAE-efficacy relation-

ship, patients without irAEs had significantly higher ORR and DCR than those with irAEs. The presence of any adverse reaction, regardless of severity, was associated with worse short-term treatment outcomes in this cohort. Future prospective studies with severity- and time-stratified analyses are needed to further clarify the complex relationship between immune-related adverse reactions and treatment efficacy.

*Clinical implications for high-risk patients*

Based on our findings, we propose the following preliminary clinical management strategies for patients identified as high-risk for immunotherapy-related adverse events (irAEs): Prior to initiating PD-1 inhibitor therapy, we recommend calculating the patient's NLR and assessing other identified risk factors (e.g., baseline liver/renal function, tumor marker levels) to assign risk category (low/intermediate/high). For high-risk patients, enhanced vigilance and proactive monitoring are advised.

## Disclosure of conflict of interest

None.

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