IJKD KIDNEY DISEASES

Risk Factors Analysis of AKI in Patients with Primary Non-small Cell Lung Cancer Treated with PD-1/PD-L1 Inhibitor

Jiong-Ming Ying, Feng Yan

Department of Medical Oncology, The First People's Hospital of Hangzhou Lin'an District, Hangzhou 311300, China

Keywords. non-small cell lung cancer, acute kidney injury, PD-1/PD-L1 inhibitor, risk factors, prediction model

Original Paper

Introduction. To investigate the risk factors of Programmed Cell Death Protein 1 (PD-1), Programmed Cell Death Ligand 1(PD-L1) inhibitor associated acute kidney injury (AKI) in patients with primary non-small cell lung cancer (NSCLC) and construct a predictive model.

Methods. 120 NSCLC patients were selected as the research subjects and their clinical data were collected. Patients were divided into AKI and Non-AKI (N-AKI) group based on the development of AKI. Exploring the risk factors of PD-1P/D-L1 inhibitor related AKI in NSCLC patients using multivariate logistic regression analysis and visualized the logistic regression analysis to obtain a nomogram model. Meanwhile, evaluate the predictive value of the model.

Results. The results of multivariate analysis showed that the presence of extrarenal immune related adverse reactions (irAEs) is a risk factor for PD-1/PD-L1 inhibitor related AKI in NSCLC patients; At the same time, the risk of developing PD-1/PD-L1 inhibitor related AKI in NSCLC patients increases with increasing serum creatinine (SCr) and C-reactive protein (CRP) levels, decreasing baseline estimated glomerular filtration rate (eGFR) levels ($P < .05$). The analysis results of receiver operator characteristic curve (ROC), calibration curve, and decision curve show that the model has good discrimination and accuracy, and can achieve a high clinical benefit rate.

Conclusion. Primary NSCLC patients with extrarenal irAEs, high levels of SCr and CRP, and low levels of eGFR have a higher risk of AKI after PD-1/PD-L1 inhibitor treatment. Establishing a predictive model with high accuracy is more conducive to early detection of high-risk patients.

IJKD 2024;18:108-117
www.ijkd.org
DOI: 10.52547/ijkd.7964

INTRODUCTION

Lung cancer is a malignant tumor that involves the trachea, bronchi, or lungs. In the 2020 global cancer statistics, lung cancer ranks second worldwide in both incidence rate (11.7%) and mortality rate (18%).[1] According to statistics, there are over 2.2 million new cases of lung cancer worldwide each year, and the number of new lung cancer deaths is as high as 1.8 million.[2] Among them, non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer, accounting for about 80% of all lung cancers. For early NSCLC patients, surgical removal of the lesion is the most effective treatment option, usually resulting in a longer survival period. For patients with advanced NSCLC, palliative treatment is mainly used to alleviate pain and ensure their

quality of life. The specific treatment methods mainly include chemotherapy, immunotherapy, and targeted therapy. Chemotherapy involves the use of medications to eliminate rapidly growing cells in the body. As chemotherapeutic medications are not selective, they can also cause damage to a large number of normal cells when eliminating cancer cells, leading to toxic side effects.[3,4]

Tumor immunotherapy is an innovative treatment used in treating malignant tumors.[5] In a large number of experiments and clinical studies, immunotherapy has exhibited advantages that traditional anti-tumor therapy cannot match. It can prolong progression-free survival and overall survival, offering benefits such as strong anti-tumor effectiveness, minimal side responses, and decreased recurrence rates.[6] In recent years, with further understanding of the immune evasion mechanism of tumors, various new immunotherapies have emerged, including immune checkpoint inhibitors, adoptive cell immunotherapy, tumor vaccines, and oncolytic virus therapy. Immune checkpoints are a type of immunosuppressive receptors that are often expressed on immune cells. Its main function is to prevent excessive activity of immune cells, causing damage to the body. Programmed death receptor 1 (PD-1) is one of the commonly used molecules in immune checkpoints.[7]

PD-1 inhibitors can block the transmission of inhibitory signals by targeting and binding to PD-1 molecules, thereby restoring T cell activity and enhancing anti-tumor immune response.[8] However, while bringing strong anti-tumor effects, PD-1 inhibitors also bring a unique autoimmune phenomenon known as immune related adverse reactions (irAEs).[9] IRAEs can affect almost all organs of the body, with the most commonly affected organs being the skin, gastrointestinal tract, endocrine glands, and liver.[10] Among them, acute kidney injury (AKI) related to ICIs not only causes great pain to patients, but may also terminate their immunotherapy, and in severe cases, even endanger their lives.[11] Previous research results showed increased rate of AKI due to drug use.[12,13] By exploring the influencing factors of AKI in lung cancer patients receiving immunotherapy, high-risk patients can be identified, and targeted interventions can be taken to reduce the risk of AKI.

Based on the above analysis, this clinical observation aims to analyze the influencing factors of AKI in NSCLC patients receiving PD-1/PD-L1 inhibitor treatment, construct predictive models to provide reference for early screening of high-risk patients.

MATERIAL AND METHODS

Data Sources

One-hundred and twenty NSCLC patients who received PD-1PD-L1 inhibitor treatment at the First People's Hospital of Lin'an District, Hangzhou, China from January 2020 to January 2023 were enrolled in this study. Inclusion criteria were: 1) age more than18 years; 2) confirmed as primary NSCLC; 3) Tumor Node Metastasis (TNM) staging is IIIB-IV stage; 4) receiving PD-1 antibody monotherapy or PD-1 antibody combination with other treatment regimens (such as chemotherapy or vascular targeted therapy); 5) the medical record information is complete. Exclusion criteria were: 1) only receive one cycle of PD-1 treatment; 2) essential organ failure; 3) intolerance to anti-tumor therapy; 4) suffering from two or more types of malignant tumors; 5) mental illness.

Data Collection

After being approved by the Hospital Ethics Committee, the data of the NSCLC patients were collected by consulting the medical record system of the First People's Hospital (the research subjects were informed of and agreed to the data collection of this study). The data collected in this study included: 1) general information: sex, age, body mass index (BMI), smoking, and drinking history; 2) clinical characteristics: hypertension, diabetes mellitus, type of lung cancer, TNM stage, medication scheme, extrarenal irAEs; 3) laboratory indicators on the first day of admission: hemoglobin (Hb), serum albumin (ALB), white blood cell count (WBC), platelet count (PLT), neutrophil count (NE), lymphocyte count (Lym), serum creatinine (SCr), estimated glomerular filtration rate (eGFR), uric acid (UA), blood sodium, blood nitrogen, blood calcium, C-reactive protein (CRP), and lactate dehydrogenase (LDH).

Pabolizumab was purchased from Mercado, Ireland (registration number: S20180019, specification: 4 mL: 100 mg), and infused 2 mg/kg intravenously over more than 30 minutes, the treatment is scheduled once every three weeks. Navolizumab was purchased from Bristol-Myers Squibb Company in the United States (registration

number: S20180015, specification: 40 mg: 4 mL), and administered intravenously at a dose of 3 mg/kg over 60 minutes, the treatment is scheduled once every two weeks. Pemetrexed was purchased from Jiangsu Haosen Pharmaceutical Group Co., Ltd. (approval number: Guoyao Zhunzi H20051288), and 500 mg/m^2 was infused intravenously over 10 minutes, the treatment is scheduled once every 21 days. Carboplatin was purchased from Kunming Guiyan Pharmaceutical Co., Ltd. (approval number: Guoyao Zhunzi H20053908, specification: 10 mL: 50 mg); administered intravenously 200 to 400 mg/m^2, the treatment is scheduled once every 3 to 4 weeks. Cisplatin was purchased from Yunnan Plant Pharmaceutical Co., Ltd. (approval number: Guoyao Zhunzi H53021740, specification: 2 mL: 10 mg), and was infused intravenously at a dose of 20 mg/m^2, once a day, continuous use for 5 days. Docetaxel was purchased from Jiangsu Hengrui Pharmaceutical Co., Ltd. (approval number: Guoyao Zhunzi H20020543, specification: 0.5 mL: 20 mg). It was administered intravenously at a dose of 75 mg/m^2 for one hour, three weeks per dose, and 16 mg of oral corticosteroids was given daily for the first three days to prevent allergies. Paclitaxel was purchased from Beijing Xiehe Pharmaceutical Factory (approval number: Guoyao Zhunzi H10980068, specification: 100 mg), intravenous infusion of 260 mg/m^2 for 30 minutes, three weeks per dose. Gemcitabine was purchased from Jiangsu Haosen Pharmaceutical Group Co., Ltd. (approval number: GYZZ H20030104, specification: 0.2 g), intravenous drip of 1000 mg/m^2 for 30 min, once a week, suspended for one week after three consecutive weeks, and then adjusted to four weeks.

In immunotherapy, monotherapy can be

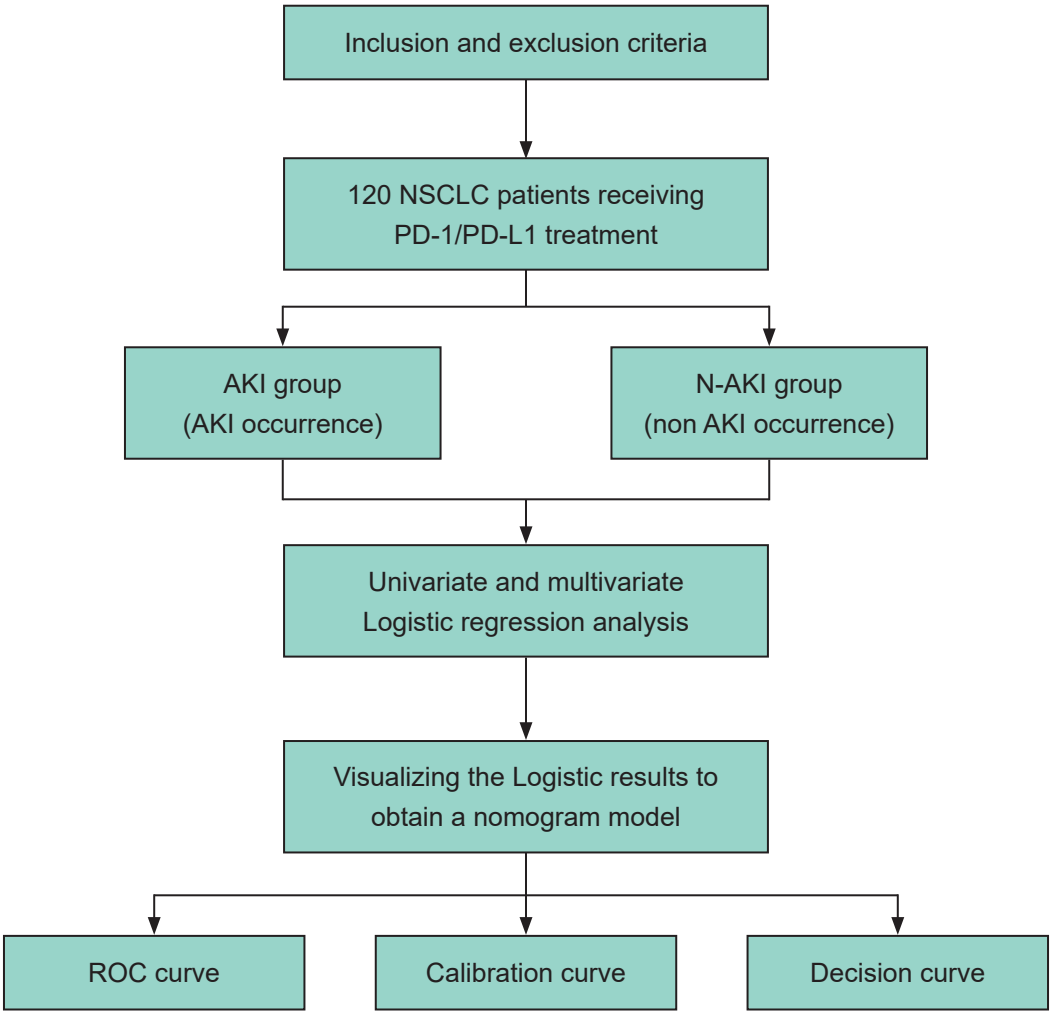


Figure 1. Research Flow Chart

performed with either PD-1/PD-L1 inhibitor treatment: pabolizumab or navulizumab. Combination therapy can be chosen of any PD-1/PD-L1 inhibitor combined with platinum containing dual drug chemotherapy regimen: pemetrexed + carboplatin/cisplatin; Docetaxel + carboplatin/cisplatin; Paclitaxel + carboplatin; Gemcitabine + carboplatin/cisplatin.

Grouping Method

Patients with AKI after treatment (n = 30) were classified as the AKI group, while the remaining patients (n = 90) were classified as the N-AKI group. The diagnostic criteria for AKI are: 1) an increased in serum creatinine > 0.3 mg/dL within 48 hours; 2) Blood creatinine increased by 1.5 times the baseline value within 7 days; 3) Urinary volume < 0.5 mL/(kg·h), lasting for more than 6 hours.[14] AKI can be divided into stages 1, 2 and 3. First, univariate analysis was conducted on the data of two groups of patients, and then the NSCLC AKI prediction model was constructed using logistic regression algorithm, and the predictive performance of the model was tested. The flowchart of this study is shown in Figure 1.

Statistical Analysis

This study used SPSS 26.0 and R 4.2.1 statistical software to conduct statistical analysis on the data of NSCLC patients. The counting data is represented by n (%), inter group comparisons are made using χ^2 Inspection; The measurement data is presented in the form of (`x ± s), and t-test is used for inter-group comparison. Multiple logistic regression analysis was conducted using the incidence of AKI in NSCLC patients as the dependent variable and the indicators with significant differences in univariate analysis as the independent variable. The specific impact of different indicators on the occurrence of AKI in NSCLC patients were evaluated by Odds ratio (OR) in logistic regression analysis. Based on the results of logistic regression analysis, a nomogram model was constructed, and the predictive performance of the model was tested using ROC curves, calibration curves, and decision curves, respectively. Data analysis showed significant differences with unilateral $P < .05$.

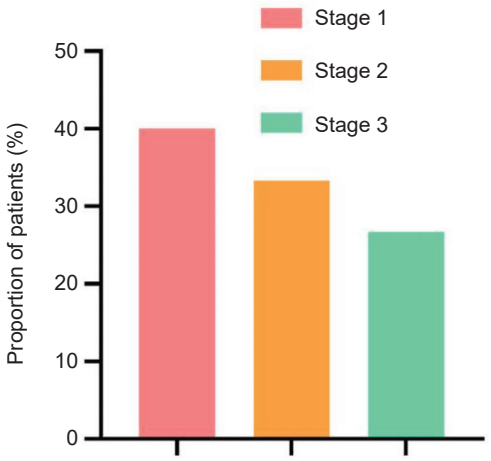
RESULTS

The Occurrence and Prognosis of AKI in NSCLC Patients

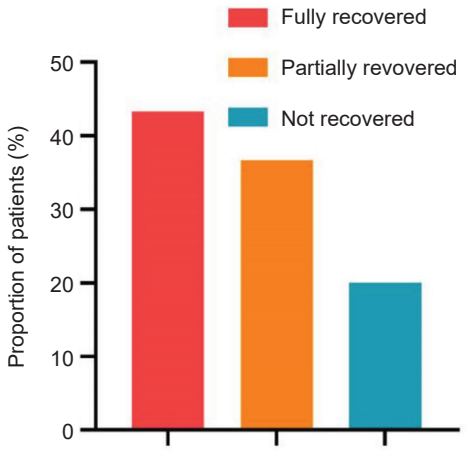
Among the 120 patients included in this study, the incidence of AKI was 25.0% (30/120). In AKI patients, the proportion of stage 1 was 40.0% (12/30), stage 2 was 33.33% (10/30), and stage 3 was 26.67% (26.67), as shown in Figure 2A. Among them, stage 3 AKI patients in phase 1 and all phase 2 and phase 3 patients stopped using PD-1/PD-L1 inhibitors. ninety days after the occurrence of AKI, the proportion of patients with complete recovery, partial recovery, and no recovery from AKI were 43.33 (13/30), 36.67 (11/30), and 20.0% (6/30); respectively, as shown in Figure 2B.

Single Factor Analysis

Preliminary analysis was conducted on the factors



A



B

Figure 2. AKI Staging and Outcome of Patients

that may affect the occurrence of AKI in NSCLC patients, and the results are shown in Table 1 below. Differentiation variables between the AKI and N-AKI groups are hypertension, extrarenal irAEs, Hb, ALB, SCr, eGFR, and CRP (All $P < .05$).

Logistic Regression Analysis

Using indicators such as hypertension, extrarenal irAEs, Hb, ALB, Scr, eGFR, and CRP that may affect the risk of AKI in NSCLC patients as independent variables, and whether AKI occurs as dependent

Table 1. Single Factor Analysis on the Occurrence of AKI in NSCLC Patients After Immunotherapy

General Information	AKI Group (n = 30)	N-AKI Group (n = 90)	t/χ^2	*P*
Gender				
Male	21 (29.17)	51 (70.83)	1.667	.197
Female	9 (18.75)	39 (81.25)		
Age, y	59.26 ± 5.49	60.85 ± 5.91	1.298	.198
BMI, kg/m^2	22.67 ± 1.74	22.93 ± 1.42	0.819	.414
Smoking History				
Yes	16 (25.81)	46 (74.19)	0.044	.833
No	14 (24.14)	44 (75.86)		
Drinking History				
Yes	19 (27.94)	49 (72.06)	0.724	.395
No	11 (21.15)	41 (78.85)		
Hypertension				
Yes	15 (40.54)	22 (59.46)	6.890	.009
No	15 (18.07)	68 (81.93)		
Diabetes				
Yes	12 (30.77)	27 (69.23)	1.026	.311
No	18 (22.22)	63 (77.78)		
Type of Lung Cancer				
Adenocarcinoma	15 (23.44)	49 (76.56)	0.268	.874
Squamous Cell Carcinoma	10 (25.64)	29 (74.36)		
Others	5 (29.41)	12 (70.59)		
TNM Stage				
IIIB	18 (21.69)	65 (78.31)	1.576	.209
IV	12 (32.43)	25 (67.57)		
Medication Scheme				
Immunotherapy	11 (20.75)	42 (79.25)	0.912	.339
Combined Therapy	19 (28.36)	48 (71.64)		
Extrarenal irAEs				
Yes	16 (37.21)	27 (62.79)	5.328	.021
No	14 (18.18)	63 (81.82)		
Hb, g/L	114.99 ± 18.25	123.05 ± 16.71	2.236	.027
ALB, g/L	38.78 ± 3.24	40.19 ± 2.97	2.201	.030
WBC, ×10^9/L	6.85 ± 1.06	6.53 ± 1.12	1.373	.172
PLT, ×10^9/L	215.26 ± 30.22	220.83 ± 27.46	0.938	.350
NE, ×10^9/L	4.42 ± 0.98	4.25 ± 0.86	0.903	.368
Lym, ×10^9/L	5.09 ± 1.13	5.24 ± 1.08	0.651	.516
Scr, μmol/L	73.32 ± 8.64	69.38 ± 7.94	2.302	.023
eGFR, mL/min	82.22 ± 7.29	89.79 ± 5.98	5.675	.000
UA, μmol/L	311.52 ± 38.55	302.08 ± 34.29	1.265	.208
Blood Sodium, mmol/L	137.42 ± 7.19	139.88 ± 6.95	1.665	.099
Blood Nitrogen, mmol/L	103.51 ± 4.85	105.49 ± 5.01	1.889	.061
Blood Calcium, mmol/L	2.63 ± 0.31	2.57 ± 0.26	1.042	.299
CRP, mg/L	19.46 ± 5.12	17.13 ± 3.26	2.907	.004
LDH, U/L	211.26 ± 31.06	208.64 ± 28.33	0.428	.669

Abbreviations: AKI, acute kidney injury; BMI, body mass index; Hb, hemoglobin; ALB, serum albumin; WBC, white blood cell count; PLT, platelet count; NE, neutrophil count; Lym, lymphocyte count; Scr, serum creatinine; eGFR, glomerular filtration rate; UA, uric acid; CRP, C-reactive protein; LDH, lactate dehydrogenase

variables, logistic regression analysis was conducted (see Table 2 for the assignment of each variable). The analysis results in Table 3 below show that the presence of extrarenal irAEs is a risk factor for PD-1/PD-L1 inhibitor related AKI in NSCLC patients; At the same time, the risk of developing PD-1/PD-L1 inhibitor related AKI in NSCLC patients increases with increased SCr and CRP levels, and increases with decreasing baseline eGFR levels (all $P < .05$). The formula for the prediction model can be expressed as: P = EXP (Y)/[1+EXP (Y)], where Y = 12.937 + 1.287 * extrarenal irAEs + 0.086 * SCr -0.228 * eGFR + 0.187 * CRP.

Table 2. Assignment Table of Various Factors

Variable	Assignment
Dependent Variable	
AKI	1 = AKI, 0 = N-AKI
Independent Variables	
Hypertension	1 = Yes, 0 = No
Extrarenal irAEs	1 = Yes, 0 = No
Hb	Input actual value
ALB	Input actual value
Scr	Input actual value
eGFR	Input actual value
CRP	Input actual value

Visualization of Logistic Regression Models

In order to improve the readability of the logistic regression model, this study visualized the regression model of PD-1/PD-L1 inhibitor related AKI in NSCLC patients and obtained a column chart model as shown in Figure 3. This model consists of segments corresponding to each variable, variable score, and risk value. Users can obtain the individual scores of each variable based on the specific situation of the subject, add the individual scores of all variables to obtain the total score of the subject. The risk of developing PD-1/PD-L1 inhibitor related AKI in NSCLC patients can be obtained based on the corresponding values of the total score on the risk value line segment.

Validation of Column Line Diagram Model

This study used ROC curves, calibration curves, and decision curves to test the discrimination, calibration, and clinical benefit rates of the model. As shown in the ROC curve in Figure 4, the AUC

Table 3. Multivariate Logistic Regression Analysis

Variable	B	SE	Waldχ^2	*P*	OR	95% CI
Hypertension	0.911	0.605	2.266	.132	2.486	0.760 to 8.137
Extrarenal irAEs	1.287	0.623	4.266	.039	3.624	1.068 to 12.295
Hb	-0.007	0.018	0.159	.690	0.993	0.959 to 1.028
ALB	-0.098	0.093	1.109	.292	0.906	0.755 to 1.088
Scr	0.086	0.039	4.758	.029	1.090	1.009 to 1.177
eGFR	-0.228	0.059	15.058	.000	0.796	0.710 to 0.893
CRP	0.187	0.073	6.570	.010	1.206	1.045 to 1.391

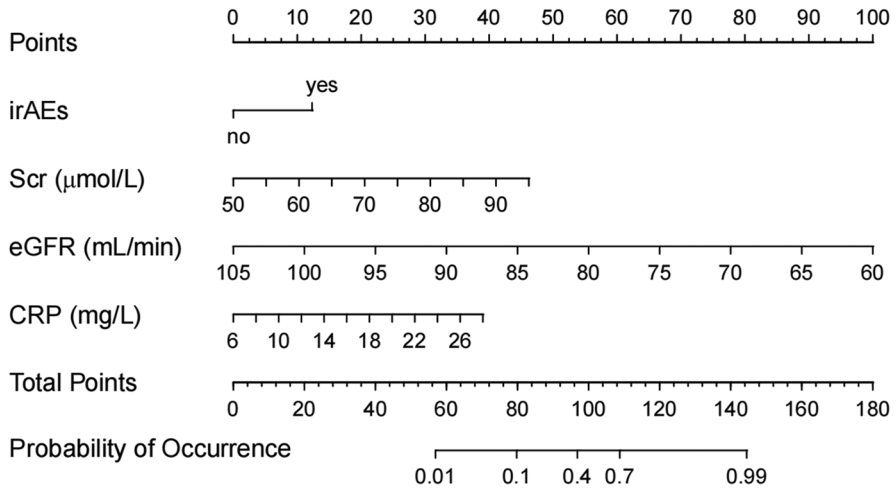


Figure 3. Nomogram Prediction Model for the Development of AKI in NSCLC Patients

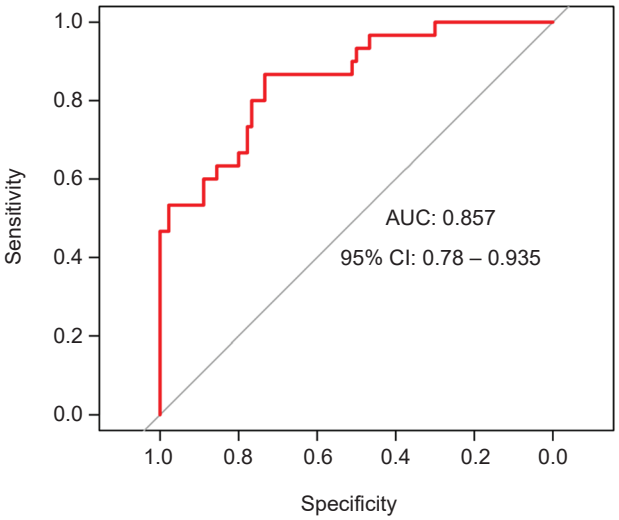


Figure 4. Differentiation of ROC Curve Test Model

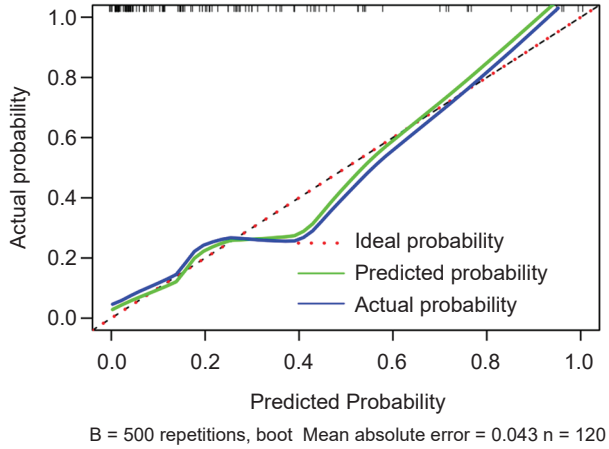


Figure 5. Calibration Curve Verification Model Calibration

of the model is 0.857 (> 0.7), indicating that the model has good discrimination power. As shown in the calibration curve in Figure 5, the predicted probability of the model is very close to the actual probability, hovering around the ideal line of 45°, indicating good calibration of the predicted model. As shown in the decision curve in Figure 6, the constructed model curve is always above the two extreme lines of AII and None. When the incidence of AKI (25.0%) is used as the benchmark, the clinical benefit rate obtained by using the predicted model is 55%.

DISCUSSION

The clinical application of PD-1/PD-L1 inhibitors has benefited patients with advanced malignant

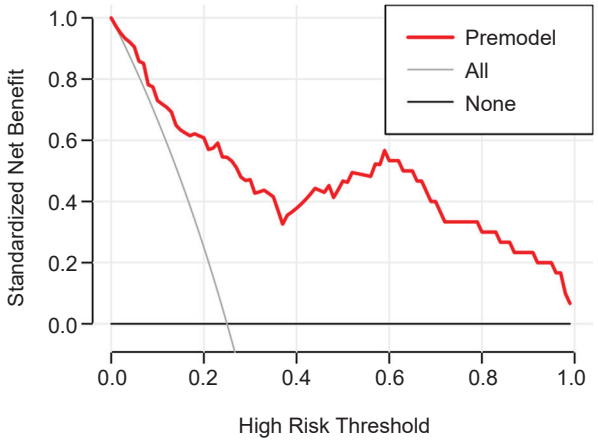


Figure 6. Clinical Benefit Rate of Decision Curve Test Model

tumors, but there have also been reports of related side effects during their application.[15,16] The renal function prognosis after the occurrence of PD-1/PD-L1 inhibitor related AKI has a significant impact on subsequent treatment plans.[17] According to the KIDGO definition, if there is still renal dysfunction after 90 days of AKI, it is considered as the existence of chronic kidney disease.[18] There is a growing number of reports of AKI related to PD-1/PD-L1 inhibitors, which is a significant complication impacting the prognosis of cancer patients.[19] However, there are few reports on the occurrence of AKI in NSCLC patients treated with PD-1/PD-L1 inhibitors in China, and there is no research on the analysis of influencing factors and predictive models.

This study collected clinical data from 120 patients with NSCLC. After analysis, it was found that the presence of extrarenal irAEs is a risk factor for PD-1/PD-L1 inhibitor related AKI in NSCLC patients. Meanwhile, the risk of developing PD-1/PD-L1 inhibitor related AKI in NSCLC patients increases with increasing SCr and CRP levels, and also with decreasing baseline eGFR levels. Meraz *et al.* analyzed the data of patients treated with PD-1/PD-L1 inhibitors in Canada, and the results showed a significant correlation between extrarenal irAEs and PD-1/PD-L1 inhibitor related AKI. The sensitivity analysis results showed that the presence of extrarenal irAEs can increase the risk of AKI by 5.5 times.[20] The risk of AKI in patients with extrarenal irAEs in this study was 3.624 times higher than in patients without extrarenal irAEs. Therefore, when NSCLC patients experience extrarenal irAEs after using PD-1 inhibitors, they

should be highly alert to the occurrence of renal injury.

High baseline SCr level is generally considered to have a vicious circle with kidney injury, that is, baseline SCr level will increase the risk of kidney injury to a certain extent, and SCr level will continue to increase after kidney injury occurs.[21] It is unclear whether PD-1 inhibitors increase the risk of immune-mediated injury to the kidneys in patients with high baseline SCr levels, since the observed decline in renal function may be due solely to a decrease in renal reserve rather than directly to immune-mediated injury.[22] But even if it cannot be determined, the baseline SCr levels of patients should still be monitored before the use of PD-1 inhibitors, and the changes in SCr should be closely monitored during the treatment period. CRP is the main indicator reflecting the inflammatory state of the body. When its concentration exceeds the physiological range, it can cause varying degrees of damage to various organs, including the kidneys.[23]

From the perspective of pathogenesis, the main reason for renal toxicity in patients with lung cancer receiving immunotherapy could be a non-specific stimulation of T cell activation.[24] Activated T cells cannot distinguish between tumor tissue and normal tissue, leading to damage to their own tissues, including the kidneys.[25] AKI can be manifested when renal tubulointerstitial injury occurs. The decrease in eGFR before treatment indicates that the patient may have a certain degree of renal dysfunction.[26] Patients with preoperative renal insufficiency have varying degrees of renal tubular atrophy, renal interstitial fibrosis, and chronic inflammatory cell infiltration in their kidneys, which significantly weakens their resistance to nephrotoxicity caused by immunotherapy, making them more prone to AKI.[27]

Nomogram as a new clinical prediction model, has many advantages over traditional prognostic analysis models, including high accuracy, strong flexibility, and easy reading of results, which are currently widely used in clinical research.[28-30] Based on the multivariate logistic regression model, the screened independent risk factors were integrated to establish a nomogram prediction model for the risk of AKI in NSCLC patients treated with PD-1 inhibitor, and the ROC curve and calibration curve were drawn. The results showed that the nomogram model constructed in this study had good discriminatory power and calibration. In terms of clinical utility, the curve of the nomogram model was far from the two extreme lines, indicating that the prediction model also has certain application value in clinical decision-making.

Study Limitations

This study conducted a systematic analysis of AKI associated with PD-1/PD-L1 inhibitors. However, this article still has three limitations: first, three patients were excluded due to lack of relevant clinical data, which presents a certain degree of selection bias. Secondly, due to the characteristics of retrospective analysis, some patients were not able to record the changes related to extrarenal irAEs after treatment in detail, so it is difficult to identify the etiology of AKI. Similarly, because lung cancer patients rarely undergo renal biopsy, pathological confirmation regarding the cause of AKI were missing in this study. Although the above-mentioned limitations have affected this study to a certain extent, in view of the widespread application of PD-1/PD-L1 inhibitors in the field of lung cancer, it is an unavoidable topic for nephrologists to fully identify the risk factors for AKI associated with PD-1/PD-L1 inhibitors as soon as possible. Through multidisciplinary communication, strengthening the monitoring of renal function indicators during the use of PD-1/PD-L1 inhibitors is a necessary way to solve the above problems.

CONCLUSION

In conclusion, in patients with primary NSCLC treated with PD-1/PD-L1 inhibitors, traditional risk factors such as reduced baseline eGFR are strongly associated with the development of AKI associated with PD-1/PD-L1 inhibitors. In addition, the occurrence of extrarenal irAEs, high level of SCr and high level of CRP highly suggests the possibility of AKI related to PD-1/PD-L1 inhibitors, and clinicians should pay close attention to the changes in renal function in such patients. In view of the high risk and severity of AKI in patients with primary NSCLC treated with PD-1/PD-L1 inhibitors, the establishment of a prediction model with high accuracy is more conducive to the early detection of high-risk patients, so as to provide a basis for targeted interventions.

DECLARATION

Funding

This research received no grant from any funding agency.

Conflicts of Interest / Competing Interests

The authors declare no conflict of interest.

Ethics Approval

This study was approved by the Ethic Committee of The First People's Hospital of Hangzhou Lin'an District (No.202328).

Availability of Data and Material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Ying JM designed and conducted the research, Yan F designed and supervised the research. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript.

REFERENCES

1. Deo SVS, Sharma J, Kumar S. GLOBOCAN 2020 Report on Global Cancer Burden: Challenges and Opportunities for Surgical Oncologists. Annals of surgical oncology. 2022,29(11):6497-6500. doi: 10.1245/s10434-022-12151-6
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021 May;71(3):209-249. doi: 10.3322/caac.21660
3. El-Hussein A, Manoto SL, Ombinda-Lemboumba S, Alrowaili ZA, Mthunzi-Kufa P. A Review of Chemotherapy and Photodynamic Therapy for Lung Cancer Treatment. Anti-cancer agents in medicinal chemistry. 2021;21(2):149-161. doi: 10.2174/1871520620666200403144945
4. Griesinger F, Korol EE, Kayaniyil S, Varol N, Ebner T, Goring SM. Efficacy and safety of first-line carboplatin-versus cisplatin-based chemotherapy for non-small cell lung cancer: A meta-analysis. Lung cancer (Amsterdam, Netherlands). 2019 Sep;135:196-204. doi: 10.1016/j.lungcan.2019.07.010
5. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol. 2020 Aug;17(8):807-821. doi: 10.1038/s41423-020-0488-6
6. Suresh K, Naidoo J, Lin CT, Danoff S. Immune Checkpoint Immunotherapy for Non-Small Cell Lung Cancer: Benefits and Pulmonary Toxicities. Chest. 2018 Dec;154(6):1416-1423. doi: 10.1016/j.chest.2018.08.1048
7. Hu X, Wang J, Chu M, Liu Y, Wang ZW, Zhu X. Emerging Role of Ubiquitination in the Regulation of PD-1/PD-L1 in Cancer Immunotherapy. Molecular therapy: the journal of the American Society of Gene Therapy. 2021 Mar 3;29(3):908-919. doi: 10.1016/j.ymthe.2020.12.032
8. Geuijen C, Tacken P, Wang LC, et al. A human CD137×PD-L1 bispecific antibody promotes anti-tumor immunity via context-dependent T cell costimulation and checkpoint blockade. Nat Commun. 2021 Jul 21;12(1):4445. doi: 10.1038/s41467-021-24767-5
9. Bhardwaj M, Chiu MN, Pilkhwal Sah S. Adverse cutaneous toxicities by PD-1/PD-L1 immune checkpoint inhibitors: pathogenesis, treatment, and surveillance. Cutaneous and ocular toxicology. 2022 Mar;41(1):73-90. doi: 10.1080/15569527.2022.2034842
10. Li N, Wang G, Hou X, et al. Adverse and unconventional reactions related to immune checkpoint inhibitor therapy for cancer. Int Immunopharmacol. 2022 Jul;108:108803. doi: 10.1016/j.intimp.2022.108803
11. Zhu J, Wu J, Chen P, et al. Acute kidney injury associated with immune checkpoint inhibitors: A pharmacovigilance study. Int Immunopharmacol. 2022 Dec;113(Pt A):109350. doi: 10.1016/j.intimp.2022.109350
12. Cho S, Kang E, Kim JE, et al. Clinical Significance of Acute Kidney Injury in Lung Cancer Patients. Cancer research and treatment. 2021 Oct;53(4):1015-1023. doi: 10.4143/crt.2020.1010
13. Knox A, Cloney T, Janssen H, et al. Immune-related acute kidney injury in Australian non-small cell lung cancer patients: Real-world results. Lung cancer (Amsterdam, Netherlands). 2023 Oct;184:107325. doi: 10.1016/j.lungcan.2023.107325
14. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2014 May 1;32(13):1302-8. doi: 10.1200/JCO.2013.51.4489
15. Lou Q, Gong J, Ye B, et al. Acute kidney injury in patients with cancer receiving anti-PD-1/PD-L1 antibodies: incidence, risk factors, and prognosis. Renal failure. 2023 Dec;45(1):2238823. doi: 10.1080/0886022X.2023.2238823
16. Barata P, Hatton W, Desai A, et al. Outcomes With First-Line PD-1/PD-L1 Inhibitor Monotherapy for Metastatic Renal Cell Carcinoma (mRCC): A Multi-Institutional Cohort. Frontiers in oncology. 2020 Oct 22;10:581189. doi: 10.3389/fonc.2020.581189
17. Lou Q, Gong J, Ye B, et al. Acute kidney injury in patients with cancer receiving anti-PD-1/PD-L1 antibodies: incidence, risk factors, and prognosis. Ren Fail. 2023 Dec;45(1):2238823. doi: 10.1080/0886022X.2023.2238823
18. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2020 Jun;97(6):1117-1129. doi: 10.1016/j.kint.2020.02.010

19. Stachyra-Strawa P, Szatkowska-Sieczek L, Cisek P, et al. Cardiac and Nephrological Complications Related to the Use of Antiangiogenic and Anti-Programmed Cell Death Protein 1 Receptor/Programmed Cell Death Protein 1 Ligand Therapy. Genes (Basel). 2024 Jan 28;15(2):177. doi: 10.3390/genes15020177
20. Meraz-Muñoz A, Amir E, Ng P, et al. Acute kidney injury associated with immune checkpoint inhibitor therapy: incidence, risk factors and outcomes. Journal for immunotherapy of cancer. 2020 Jun;8(1):e000467. doi: 10.1136/jitc-2019-000467
21. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. Nature reviews. Disease primers. 2021 Jul 15;7(1):52. doi: 10.1038/s41572-021-00284-z
22. Hong C, Zhu Q, Li Y, et al. Acute kidney injury defined by cystatin C may be superior for predicting the outcomes of liver cirrhosis with acute gastrointestinal bleeding. Renal failure. 2022 Dec;44(1):398-406. doi: 10.1080/0886022X.2022.2039193
23. Huang JW, Su T, Tan Y, et al. Serum anti-CRP antibodies differentiate etiology and predict relapse in acute tubulointerstitial nephritis. Clinical kidney journal. 2021 Jul 6;15(1):51-59. doi: 10.1093/ckj/sfab119
24. Kagamu H. Immunotherapy for non-small cell lung cancer. Respir Investig. 2024 Mar;62(2):307-312. doi: 10.1016/j.resinv.2024.01.011
25. Ma Z, Han K, Dai X, et al. Precisely Striking Tumors without Adjacent Normal Tissue Damage via Mitochondria-Templated Accumulation. ACS Nano. 2018 Jun 26;12(6):6252-6262. doi: 10.1021/acsnano.8b03212
26. Obed M, Gabriel MM, Dumann E, Vollmer Barbosa C, Weißenborn K, Schmidt BMW. Risk of acute kidney injury after contrast-enhanced computerized tomography: a systematic review and meta-analysis of 21 propensity score-matched cohort studies. European radiology. 2022 Dec;32(12):8432-8442. doi: 10.1007/s00330-022-08916-y
27. Sprangers B, Leaf DE, Porta C, et al. Diagnosis and management of immune checkpoint inhibitor-associated acute kidney injury. Nat Rev Nephrol. 2022 Dec;18(12):794-805. doi: 10.1038/s41581-022-00630-8
28. Fan T, Wang H, Wang J, Wang W, Guan H, Zhang C. Nomogram to predict the risk of acute kidney injury in patients with diabetic ketoacidosis: an analysis of the MIMIC-III database. BMC endocrine disorders. 2021 Mar 4;21(1):37. doi: 10.1186/s12902-021-00696-8
29. Xu L, Li C, Zhao L, et al. Acute kidney injury after nephrectomy: a new nomogram to predict postoperative renal function. BMC nephrology. 2020 May 14;21(1):181. doi: 10.1186/s12882-020-01839-0
30. Wu S, Zhou Q, Cai Y, Duan X. Development and validation of a prediction model for the early occurrence of acute kidney injury in patients with acute pancreatitis. Renal failure. 2023 Dec;45(1):2194436. doi: 10.1080/0886022X.2023.2194436

Correspondence to:
Feng Yan
Department of Medical Oncology, The First People's Hospital of Hangzhou Lin'an District, No.360, Yikang Street, Jinnan Street, Lin'an District, Hangzhou 311300, China
ORCID ID: 0009-0009-6305-6160
E-mail: yanfengfy@126.com

Received November 2023
Revised January 2024
Accepted February 2024