

Analysis of risk factors for immune checkpoint inhibitor-related pneumonitis and the establishment of nomogram prediction model

Xiaohui Lu, Guili Zheng, Xiuju Liang, JiaHong Tang, Chen Zhong

Submitted to: JMIR Formative Research
on: April 22, 2025

Disclaimer: © The authors. All rights reserved. This is a privileged document currently under peer-review/community review. Authors have provided JMIR Publications with an exclusive license to publish this preprint on its website for review purposes only. While the final peer-reviewed paper may be licensed under a CC BY license on publication, at this stage authors and publisher expressly prohibit redistribution of this draft paper other than for review purposes.

Table of Contents

Original Manuscript.....	5
---------------------------------	----------

Preprint
JMIR Publications

Analysis of risk factors for immune checkpoint inhibitor-related pneumonitis and the establishment of nomogram prediction model

Xiaohui Lu^{1, 2}; Guili Zheng¹; Xiuju Liang¹; JiaHong Tang³; Chen Zhong¹

¹ Department of Oncology, No. 960 Hospital of PLA, Jinan, China Jinan CN

² Jinzhou Medical University Jinzhou CN

³ Department of Hematology and Oncology, No.988 Hospital of joint logistics Support Force, Zhengzhou, China. Zhengzhou CN

Corresponding Author:

Chen Zhong

Department of Oncology, No. 960 Hospital of PLA, Jinan, China
25 Normal Road, Tianqiao District, Jinan City, Shandong Province, China
Jinan
CN

Abstract

Objective: Immune checkpoint inhibitors (ICIs) are widely used in the treatment of tumors, especially in lung cancer, ICIs can improve the overall survival (OS) and progression-free survival (PFS) of lung cancer patients. However, ICIs have unique adverse effects called immune-related adverse events (irAEs). The purpose of this study was to analyze the risk factors for immune-associated pneumonia (ICI-P) in lung cancer patients treated with ICIs, and to establish a risk factor prediction model to help identify patients at high risk of ICI-P.

Methods: Records of 329 patients with advanced lung cancer who were treated with ICIs between 1 June 2019 and 30 June 2024 in No. 960 Hospital of PLA were reviewed. According to whether ICI-P occurred, patients were divided into ICI-P group and non-ICI-P group. The influencing factors of ICI-P were analyzed by differential analysis and binary logistic regression, constructed a forest plot of the results of multivariate logistic regression analysis. The nomogram prediction model of risk factors was constructed, and the goodness of fit, accuracy, and discrimination of the nomogram were evaluated by calibration curve, receiver operating characteristic curve (ROC) and decision curve analysis (DCA).

Results: ICI-P was found in 9.73%(n=32) of patients with advanced lung cancer who received ICIs. Difference analysis and binary logistic regression analysis showed that smoking history, preexisting lung diseases, combined targeted therapy, combined radiotherapy, as well as low absolute lymphocyte count (ALC) and high absolute eosinophil count (AEC) in baseline peripheral blood cell count were significantly associated with ICI-P risk. The nomograms were constructed on the above risk factors, The calibration curve of the nomogram prediction model was consistent ($P>0.05$). And AUC of the nomogram is 0.840 (95%CI 0.775-0.906) indicates a good predictive value.

Conclusions: The following factors were significantly associated with an increased risk of ICI-P: smoking history, preexisting lung diseases, combined targeted therapy, combined radiotherapy, low ALC and high AEC. We established a valid nomogram for predicting ICI-P in lung cancer patients treated with ICIs, and the accuracy of the prediction nomogram is evaluated.

(JMIR Preprints 22/04/2025:76407)

DOI: <https://doi.org/10.2196/preprints.76407>

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**

Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.

No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**

Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain visible to all users.
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <https://www.jmir.org/preprint/76407>, the full manuscript will be made available to all users.
No. Please do not make my accepted manuscript PDF available to anyone. I understand that if I later pay to participate in <https://www.jmir.org/preprint/76407>, the full manuscript will be made available to all users.



Original Manuscript

Analysis of risk factors for immune checkpoint inhibitor-related pneumonitis and the establishment of nomogram prediction model

Xiao-Hui Lu^{1,2}, Gui-Li Zheng¹, Xiu-Ju Liang¹, Jia-Hong Tang^{3,*}, Chen Zhong^{1,*}

¹Department of Oncology, No. 960 Hospital of PLA, Jinan, China;

²Department of Oncology, The Postgraduate Training Base of Jinzhou Medical University (No. 960 Hospital of PLA), Jinan, China;

³Department of Hematology and Oncology, No.988 Hospital of joint logistics Support Force, Zhengzhou, China.

* Contributed equally to this work.

Abstract

Objective: Immune checkpoint inhibitors (ICIs) are widely used in the treatment of tumors, especially in lung cancer, ICIs can improve the overall survival (OS) and progression-free survival (PFS) of lung cancer patients. However, ICIs have unique adverse effects called immune-related adverse events (irAEs). The purpose of this study was to analyze the risk factors for immune-associated pneumonia (ICI-P) in lung cancer patients treated with ICIs, and to establish a risk factor prediction model to help identify patients at high risk of ICI-P.

Methods: Records of 329 patients with advanced lung cancer who were treated with ICIs between 1 June 2019 and 30 June 2024 in No. 960 Hospital of PLA were reviewed. According to whether ICI-P occurred, patients were divided into ICI-P group and non-ICI-P group. The influencing factors of ICI-P were analyzed by differential analysis and binary logistic regression, constructed a forest plot of the results of multivariate logistic regression analysis. The nomogram prediction model of risk factors was constructed, and the goodness of fit, accuracy, and discrimination of the nomogram were evaluated by calibration curve, receiver operating characteristic curve (ROC) and decision curve analysis (DCA).

Results: ICI-P was found in 9.73%(n=32) of patients with advanced lung cancer who received ICIs. Difference analysis and binary logistic regression analysis showed that smoking history, preexisting lung diseases, combined targeted therapy, combined radiotherapy, as well as low absolute lymphocyte count (ALC) and high absolute eosinophil count (AEC) in baseline peripheral blood cell count were significantly associated with ICI-P risk. The nomograms were constructed on the above risk factors, The calibration curve of the nomogram prediction model was consistent ($P>0.05$). And AUC of the nomogram is 0.840 (95%CI 0.775-0.906) indicates a good predictive value.

Conclusions: The following factors were significantly associated with an increased risk of ICI-P: smoking history, preexisting lung diseases, combined targeted therapy, combined radiotherapy, low ALC and high AEC. We established a valid nomogram for predicting ICI-P in lung cancer patients treated with ICIs, and the accuracy of the prediction nomogram is evaluated.

Keywords: Immune checkpoint inhibitors, Immune checkpoint inhibitor-related pneumonitis, Prediction model, Nomograms, Lung cancer.

Introduction

Lung cancer is the most frequently diagnosed cancer globally and is also the leading cause of cancer death[1]. Immune checkpoint inhibitors (ICIs), such as monoclonal antibodies directed against programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), or cytotoxic T-lymphocyte antigen 4 (CTLA-4), are now widely used in the treatment of several types of cancer in clinical practice[2]. ICIs play an important role in the era of immunotherapy, and compared with conventional chemotherapy and molecularly targeted therapy, ICIs can significantly improve the overall survival (OS) and progression-free survival (PFS) of lung cancer patients[3]. However, with the widespread use of ICIs, immunotherapy-related adverse events (irAEs) are gradually attracting attention. The adverse effects of irAEs are completely different from those produced by conventional chemotherapy[4]. Among irAEs, immune checkpoint inhibitor-associated pneumonia (ICI-P) is a relatively rare but high-mortality adverse reaction when patients develop dyspnea or other respiratory

symptoms after receiving ICIs and develop new infiltrative shadows after chest imaging excludes lung infection or tumor progression[5]. The incidence of ICI-P varies widely in some clinical studies, ranging from 3% to 19% in lung cancer[6,7]. Among patients treated with ICIs, the median time to develop ICI-P in lung cancer patients was 82 days, which was earlier than that of non-lung cancer patients[6,8]. Clinically, most ICI-P grades 1-2, and grade 3-4 are rare, which can be improved by drug discontinuation and glucocorticoid (GC) therapy. However, ICI-P is still a lethal irAEs. A meta-analysis, anti-PD-1/PD-L1-related fatalities were often from pneumonitis (35%)[9]. Therefore, for lung cancer patients treated with ICIs, clinicians should quickly and accurately predict the possibility of severe ICI-P and provide reasonable and effective prevention and treatment measures. With the widespread use of ICIs in lung cancer, clinicians need to identify irAEs in a timely and accurate manner, especially ICI-P, which can lead to respiratory failure and often threaten the lives of patients[10]. Clinicians should assess and pay attention to high-risk groups before medication, and it is extremely important to provide reasonable and effective treatment for high-risk patients with ICI-P quickly and accurately. At present, there is still a lack of a simple and effective clinical prediction model to quickly identify the high-risk patients with ICI-P. This paper aims to analyze the risk factors for developing ICI-P after ICIs treatment in advanced lung cancer patients, and establish a nomograms prediction model based on these risk factors.

Material and methods

Patients

Records were retrospectively collected patients with advanced lung cancer who were treated with ICIs in No. 960 Hospital of PLA between 1 June 2019 and 30 June 2024 and were reviewed. The study included 329 patients. These patients all had a definite pathological diagnosis of malignancy and were treated with PD1/PD-L1 monoclonal antibodies for no less than 2 cycles. Patients with the following characteristics should be excluded: (1) History of autoimmune diseases: Patients with severe autoimmune disorders (such as the active phase of systemic lupus erythematosus, the active phase of rheumatoid arthritis, myasthenia gravis, etc.) are usually excluded. (2) Severe allergic history: Life-threatening conditions such as severe anaphylactic shock may occur after administration. (3) Severe cardiopulmonary dysfunction, such as acute exacerbation of severe chronic obstructive pulmonary disease (COPD), severe heart failure (New York Heart Association Heart Function Scale III - IV). These patients might not be able to tolerate the adverse reactions that may arise during immunotherapy, such as immune-related pneumonia, cardiotoxicity, which will also heighten the risk of death during treatment and influence the judgment of the study results.

Among the 329 patients who were treated with ICIs, 32 patients were diagnosed with ICI-P. ICI-P was diagnosed by experienced oncologists and confirmed by two experienced radiologists. The date of ICI-P diagnosis, time of occurrence and maximum ICI-P grade (according to the NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities) were recorded[11]. And 297 patients did not develop ICI-P after receiving multi-cycle ICIs. The demographic characteristics and clinical treatment data of the two groups were compared.

Clinical data collection

The recorded clinical characteristics comprised sex, age, smoking history, Smoking history, the pathological type of lung cancer, history of hypertension, history of diabetes, Eastern Cooperative Oncology Group performance status (ECOG PS), patients with previous lung diseases such as emphysema, pulmonary infection, chronic obstructive pulmonary disease (COPD), asthma, interstitial pneumonia, pneumothorax, pleural effusion, combined radiotherapy and targeted therapy, etc. And baseline peripheral blood cell counts, such as, white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), absolute eosinophil count (AEC), and hemoglobin, platelets, albumin, creatinine.

Statistical analysis

The clinical and demographic data of the patients were analyzed with the chi-square test or

Fisher's exact test for categorical variables, continuous variables were expressed as means $\pm$ standard deviation, and differences between groups were compared using Student's T-test or Mann-Whitney U test. Cut-off values of the continuous variables were determined via ROC analysis. Difference analysis and binary logistic regression analyses were used to analyze the risk factors, and the risk factors with $P < 0.1$ in the difference analysis were included in the binary logistic regression analysis. All statistically significant risk factors in the multivariate analysis were used to construct the nomogram using R statistical software. We used calibration curves to measure the goodness of fit and the consistency between the predicted and actual outcomes[12]. The predictive ability of the nomogram was assessed according to the area under the curve (AUC) of the ROC curve with an AUC closer to 1.0 indicating better results[13]. The overall area under each probable risk threshold was calculated using DCA. In difference analysis and binary logistic regression analyses, $P < 0.05$ was considered to indicate statistical significance. SPSS 29.0 and R Studio software were used for statistical analysis of the data.

Results

Patient Characteristics

A total of 329 patients with advanced lung cancer who received ICIs were included in this study. Among these patients, 32 developed ICI-P post-treatment, resulting in an incidence rate of 9.73%. The median onset time of ICI-P was 51.5 days. Table 1 provides a summary of the clinical characteristics of the enrolled patients. Statistically significant differences were observed between the two groups in terms of smoking history, preexisting lung diseases (including emphysema, pulmonary infection, COPD, asthma, interstitial pneumonia, pneumothorax, and pleural effusion), combined targeted therapy, combined radiotherapy, as well as baseline peripheral blood cell counts, particularly the absolute values of lymphocytes and eosinophils ($P < 0.05$).

Table1. Baseline characteristics of lung cancer patients treated with ICIs

Variables	All (%) [N=329]	ICI-P Diagnosis		P value
		Yes [N=32]	No [N=297]	
Gender				0.556
Male	260(79.0)	24(75)	236(79.5)	
Female	69(21.0)	8(25)	61(20.5)	
Ages				
Mean $\pm$ SD	64.2 $\pm$ 9.68	64.00 $\pm$ 9.26	64.22 $\pm$ 9.74	0.627
≥ 65	181(55.02)	18(56.2)	163(54.88)	
< 65	148(44.98)	14(43.8)	134(45.12)	
Smoking history				0.037
Never smoker	105(31.9)	5(15.6)	100(33.7)	
Anytime smoker	224(68.1)	27(84.4)	197(66.3)	
Histologic type				0.241
Adenocarcinoma	141(42.9)	14(43.8)	127(42.8)	
Squamous	115(35.0)	15(46.9)	100(33.7)	
Small cell lung cancer	67(20.4)	3(9.4)	64(21.5)	
Large cell cancer	6(1.8)	0(0)	6(2.0)	
Hypertension				0.921
Yes	95(28.9)	9(28.1)	86(29.0)	
No	234(71.1)	23(71.9)	211(71.0)	

Diabetes				0.429
Yes	46(14.0)	3(9.4)	43(14.5)	
No	283(86)	29(90.6)	254(85.5)	
ECOG PS				0.075
0-1	311(94.5)	28(87.5)	283(95.3)	
≥ 2	18(5.5)	4(12.5)	14(4.7)	
Preexisting lung diseases				<0.001
Yes	134(40.7)	27(84.4)	107(36.0)	
No	195(59.3)	5(15.6)	190(64.0)	
Treatment data				
Combined chemotherapy	307(93.3)	28(87.5)	279(93.9)	0.166
Combined targeted therapy	120(36.5)	19(59.4)	101(34.0)	0.005
Combined radiotherapy	54(16.4)	10(31.3)	44(14.8)	0.017
Peripheral blood biomarkers				
Mean ± SD				
WBC	6.31±2.13	6.33±2.07	6.30±2.15	0.76
ANC	4.35±1.96	4.54±1.74	4.33±1.98	0.343
ALC	1.40±0.56	1.18±0.56	1.42±0.56	0.036
AMC	0.40±0.24	0.45±0.29	0.39±0.23	0.317
AEC	0.13±0.13	0.16±0.12	0.13±0.13	0.021
Hemoglobin	121.88±16.98	121.66±14.33	121.91±17.26	0.183
Albumin	37.77±3.93	37.20±4.13	37.84±3.91	0.712
Creatinine	61.55±15.39	59.88±21.24	61.73±14.66	0.276

ICIs, immune checkpoint inhibitors; ICI-P, immune checkpoint inhibitor-related pneumonitis; ECOG PS, Eastern Cooperative Oncology Group performance status; Preexisting lung diseases, WBC, white blood cell count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; AEC, absolute eosinophil count; SD, standard deviation.

Correlation between baseline ALC, AEC and ICI-P

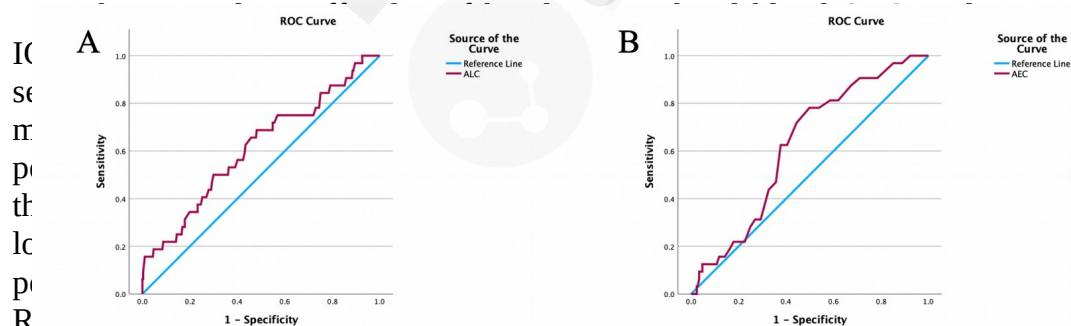
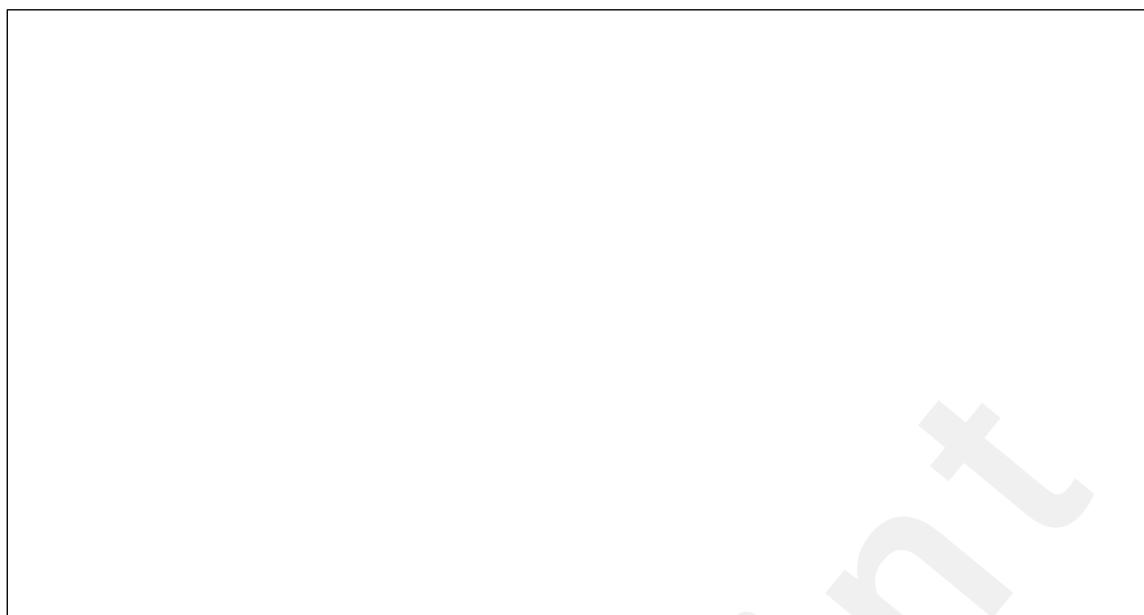


Fig. 1 ROC Curve analysis showing the correlation between baseline ALC and ICI-P (A) and baseline AEC and ICI-P (B). The correlation between baseline ALC and ICI-P was moderate (AUC=0.613, sensitivity = 68.8%, specificity = 51.9%, cut-off 1.305×10^9 cells/L). The correlation between baseline AEC and ICI-P was moderate (AUC=0.624, sensitivity = 78.1%, specificity = 50.2%, cut-off 0.095×10^9 cells/L). The occurrence of ICI-P was significantly associated with baseline ALC (OR 0.505-0.720, 95% CI 0.305-0.820, P=0.002) and AEC (OR 0.505-0.720, 95% CI 0.305-0.820, P=0.002) in patients as shown in the Table 2. (Table 2).

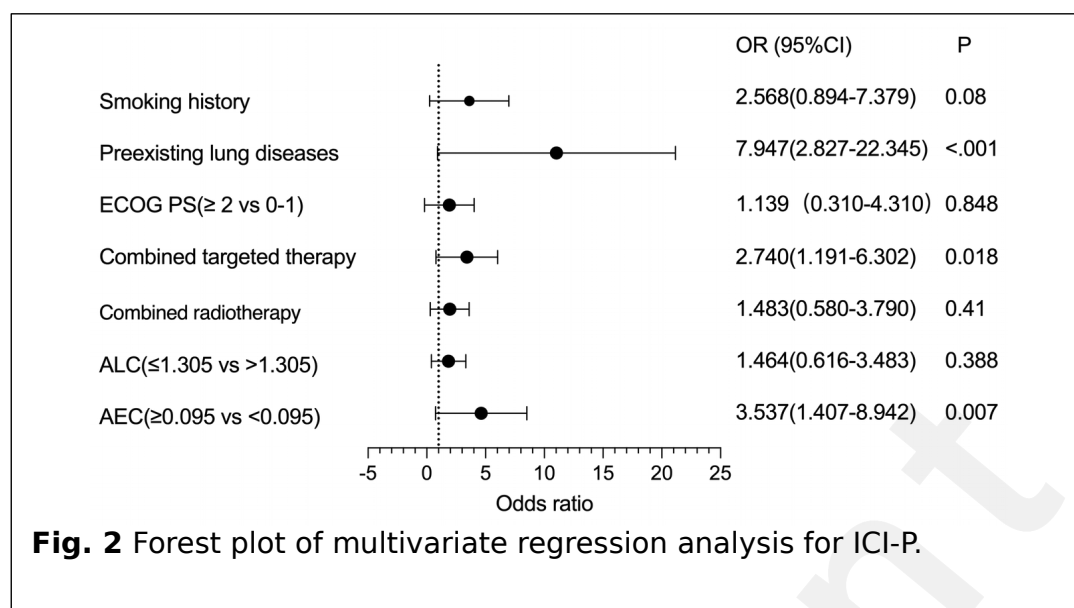


Binary logistic regression

Risk factors with a $P < 0.1$ in the difference analysis of clinical data were included in binary logistic regression analysis. The results are summarized in Table 2. Univariate logistic regression analysis revealed that the following factors were significantly associated with an increased risk of ICI-P: smoking history (OR=2.714, 95% CI 1.025-7.334, $p < 0.05$), preexisting lung diseases (OR=9.589, 95% CI 3.587-25.631, $p < 0.01$), combined targeted therapy (OR=2.836, 95% CI 1.346-5.976, $p < 0.01$), radiotherapy history (OR=2.614, 95% CI 1.159-5.894, $p < 0.05$), ALC ≤ 1.305 (OR=2.369, 95% CI 1.085-5.176, $p < 0.05$), and AEC ≥ 0.095 (OR=3.547, 95% CI 1.489-8.454, $p < 0.01$). Multivariate logistic regression analysis further indicated that preexisting lung diseases (OR=7.947, 95% CI 2.827-22.345, $p < 0.01$), combined targeted therapy (OR=2.740, 95% CI 1.191-6.302, $p < 0.05$), and AEC ≥ 0.095 (OR=3.537, 95% CI 1.407-8.942, $p < 0.01$) remained significant predictors of ICI-P. The forest plot of multivariate logistic regression analysis results was developed by using Graph Pad Prism software (**Fig. 2**).

Table 2. Univariate and multivariate logistic regression analysis for the risk factors of ICI-P (n =329)

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95%CI)	P	OR (95%CI)	P
Smoking history	2.741(1.025-7.334)	0.045	2.568(0.894-7.379)	0.08
Preexisting lung diseases	9.589(3.587-25.631)	<.001	7.947(2.827-22.345)	<.001
ECOG PS (≥ 2 vs 0-1)	2.888(0.890-9.370)	0.077	1.139[0.310-4.310]	0.848
Combined targeted therapy	2.836(1.346-5.976)	0.006	2.740(1.191-6.302)	0.018
Radiotherapy history	2.614(1.159-5.894)	0.021	1.483(0.580-3.790)	0.41
ALC (≤ 1.305 vs > 1.305)	2.369(1.085-5.176)	0.03	1.464(0.616-3.483)	0.388
AEC (≥ 0.095 vs < 0.095)	3.547(1.489-8.454)	0.004	3.537(1.407-8.942)	0.007



Nomogram construction and evaluation

These independently associated risk factors were used to form ICI-P risk estimation nomogram (Fig. 3). The sum of points in the bottom scales of the nomogram demonstrated the probability of ICI-P. The nomogram shows that Preexisting lung diseases is the most influential risk factor, followed by baseline peripheral AEC $\geq 0.095 \times 10^9$ cells/L. In addition, smoking history and combined targeted therapy also had a moderate effect on ICI-P, while combined radiotherapy and baseline peripheral ALC $\leq 1.305 \times 10^9$ cells/L had a small effect.

The accuracy of the prediction value of the nomogram was assessed by the calibration curves, and the fitting degree of the nomogram model was predicted by the ICI-P constructed by the Hosmer-Lemeshow test, and the final model H-L test $\chi^2=7.341$, $P=0.5$ with excellent accuracy (Fig. 4). The area under the ROC curve (AUC) of the nomogram is 0.840 (95%CI 0.775-0.906) indicates a good predictive value for ICI-P risk (Fig. 5). In addition, the DCA illustrated that the nomogram had favorable potential clinical applicability in predicting the ICI-P risk, with a 0-0.6 threshold probability (Fig. 6). In conclusion, validation of the nomogram showed a good level of agreement with the predictive value.

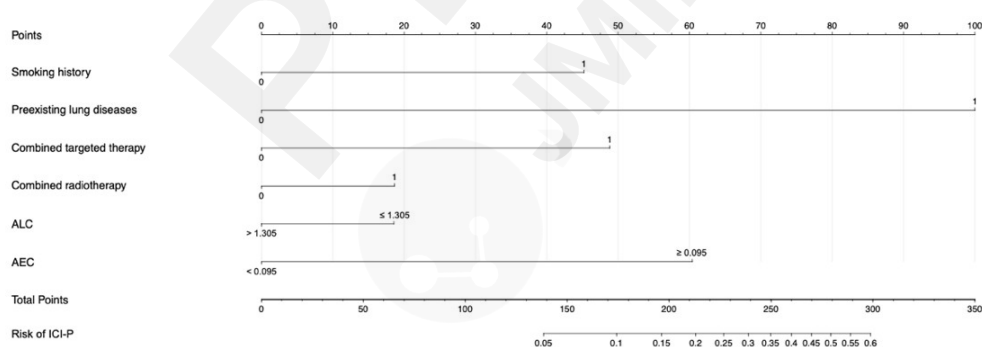


Fig. 3 The establishment of clinical prognostic nomogram models for prediction ICI-P risk.

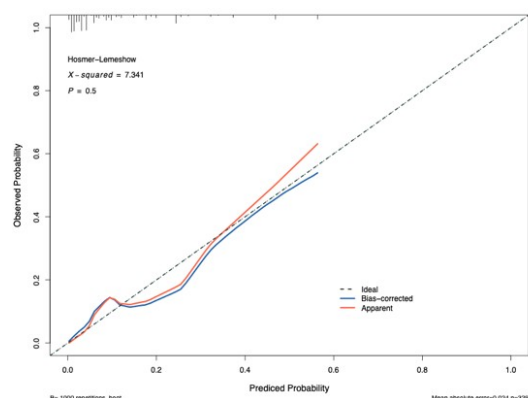


Fig. 4 Calibration curve of the nomogram model for prediction ICI-P risk.

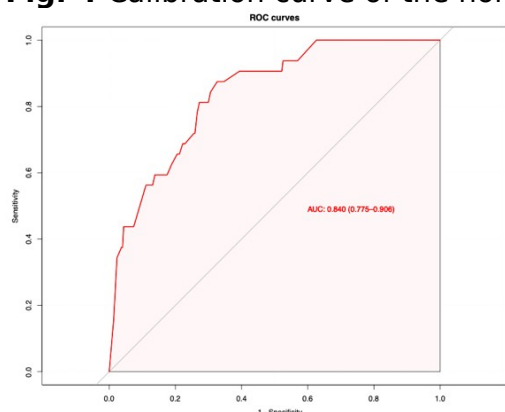


Fig. 5 ROC curve analysis of the nomogram model for prediction ICI-P risk.

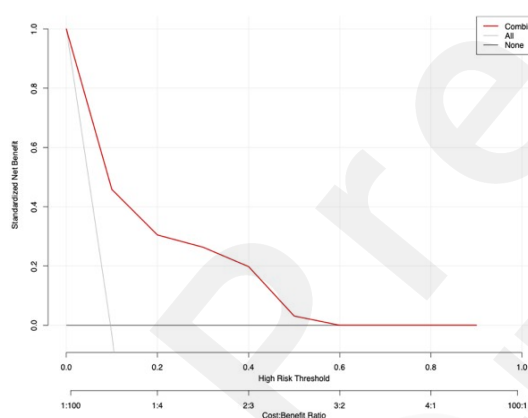


Fig. 6 Decision curve analysis of the nomogram model for prediction ICI-P risk.

Discussion

With the widespread use of ICIs therapy in lung cancer, treatment with these ICIs is often accompanied by irAEs[14,15]. It is necessary for clinicians to accurately identify irAEs in a timely manner, especially since ICI-P is prone to life-threatening conditions. Therefore, it is important to assess and pay attention to high-risk groups before taking medication. After the use of ICIs drugs, patients should be closely monitored for changes in their condition. Studies have confirmed that the occurrence of irAEs is associated with the survival benefit in non-small cell lung cancer (NSCLC) patients treated with ICIs[16]. The occurrence of irAEs indicates that immunotherapy activates the immune system of patients, and the efficacy of immunotherapy is better in patients with higher toxicity of immune drugs, with prolonged PFS and OS[17]. However, it is important to note that the mortality rate for severe ICI-P is higher than that for other irAEs, and the survival benefit of ICIs treatment in patients with G3-4 grade ICI-P is controversial and needs to be further confirmed in clinical studies[18].

In this study, difference analysis and binary Logistic regression were used to analyze the

influencing factors of ICI-P. Nomogram risk factor prediction model was constructed based on these risk factors and its accuracy was evaluated. Nomogram is an intuitive tool to assess the probability of clinical events based on a statistical predictive model that is also used to predict the risk of adverse events associated with cancer treatment[19]. The following factors were significantly associated with an increased risk of ICI-P: smoking history, preexisting lung diseases, combined targeted therapy, combined radiotherapy, low ALC and high AEC. Studies have shown that many factors can damage alveolar epithelial cells, such as preexisting lung diseases, including COPD, asthma, interstitial pneumonia and pleural effusion[20,21], as well as some anti-cancer treatments, such as chemotherapy, targeted therapy and radiotherapy[22,23]. Preexisting lung diseases is an important independent risk factor for ICI-P. It is also easily accessible information that can be used as a guide for predicting ICI-P in clinical practice. Smoking history are associated with ICI-P, and smoking history is an independent risk factor for ICI-P [24]. Research has found that the probability of treatment-related pulmonary toxicity is higher in patients who have received radiotherapy than in patients who have not received radiotherapy[25], patients who have received thoracic radiotherapy are more likely to have ICI-P[26]. Patients treated with ICIs combined with targeted drugs had a higher probability of developing ICI-P than those treated with combination chemotherapy and those who did not receive chemotherapy[27]. Peripheral-blood AEC prior to ICIs therapy are correlated with the incidence of ICI-P and clinical outcomes in patients with advanced NSCLC[28]. These are consistent with this study. In addition, increased levels of inflammatory cytokines were associated with the development of irAEs. Cytokines may be predictive biological markers of irAEs, and their elevation correlates with the severity of irAEs[29,30]. Some studies have also found that the pathogenesis of ICI-P is related to immune response, overexpression of T lymphocyte subsets, and inflammatory factors[31]. The higher the proportion of CD8 + T cells in lung cancer tissue was, the higher the probability of ICI-P[32]. But the relationship between ICI-P and peripheral blood lymphocytes before treatment has not been confirmed. We found that lung cancer patients treated with ICIs with a lower baseline ALC may be more likely to develop ICI-P, further research is needed to confirm this.

In conclusion, the nomogram model based on our research results has a certain degree of the goodness of fit, accuracy, and discrimination of the nomogram. However, the probability of ICI-P risk prediction by nomogram model is limited. There are also many shortcomings of this study. First, this is a single-center retrospective review, which suggests the possibility of information bias and the possibility of limited results cannot be ruled out. Secondly, the sample size of this study was small. Finally, only a subset of lung cancer patients was treated with ICIs, which may not be representative of the majority of lung cancer patients at other centers. We hope to conduct a large-scale, multicenter prospective study in the future to explore additional irAEs, especially on the pathogenesis and predictors of ICI-P.

Conclusion

Difference analysis and binary logistic regression analysis showed that smoking history, preexisting lung diseases, combined targeted therapy, combined radiotherapy, as well as absolute values of low lymphocytes and high eosinophils in baseline peripheral blood cell count were significantly associated with ICI-P risk. The nomograms were constructed on the above risk factors and its accuracy verified can be predicted with greater accuracy. The models provide an early prediction method for ICI-P, before ICIs administration, which facilitates early diagnosis and rational treatment.

Acknowledgements

We thank all the staff of Department of Oncology, No. 960 Hospital of PLA for their support of

our research.

Declaration of conflict of interest: None.

Abbreviations

AECs: Alveolar epithelial cells; AUC: Area under the curve; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; COPD: Chronic obstructive pulmonary disease; DCA: Decision curve analysis; ECOG PS: Eastern Cooperative Oncology Group performance status; ICI-P: Immune checkpoint inhibitor-related pneumonia; ICIs: Immune checkpoint inhibitors; irAEs: Immunotherapy related adverse events; PD-(L)1: Programmed Death-(Ligand) 1; ROC: Receiver operating characteristic; OS: Overall survival; PFS: progression-free survival; NSCLC, non-small cell lung cancer; WBC, white blood cell count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; AEC, absolute eosinophil count; SD, standard deviation.

Availability of data and materials

All data generated or analyzed in this study (with patient information hidden) can be obtained from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate

This research was approved by the Ethics Committee of No. 960 Hospital of PLA, and it was conducted in accordance with the Declaration of Helsinki.

Author contributions

Xiao-Hui Lu contributed to the conceptualization and design of the study, and performed data collection, statistical analysis, and the completion of the first draft. Gui-Li Zheng, Xiu-Ju Liang, Jia-Hong Tang and Chen Zhong performed diagnostic and imaging analysis of the patient. All authors read and approved the final manuscript.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. May-Jun 2024;74(3):229-263. doi:10.3322/caac.21834
2. Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. *Nat Rev Endocrinol*. Apr 2017;13(4):195-207. doi:10.1038/nrendo.2016.205
3. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. May 21 2015;372(21):2018-28. doi:10.1056/NEJMoa1501824
4. Ramos-Casals M, Brahmer JR, Callahan MK, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers*. May 7 2020;6(1):38. doi:10.1038/s41572-020-0160-6
5. Tone M, Izumo T, Awano N, et al. High mortality and poor treatment efficacy of immune checkpoint inhibitors in patients with severe grade checkpoint inhibitor pneumonitis in non-small cell lung cancer. *Thorac Cancer*. Oct 2019;10(10):2006-2012. doi:10.1111/1759-7714.13187
6. Suresh. K, Voong. KR, Shankar. B, et al. Pneumonitis in Non-Small Cell Lung Cancer Patients Receiving Immune Checkpoint Immunotherapy: Incidence and Risk Factors. *J Thorac Oncol*. 2018;13(12):1930–1939. doi:10.1016/j.jtho.2018.08.2035

7. Peng L, Stebbing J, Liang F, Xia Y. Dual immune checkpoint blockade for non-small cell lung cancer patients with PD-L1 high expression: calling an end? *AME Publishing Company*. 2021;(9)
8. Nobashi TW, Nishimoto Y, Kawata Y, et al. Clinical and radiological features of immune checkpoint inhibitor-related pneumonitis in lung cancer and non-lung cancers. *Br J Radiol*. Nov 1 2020;93(1115):20200409. doi:10.1259/bjr.20200409
9. Wang DY, Salem JE, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. *JAMA Oncol*. Dec 1 2018;4(12):1721-1728. doi:10.1001/jamaoncol.2018.3923
10. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol*. Mar 2017;35(7):709-717. doi:10.1200/JCO.2016.68.2005
11. Thompson JA, Schneider BJ, Brahmer J, et al. NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1.2020. *J Natl Compr Canc Netw*. Mar 2020;18(3):230-241. doi:10.6004/jnccn.2020.0012
12. Alba AC, Agoritsas T, Walsh M, Hanna S, Guyatt G. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. *JAMA The Journal of the American Medical Association*. 2017;318(14):1377.
13. Janssens A, Martens FK. Reflection on modern methods: Revisiting the area under the ROC Curve. *Int J Epidemiol*. Aug 1 2020;49(4):1397-1403. doi:10.1093/ije/dyz274
14. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. Aug 2016;13(8):473-86. doi:10.1038/nrclinonc.2016.58
15. Yin Q, Wu L, Han L, et al. Immune-related adverse events of immune checkpoint inhibitors: a review. *Front Immunol*. 2023;14:1167975. doi:10.3389/fimmu.2023.1167975
16. Haratani K, Hayashi H, Chiba Y, et al. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. *JAMA Oncol*. Mar 1 2018;4(3):374-378. doi:10.1001/jamaoncol.2017.2925
17. Ono K, Ono H, Toi Y, et al. Association of immune-related pneumonitis with clinical benefit of anti-programmed cell death-1 monotherapy in advanced non-small cell lung cancer. *Cancer Med*. Jul 2021;10(14):4796-4804. doi:10.1002/cam4.4045
18. Cui P, Huang D, Wu Z, et al. Association of immune-related pneumonitis with the efficacy of PD-1/PD-L1 inhibitors in non-small cell lung cancer. *SAGE PublicationsSage UK: London, England*. 2020;
19. Cai G, Yu J, Meng X. Predicting Prognosis and Adverse Events by Hematologic Markers in Patients with Locally Advanced Esophageal Squamous Cell Carcinoma Treated with Neoadjuvant Chemoradiotherapy. *Cancer Management and Research*. 2020;
20. Zhang Q, Tang L, Zhou Y, He W, Li W. Immune Checkpoint Inhibitor-Associated Pneumonitis in Non-Small Cell Lung Cancer: Current Understanding in Characteristics, Diagnosis, and Management. *Front Immunol*. 2021;12:663986. doi:10.3389/fimmu.2021.663986
21. Isono T, Kagiya N, Takano K, et al. Outcome and risk factor of immune-related adverse events and pneumonitis in patients with advanced or postoperative recurrent non-small cell lung cancer treated with immune checkpoint inhibitors. *Thorac Cancer*. Jan 2021;12(2):153-164. doi:10.1111/1759-7714.13736
22. A CS, B CGA, C GCB. Gemcitabine and nab-paclitaxel induced interstitial pneumonia. *Retour au numéro*. 2021;
23. Nakano K, Seto A, Sasaki T, Shimbashi W, Takahashi S. Incidence and risk factors of interstitial lung disease of patients with head and neck cancer treated with cetuximab. *Head & Neck*. 2019;41(Suppl 2)
24. Li X, Lv F, Wang Y, Du Z. Establishment and validation of nomogram for predicting immuno checkpoint inhibitor related pneumonia. *BMC Pulmonary Medicine*. 2022;22(1):1-10.

25. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol.* Jul 2017;18(7):895-903. doi:10.1016/S1470-2045(17)30380-7
26. Shaverdian N, Beattie J, Thor M, et al. Safety of thoracic radiotherapy in patients with prior immune-related adverse events from immune checkpoint inhibitors. *Ann Oncol.* Dec 2020;31(12):1719-1724. doi:10.1016/j.annonc.2020.09.016
27. Jung J, Kim HY, Kim DG, et al. Sequential Treatment with an Immune Checkpoint Inhibitor Followed by a Small-Molecule Targeted Agent Increases Drug-Induced Pneumonitis. *Cancer Res Treat.* Jan 2021;53(1):77-86. doi:10.4143/crt.2020.543
28. A XC, A JZ, A JZ, et al. Association of baseline peripheral-blood eosinophil count with immune checkpoint inhibitor-related pneumonitis and clinical outcomes in patients with non-small cell lung cancer receiving immune checkpoint inhibitors. *Lung Cancer.* 2020;150:76-82.
29. Johnson DB, Balko JM. Biomarkers for Immunotherapy Toxicity: Are Cytokines the Answer? *Clin Cancer Res.* Mar 1 2019;25(5):1452-1454. doi:10.1158/1078-0432.CCR-18-3858
30. Naqash AR, Yang LV, Sanderlin EJ, al e. Interleukin-6 as one of the potential mediators of immune-related adverse events in non-small cell lung cancer patients treated with immune checkpoint blockade: evidence from a case report. *Acta Oncol.* May 2018;57(5):705-708. doi:10.1080/0284186X.2017.1374556
31. Catacchio I, Scattone A, Silvestris N, Mangia A. Immune Prophets of Lung Cancer: The Prognostic and Predictive Landscape of Cellular and Molecular Immune Markers. *Transl Oncol.* Jun 2018;11(3):825-835. doi:10.1016/j.tranon.2018.04.006
32. Bi J, Qian J, Yang D, et al. Dosimetric Risk Factors for Acute Radiation Pneumonitis in Patients With Prior Receipt of Immune Checkpoint Inhibitors. *Front Immunol.* 2021;12:828858. doi:10.3389/fimmu.2021.828858