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Original Article

Comprehensive nomogram models for predicting checkpoint inhibitor pneumonitis

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Abstract: Checkpoint inhibitor pneumonitis (CIP) is a common type of immune-related adverse events (irAEs) with poor clinical prognosis. Currently, there is a lack of effective biomarkers and predictive models to predict the occurrence of CIP. This study retrospectively enrolled 547 patients who received immunotherapy. The patients were divided into CIP cohorts of any grade, or grade ≥2 or ≥3. Multivariate logistic regression analysis was used to determine the independent risk factors, based on which we established Nomogram A and B for respectively predicting any grade or grade ≥2 CIP. For Nomogram A to predict any grade CIP, the C indexes in the training and validation cohorts were 0.827 (95% CI=0.772-0.881) and 0.860 (95% CI=0.741-0.918), respectively. Similarly, for Nomogram B to predict grade 2 or higher CIP, the C indexes of the training and validation cohorts were 0.873 (95% CI=0.826-0.921) and 0.904 (95% CI=0.804-0.973), respectively. In conclusion, the predictive power of nomograms A and B has proven satisfactory following internal and external verification. They are promising clinical tools that are convenient, visual, and personalized for assessing the risks of developing CIP.

Keywords: Immunotherapy, biomarkers, nomogram, checkpoint inhibitor pneumonitis, cancers

Introduction

In recent years, multiple immune checkpoint inhibitors (ICIs) have been widely used to treat a variety of tumors and achieved satisfactory efficacy [1, 2]. The enthusiasm for ICI is largely based on its long-term clinical efficacy. However, their clinical benefits depend on not only their anti-tumor effectiveness, but also potential adverse events. Any adverse event due to the unique anti-tumor mechanism of ICI has been termed immune-related adverse event (irAE) [3], which is common in organs such as skin, intestine, endocrine organs, and lung [4-6].

Checkpoint inhibitor pneumonitis (CIP) is a type of irAEs with poor prognosis. CIP has been reported to occur in approximately 3-5% patients in previous clinical studies [7, 8], but several real-world studies have suggested an occurrence of as high as 10-20% [9]. The fatality rate of severe CIP was high, up to 14-35% [3]. While mild CIP may have a good prognosis, severe CIP often has a poor prognosis due to its single clinical treatment [3]. Although previous studies indicated that mild to moderate irAEs were associated with better outcomes with ICI therapy [10, 11], severe irAEs might lead to forced termination of ICI, even death. Furthermore, CIP has delayed radiological changes and lacks specific manifestations in early stages, which makes it difficult to differentiate from other respiratory diseases and thus easy to misdiagnosis. Additionally, CIP is difficult to treat, which can progress rapidly and patient conditions deteriorate precipitously. Steroid intervention is the main treatment at present, but

they may bring other adverse events including the risk of tumor progression. In fact, for patients who are susceptible to serious CIP, immunotherapy does not prolong survival and may even endanger life. For patients with severe CIP, the quality of life is significantly reduced, the risk of death is significantly elevated, and the cost of healthcare is also markedly increased. Therefore, how to reduce the incidence of CIP, especially severe CIP, is key to improving the efficacy and safety of immunotherapy in clinical practice.

At present, there is still a lack of authoritative and unified judgment method for the screening and early warning of groups at high risk of CIP development. Previous studies have manifested that age, smoking history, non-small cell lung cancer, interstitial lung disease (ILD), and emphysema at baseline are high-risk factors for CIP [9, 12-15]. Salahaldin et al. reported that the increase of CD74 autoantibody significantly correlated with the occurrence of CIP [16]. CD74 is an autoantibody active protein, mainly expressed on the cell membrane of immune cells including macrophages, which can stimulate the release of inflammatory mediators and participate in specific humoral immune response [17]. Su et al. showed that basal eosinophil levels in CIP patients were significantly higher than those in non-CIP patients [18]. Unfortunately, in general, there are still limitations in such preliminary studies. The single dimension prediction has different emphasis, and its clinical predictive ability is limited, with poor specificity and low stability. There is a lack of effective biomarkers and comprehensive predictive models to predict the risk of CIP and the subpopulation of CIP-susceptible patients. This study aims to explore new biomarkers that can predict CIP, and to establish a novel nomogram model to predict the incidence of CIP so as to reduce the risk of toxicity and maximize the benefits for patients.

Materials and methods

Study population

We selected patients with malignant tumors who received PD-1/PD-L1 inhibitors for the first time from January 2019 to January 2021 in the First Affiliated Hospital of Xi'an Jiaotong University. CIP diagnosis was based on the guidelines for management of immunotherapy-related toxicities published by the national comprehensive cancer network in 2020 [19], and made by three professional clinical oncologists along with two professional radiologists for double-blind review. If their final diagnosis was inconsistent, a third experienced radiologist was invited to re-evaluate to minimize the risk of misdiagnosis or missed diagnosis. CIP was classified as grade 1-5 in order of light to severe illness according to common terminology criteria for adverse events (CTCAE) version 5.0. In clinical practice, grade 1 CIP mostly has no obvious clinical manifestations, and can only be detected by imaging or other clinical examinations. Moreover, for grade 1 CIP, multiple clinical management guidelines and expert consensus recommend that ICI treatment should not be suspended and close follow-up should be sufficient. However, grade 2 or higher CIP requires not only steroid therapy but also suspension or even permanent cessation of ICI treatment. Moreover, the clinical treatment method of CIP is single with poor therapeutic effects, especially for grade 3 or higher CIP patients, where the risk of clinical mortality and disability is high [3]. In order to prospectively screen or identify patients with grade ≥2 and grade ≥3 CIP, we established three cohorts based on the CTCAE grade: (1) Any grade CIP cohort (experimental group: patients with CIP, control group: patients without CIP); (2) Grade ≥2 CIP cohort (experimental group: patients with grade 2 or higher CIP, control group: patients without or with grade 1 CIP); (3) Grade ≥3 CIP cohort (experimental group: patients with grade 3 or higher CIP, control group: patients without or with grade 1-2 CIP). Inclusion criteria for patients were as follows: (1) Age ≥18 years; (2) Patients with histologically or cytologically proven malignant solid tumors that could be treated with ICI as assessed by professional oncologists, regardless of cancer type or stage; (3) Eastern Cooperative Oncology Group (ECOG) physical status score was 0-2 when receiving immunotherapy; (4) No previous use of immunotherapy; (5) No previous exposure to immune-mediated therapy. Exclusion criteria were: (1) A history of another primary malignancy; (2) Lack of baseline characteristic peripheral blood indicator and radiologic images. The minimum observation duration was one civil year for all enrolled patients and 180 days for patients diagnosed with CIP from the date of diagnosis of CIP. The detailed flow chart is shown in **Figure 1**.

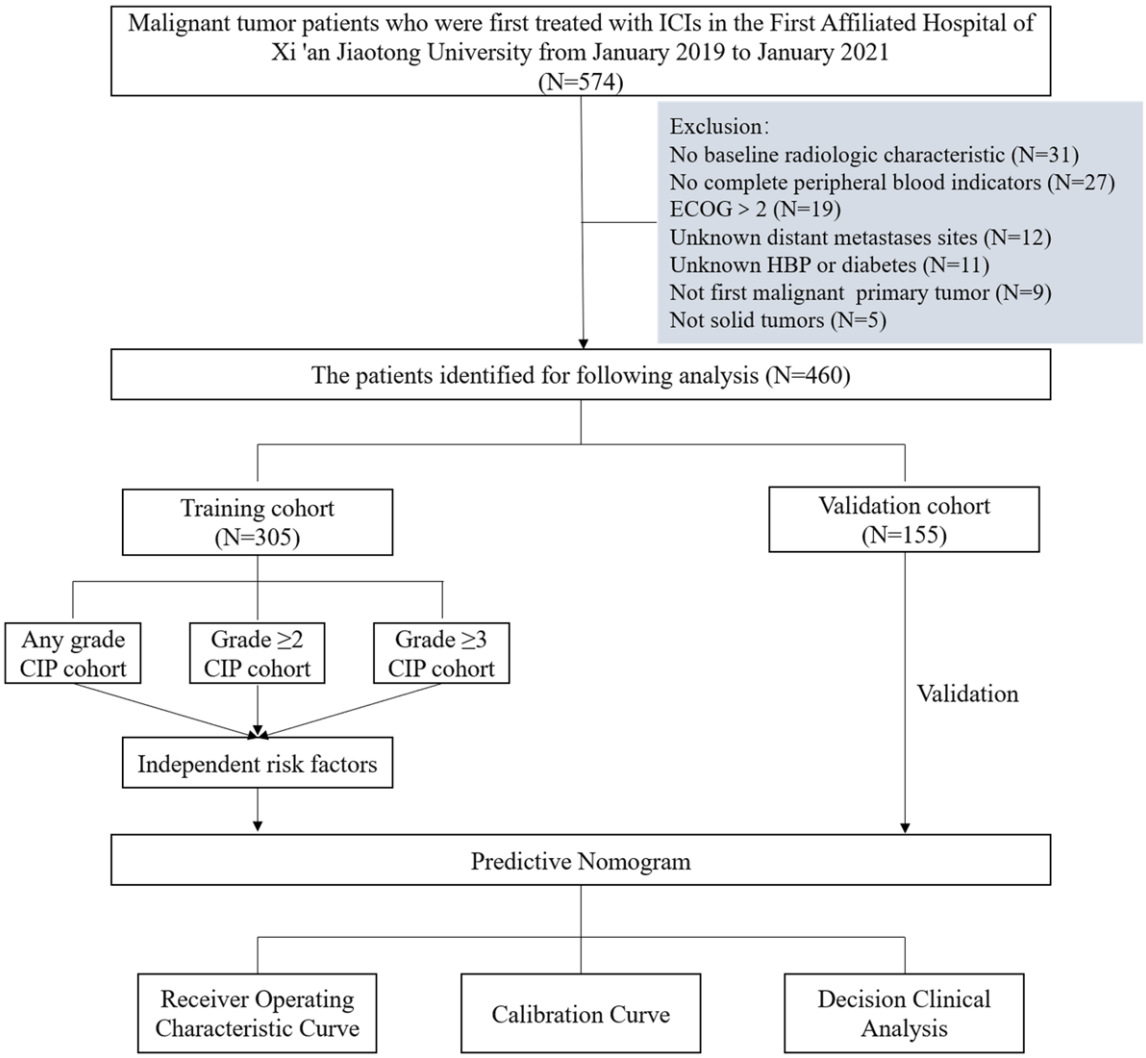


Figure 1. Flow diagram. Based on the inclusion and exclusion criteria, 547 patients were included in this study. After random assignment, 305 and 155 patients were assigned into the training cohort and the validation cohort, respectively. ICI, immune checkpoint inhibitors; CIP, checkpoint inhibitor pneumonitis; ECOG, Eastern Cooperative Oncology Group.

Data collection

We collected all baseline characteristics of patients. At the same time, we also collected baseline information of peripheral blood such as C reactive protein (CRP), absolute neutrophil count (ANC), absolute eosinophil count (AEC), absolute lymphocyte count (ALC), and serum albumin. The platelet/lymphocyte ratio (PLR), neutrophils/lymphocyte ratio (NLR), systemic immune-inflammation index (SII) (%) and prognostic nutritional index (PNI) (%) were calculated by the following methods: PLR = platelet (× 10^9 cells/L)/ALC (× 10^9 cells/L), NLR = ANC (× 10^9 cells/L)/ALC (× 10^9 cells/L), SII = platelet (× 10^9 cells/L) × ANC (× 10^9 cells/L)/ALC (× 10^9 cells/L), PNI = serum albumin level (g/L) + 5 × ALC (× 10^9 cells/L). Patients were assessed for ILD and emphysema at the baseline before receiving ICI.

Statistical analysis

Statistical analysis was performed using the SPSS 22.0 statistical Software package (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA). The receiver operating characteristic (ROC) curve and Youden index were used to determine the optimal cut-off value of laboratory indicators. The *t*-test, chi-square test or Mann-Whitney U test were used for comparison between groups,

Table 1. The demographic and clinicopathological features

	Training cohort (N=305) (N/%)	Validation cohort (N=155) (N/%)	*P value*
Patient Characteristic			
Sex			
Female	60 (19.7)	39 (25.2)	0.176
Male	245 (78.5)	116 (74.8)	
Age			
<75	284 (93.1)	143 (92.3)	0.736
≥75	21 (3.9)	12 (7.7)	
History of smoking			
Never	131 (43.0)	80 (51.6)	0.078
Smoker	174 (57.0)	75 (48.4)	
Tumor Characteristic			
Cancer type			
Lung cancer	262 (85.9)	115 (74.2)	0.051
Hepatocellular carcinoma	21 (6.9)	12 (7.7)	
Stomach and esophagus cancer	11 (3.6)	13 (8.4)	
Colorectal cancer	5 (1.6)	5 (3.2)	
Others	6 (2.0)	10 (6.5)	
Subgroup analysis of cancer type			
Lung cancer	262 (85.9)	123 (79.4)	0.072
Non-lung cancer	43 (14.1)	32 (20.6)	
ECOG			
0	49 (16.07)	17 (10.97)	0.330
1	129 (42.30)	68 (43.87)	
2	127 (41.64)	70 (45.16)	
NMS			
≥2	143 (46.9)	60 (38.7)	0.095
<2	162 (53.1)	65 (61.3)	
PM			
No	211 (69.2)	119 (76.8)	0.087
Yes	94 (30.8)	36 (23.2)	
Lymphatic metastasis			
No	149 (48.9)	75 (48.4)	0.925
Yes	156 (51.1)	80 (51.6)	
Bone metastasis			
No	207 (67.9)	107 (69.0)	0.800
Yes	98 (32.1)	48 (31.0)	
Hepatic metastases			
No	255 (83.6)	123 (79.4)	0.260
Yes	50 (16.4)	32 (20.6)	
Brain metastases			
No	257 (84.3)	129 (83.2)	0.775
Yes	48 (15.7)	26 (16.8)	
Adrenal metastasis			
No	275 (90.2)	146 (94.2)	0.143
Yes	30 (9.8)	9 (5.8)	

and the Fisher's exact test was used when necessary. Univariate and multivariate logistic regression analysis was used to determine the independent risk factors directly related to the incidence of CIP. To ensure the inclusion of all important independent risk factors, all recognized potential confounders were analyzed by multivariate logistic regression. $P<0.05$ (double-tailed) was considered statistically significant.

R Foundation for Statistical Computing (Vienna, Austria) version 3.6.3 was used to establish the nomogram model, calibration curve, ROC curve, and decision curve analysis (DCA). The nomogram was used to establish a predictive model, and every independent risk factor corresponds to their respective scores, based on which total scores can be obtained. The risk of CIP can be estimated according to the corresponding risk value of total scores. Harrell's concordance index (C-index) was used to evaluate the performance of prediction and discrimination [20]. The ROC curve shows the predictive power of each risk factor and the combined nomogram model, and the area under curve (AUC) was listed. The calibration curve was generated by the rms package in R language, which reflects the relationship between the predicted vs. the actual incidence. The abscissa is the predicted

Treatment Characteristic			
Combined treatment			
IO monotherapy	29 (9.5)	24 (15.5)	0.058
Combined IO	276 (90.5)	131 (84.5)	
Specific combined treatment			
IO monotherapy	29 (9.5)	24 (15.5)	0.292
IO + Chemo	218 (71.5)	103 (66.5)	
IO + AVEGFR/AVEGF	35 (11.5)	18 (11.6)	
IO + Chemo + AVEGFR/AVEGF	23 (7.5)	10 (6.5)	
History of radiation therapy			
No	254 (83.3)	118 (76.1)	0.065
Yes	51 (16.7)	37 (23.9)	
History of EGFR-TKI drug therapy			
No	269 (88.2)	131 (84.5)	0.268
Yes	36 (11.8)	24 (15.5)	
History of AVEGFR/AVEGF drug therapy			
No	233 (76.4)	113 (72.9)	0.412
Yes	72 (23.6)	42 (27.1)	
Characteristics of comorbidities			
HBP			
No	248 (81.3)	125 (80.6)	0.863
Yes	57 (18.7)	30 (19.4)	
Diabetes			
No	283 (92.8)	142 (91.6)	0.654
Yes	22 (7.2)	13 (8.4)	
Baseline ILD			
No	216 (70.8)	123 (79.4)	0.064
Yes	89 (29.2)	32 (20.6)	
Baseline emphysema			
No	233 (78.0)	131 (84.5)	0.099
Yes	67 (22.0)	24 (15.5)	

ECOG, Eastern Cooperative Oncology Group; NMS, number of metastatic sites; PM, pulmonary metastasis; IO, immunotherapy; Chemo, chemotherapy; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; AVEGFR, anti-vascular endothelial growth factor receptor; AVEGF, anti-vascular endothelial growth factor; HBP, high blood pressure; ILD, interstitial lung disease.

probability, and the ordinate is the actual probability of the patient (the actual incidence). DCA was used to evaluate the clinical value of the nomogram [21]. The cut-off value of the total score in the nomogram model was determined according to the ROC curve, and patients were thus divided into high- and low-risk groups.

Results

Demographic and clinicopathological features of the cohorts

This study retrospectively analyzed 574 patients who were first treated with PD-1/PD-L1 inhibitors for malignant solid tumors in the First Affiliated Hospital of Xi'an Jiaotong University from January 1 2019 to January 1 2021. Following strict inclusion and exclusion criteria, 31 patients were excluded due to their lack of baseline imaging features, 19 due to ECOG scores (>2), and 12 due to a lack of records of distant metastatic sites. In addition, 11 patients were excluded for their lack of records on hypertension or diabetes, 27 patients were excluded for their lack of CRP or AEC, and 9 patients were excluded because their primary tumors were in multiple sites. Five patients were ruled out because they were diagnosed with hematological tumors. The 460 included patients cover 13 types of malignant tumors, including lung cancer (85.9%), hepatocellular carcinoma (6.9%), stomach and esophagus cancer (3.6%), colorectal cancer (1.6%), and other cancers (2.0%). Patients were randomly divided into the training and validation cohorts at a ratio of approximately 2:1, with 305 in the training cohort and 155 in the validation cohort. The demographic and clinicopathological features of the training and validation cohorts are shown in **Table 1**.

Among the patients finally analyzed, the median age was 60 years (24-86 years), and a total of 89 patients developed CIP, with an overall incidence of 19.35%. Of these CIP patients, most presented with grade 1-2 including 33 patients (7.17%) with grade 1 CIP and 37 patients (8.04%) with grade 2 CIP. There were 19 patients (4.13%) with grade 3 or higher CIP (**Figure 2A**). The average time to CIP onset was 94 days after immunotherapy initiation, indicat-

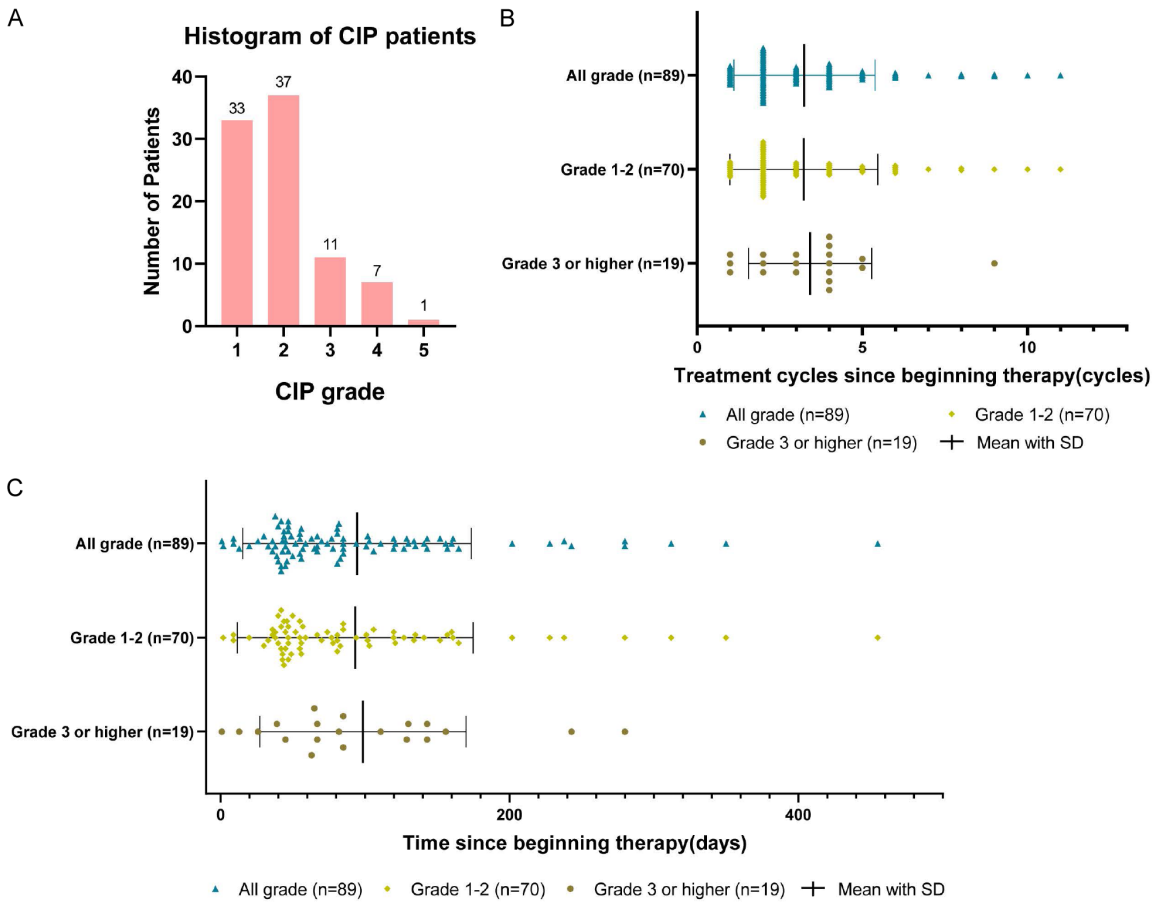


Figure 2. The occurance of CIP. A. Most patients with CIP present with grade 1-2 CIP; B. Most patients with any grade or grade 1-2 CIP occurred at the first to second immunotherapy cycles, however, patients with grade 3 and higher CIP seem to later, which more possibly appear to the third to fourth cycle of immunotherapy; C. CIP occurred more frequently within 4 months of ICI treatment and this was true for any grade CIP, grade ≥2 CIP, and grade ≥3 CIP. CIP, checkpoint inhibitor pneumonitis.

ing that in most patients CIP occurred around 3 months after the beginning of immunotherapy. Moreover, in >80% of these patients CIP occurred within 4 cycles of immunotherapy, especially within the first or second cycle. However, grade 3 and higher CIP occurred more often after the third to fourth cycle of immunotherapy, which seemed to occur later than lower grade CIP (**Figure 2B**, **2C**).

Baseline characteristics of the training cohort

We analyzed the baseline characteristics of the training cohort (**Table 2**). Male patients appeared more likely to develop CIP (P=0.024). Additionally, patients with fewer than two metastatic sites and with bone metastases were more likely to develop CIP compared with patients without CIP. The difference was statistically significant (P=0.018 and 0.004, respectively). In subgroup analysis of tumor type, lung cancer patients were more likely to develop CIP (P=0.029). As for comorbidities, patients with ILD and emphysema at baseline had a higher risk of CIP, with statistically significant differences (P<0.001 for both).

In the Grade ≥2 CIP cohort, male patients were more likely to suffer from CIP, with statistically significant differences between the two groups (P=0.020). For comorbidities, patients with ILD and emphysema at baseline were more likely to develop grade 2 or higher CIP, with statistically significant differences (P<0.001 for both). The remaining factors were not statistically significant in this cohort.

The presence of ILD and emphysema at baseline was statistically different in Grade ≥3 CIP

Table 2. Baseline characteristics of the training cohort

	Any grade CIP cohort			Grade ≥2 CIP cohort			Grade ≥3 CIP cohort		
	No CIP (%)	CIP (%)	*P value*	No CIP or Grade 1 CIP (%)	Grade 2 or higher CIP (%)	*P value*	No CIP or Grade 1-2 CIP (%)	Grade 3 or higher CIP (%)	*P value*
All patients (n=305)	236 (77.38)	69 (22.62)		261 (85.57)	44 (14.43)		290 (95.08)	15 (4.92)	
Patient Characteristic									
Sex									
Female	53 (22.46)	7 (10.14)		57 (21.84)	3 (6.82)		58 (20.00)	2 (13.33)	
Male	183 (77.54)	62 (89.86)	0.024	204 (78.16)	41 (93.18)	0.020	232 (80.00)	13 (86.67)	0.527
Age/year, mean (range)	59.2 (27-80)	63.3 (29-82)		59.3 (27-80)	64.7 (29-82)		60.5 (27-82)	62.1 (29-76)	
<75	223 (94.50)	61 (88.41)		246 (94.25)	38 (86.36)		270 (93.10)	14 (93.33)	
≥75	13 (5.50)	8 (11.59)	0.079	15 (5.75)	6 (13.64)	0.056	20 (6.90)	1 (6.67)	0.973
History of smoking									
Never	108 (45.76)	23 (33.33)		117 (44.83)	14 (31.82)		127 (43.79)	4 (26.67)	
Smoker	128 (54.24)	46 (66.67)	0.067	144 (55.17)	30 (68.18)	0.107	163 (56.21)	11 (73.33)	0.191
ECOG									
0	42 (17.80)	7 (10.14)	0.306	44 (16.86)	5 (11.36)	0.282	45 (15.52)	4 (26.67)	0.348
1	97 (41.10)	32 (46.38)		113 (43.30)	16 (36.36)		125 (43.10)	4 (26.67)	
2	97 (41.10)	30 (43.48)		104 (39.85)	23 (52.27)		120 (41.38)	7 (46.67)	
Tumor Characteristic									
Cancer type									
Lung cancer	197 (83.47)	65 (94.20)	0.239	221 (84.67)	41 (93.18)	0.533	247 (85.17)	15 (100.00)	0.629
Hepatocellular carcinoma	19 (8.05)	2 (2.90)		20 (7.66)	1 (2.27)		21 (7.24)	0 (0.00)	
Stomach and esophagus cancer	10 (4.24)	1 (1.45)		10 (3.83)	1 (2.27)		11 (3.79)	0 (0.00)	
Colorectal cancer	5 (2.12)	0 (0.00)		5 (1.92)	0 (0.00)		5 (1.72)	0 (0.00)	
Others	5 (2.12)	1 (1.45)		5 (1.92)	1 (2.27)		6 (2.07)	0 (0.00)	
Subgroup analysis of cancer type									
Lung cancer	197 (83.47)	65 (94.20)	0.029	221 (84.67)	41 (93.18)	0.134	247 (85.17)	15 (100.00)	0.108
Non-lung cancer	39 (16.52)	4 (5.80)		40 (15.33)	3 (6.82)		43 (14.83)	0 (0.00)	
NMS									
<2	134 (56.78)	28 (40.58)		140 (53.64)	22 (50.00)		154 (53.10)	8 (53.33)	
≥2	102 (43.22)	41 (59.42)	0.018	121 (46.36)	22 (50.00)	0.654	136 (46.90)	7 (46.67)	0.986
Pulmonary metastasis									
No	168 (71.19)	43 (62.32)		184 (70.50)	27 (61.36)		202 (69.66)	9 (60.00)	
Yes	68 (28.81)	26 (37.68)	0.161	77 (29.50)	17 (38.64)	0.225	88 (30.34)	6 (40.00)	0.430

Lymphatic metastasis									
No	121 (51.27)	28 (40.58)		130 (49.81)	19 (43.18)		142 (48.97)	7 (46.67)	
Yes	115 (48.73)	41 (59.42)	0.118	131 (50.19)	25 (56.82)	0.416	148 (51.03)	8 (53.33)	0.862
Bone metastasis									
No	170 (72.03)	37 (53.62)		182 (69.73)	25 (56.82)		197 (67.93)	10 (66.67)	
Yes	66 (27.97)	32 (46.38)	0.004	79 (30.27)	19 (43.18)	0.090	93 (32.07)	5 (33.33)	0.919
Hepatic metastases									
No	198 (83.90)	57 (82.61)		217 (83.14)	38 (86.36)		242 (83.45)	13 (86.67)	
Yes	38 (16.10)	12 (17.39)	0.799	44 (16.86)	6 (13.63)	0.593	48 (16.55)	2 (13.33)	0.743
Brain metastases									
No	198 (83.90)	59 (85.51)		218 (83.52)	39 (88.64)		244 (84.14)	13 (86.67)	
Yes	38 (16.10)	10 (14.49)	0.747	43 (16.48)	5 (11.36)	0.389	46 (15.86)	2 (13.33)	0.793
Adrenal metastasis									
No	216 (91.53)	59 (85.51)		237 (90.80)	38 (86.36)		262 (90.34)	13 (86.67)	
Yes	20 (8.47)	10 (14.49)	0.140	24 (9.20)	6 (13.64)	0.360	28 (9.66)	2 (13.33)	0.641
Treatment Characteristic									
ICIs agent									
Pembrolizumab	101 (42.80)	35 (50.72)	0.235	115 (44.06)	21 (47.73)	0.116	127 (43.79)	9 (60.00)	0.527
Nivolumab	0 (0.00)	1 (1.45)		0 (0.00)	1 (2.27)		0 (0.00)	1 (6.67)	
Camrelizumab	51 (21.61)	16 (23.19)		53 (20.31)	14 (31.82)		65 (22.41)	2 (13.33)	
Toripalimab	18 (7.63)	5 (7.25)		20 (5.54)	3 (6.82)		22 (7.59)	1 (6.67)	
Sintilimab	65 (27.54)	12 (17.39)		72 (19.94)	5 (11.36)		75 (25.86)	2 (13.33)	
Atezolizumab	1 (0.42)	0 (0.00)		1 (0.28)	0 (0.00)		1 (0.34)	0 (0.00)	
Combined treatment									
IO monotherapy	23 (9.75)	6 (8.70)		26 (9.96)	3 (6.82)		28 (9.67)	1 (6.67)	
Combined IO	213 (90.25)	63 (91.30)	0.794	235 (90.04)	41 (93.18)	0.511	262 (90.34)	14 (93.33)	0.700
Specific combined treatment									
IO monotherapy	23 (9.75)	6 (8.70)	0.182	26 (9.96)	3 (6.82)	0.286	28 (9.67)	1 (6.67)	0.481
IO + chemotherapy	163 (69.07)	55 (79.71)		184 (70.50)	34 (77.27)		205 (70.69)	13 (86.67)	
IO + AVEGFR/AVEGF	32 (13.56)	3 (4.35)		33 (12.64)	2 (4.55)		35 (12.07)	0 (0.00)	
IO + Chemo + AVEGFR/AVEGF	18 (7.63)	5 (7.25)		18 (6.90)	5 (11.36)		22 (7.58)	1 (6.67)	
History of radiation therapy									
No	194 (82.20)	60 (86.96)		215 (82.38)	39 (88.64)		240 (82.76)	14 (93.33)	
Yes	42 (17.80)	9 (13.04)	0.352	46 (17.62)	5 (11.36)	0.303	50 (17.24)	1 (6.67)	0.285

History of EGFR-TKI drug therapy									
No	208 (88.14)	61 (88.41)		229 (87.74)	40 (90.91)		254 (87.59)	15 (100.00)	
Yes	28 (11.86)	8 (11.59)	0.951	32 (12.26)	4 (9.09)	0.547	36 (12.41)	0 (0.00)	0.146
History of AVEGFR drug therapy									
No	181 (76.69)	52 (75.36)		201 (77.01)	32 (72.73)		221 (76.21)	12 (80.00)	
Yes	55 (23.31)	17 (24.64)	0.819	60 (22.99)	12 (27.27)	0.536	69 (23.79)	3 (20.00)	0.736
Characteristics of comorbidities									
HBP									
No	197 (83.47)	51 (73.91)		215 (82.38)	33 (75.00)		237 (81.72)	11 (73.33)	
Yes	39 (16.53)	18 (26.09)	0.073	46 (17.62)	11 (25.00)	0.246	53 (18.28)	4 (26.67)	0.416
Diabetes									
No	219 (92.80)	64 (92.75)		242 (92.72)	41 (93.18)		269 (92.76)	14 (93.33)	
Yes	17 (7.20)	5 (7.25)	0.990	19 (7.28)	3 (6.82)	0.913	21 (7.24)	1 (6.67)	0.933
Baseline ILD									
No	191 (80.93)	25 (36.23)		201 (77.01)	15 (34.09)		210 (72.41)	6 (40.00)	
Yes	45 (19.07)	44 (63.77)	<0.001	60 (22.99)	29 (65.91)	<0.001	80 (27.59)	9 (60.00)	0.007
Baseline emphysema									
No	202 (85.59)	36 (52.17)		220 (84.29)	18 (40.91)		231 (79.66)	7 (46.67)	
Yes	34 (14.41)	33 (47.83)	<0.001	41 (15.71)	26 (59.09)	<0.001	59 (20.34)	8 (53.33)	0.003

CIP, checkpoint inhibitor pneumonitis; NMS, number of metastatic sites; ICIs, immune checkpoint inhibitors; IO, immunotherapy; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; AVEGFR, anti-vascular endothelial growth factor receptor; AVEGF, anti-vascular endothelial growth factor; HBP, high blood pressure; ILD, interstitial lung disease.

Table 3. AUC for every variable

Variable	Any grade CIP cohort			Grade ≥2 CIP cohort			Grade ≥3 CIP cohort		
	AUC	*P value*	95% CI	AUC	*P value*	95% CI	AUC	*P value*	95% CI
CRP	0.687	<0.001	0.587-0.773	0.732	0.046	0.521-0.754	0.593	0.378	0.426-0.760
ANC	0.536	0.659	0.359-0.691	0.516	0.815	0.388-0.643	0.603	0.331	0.389-0.817
ALC	0.546	0.415	0.427-0.665	0.556	0.401	0.426-0.686	0.616	0.271	0.402-0.831
AEC	0.568	0.229	0.457-0.679	0.632	0.047	0.511-0.753	0.688	0.076	0.528-0.847
NLR	0.497	0.935	0.316-0.603	0.521	0.501	0.412-0.625	0.471	0.823	0.302-0.619
PLR	0.547	0.869	0.397-0.622	0.540	0.547	0.414-0.667	0.411	0.401	0.204-0.619
PCT	0.351	0.436	0.203-0.629	0.319	0.492	0.163-0.472	0.327	0.249	0.107-0.473
SII	0.575	0.658	0.361-0.689	0.523	0.730	0.401-0.645	0.529	0.782	0.328-0.730
PNI	0.473	0.698	0.309-0.613	0.437	0.353	0.366-0.562	0.492	0.515	0.417-0.684

AUC, area under curve; CIP, checkpoint inhibitor pneumonitis; CRP, C reactive protein; ANC, neutrophil count; ALC, absolute lymphocyte count; AEC, absolute eosinophil count; NLR, neutrophils/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PCT, procalcalonin; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; CI, confidence interval.

cohort (*P*=0.007 and 0.003, respectively), while no statistically significant differences were found for other factors.

Correlation between peripheral blood indicators and CIP

ROC curves were plotted for 11 peripheral blood indicators and the AUC of each indicator was shown in **Table 3**. The results showed that patients with any grade CIP had higher baseline CRP (cut-off value =16.25 g/L), AEC (cut-off value =0.22 × 10^9 cells/L) and SII index (cut-off value =1592.97), compared with patients without CIP. The differences were statistically significant (*P*=0.001, 0.003, 0.031, respectively). In the Grade ≥2 CIP cohort, the results suggest that patients with grade ≥2 CIP had higher baseline CRP (cut-off value =12.65 g/L), AEC (cut-off value =0.22 × 10^9 cells/L) and SII index (cut-off value =411.14), with statistically significant differences (*P*<0.05 for all). Similar analysis of the Grade ≥3 CIP cohort suggests that patients with grade 3 and higher CIP had a higher level of AEC (cut-off value =0.22 × 10^9 cells/L, *P*=0.001).

Exploration of independent risk factors for CIP in the training cohort

To investigate independent risk factors associated with CIP, univariate and multivariate logistic regression analysis was performed for 25 factors, including baseline, tumor, treatment, and comorbidity characteristics and peripheral blood indicators (**Table 4**). In the any grade CIP cohort, multivariate logistic regression analysis showed that several variables, including ILD at baseline, emphysema at baseline, higher baseline CRP level, and higher baseline AEC level (*P*<0.05 of all) were independent risk factors for CIP (**Table 4**).

For the Grade ≥2 CIP cohort, pulmonary metastasis (PM), ILD at baseline, emphysema at baseline, higher baseline CRP level, higher baseline AEC level, and higher baseline SII level were independent risk factors (*P*<0.05 of all) (**Table 4**). However, no independent risk factors were found to associate with grade 3 or higher CIP (**Table 4**).

Construction and validation of nomogram models

Based on the independent risk factors, the predictive nomogram model was established from multivariate regression analysis. We used ILD and emphysema at baseline and baseline CRP and AEC as key factors to construct a nomogram for predicting any grade CIP, named Nomogram A (**Figure 3A**). The calibration curves suggest almost identical predicted and actual incidence rates between the training and validation cohorts, indicating that Nomogram A performed well in predicting any grade CIP (**Figure 3B**, **3C**). The C indexes in the training and validation cohorts were 0.827 (95% CI= 0.772-0.881) and 0.860 (95% CI=0.741-0.918), respectively (**Figure 3D**, **3E**). Additionally, the DCA curve showed that Nomogram A had better clinical predictive power than any single predictor, pointing to its potential as an effective diagnostic tool for CIP (**Figure 3F**, **3G**, respec-

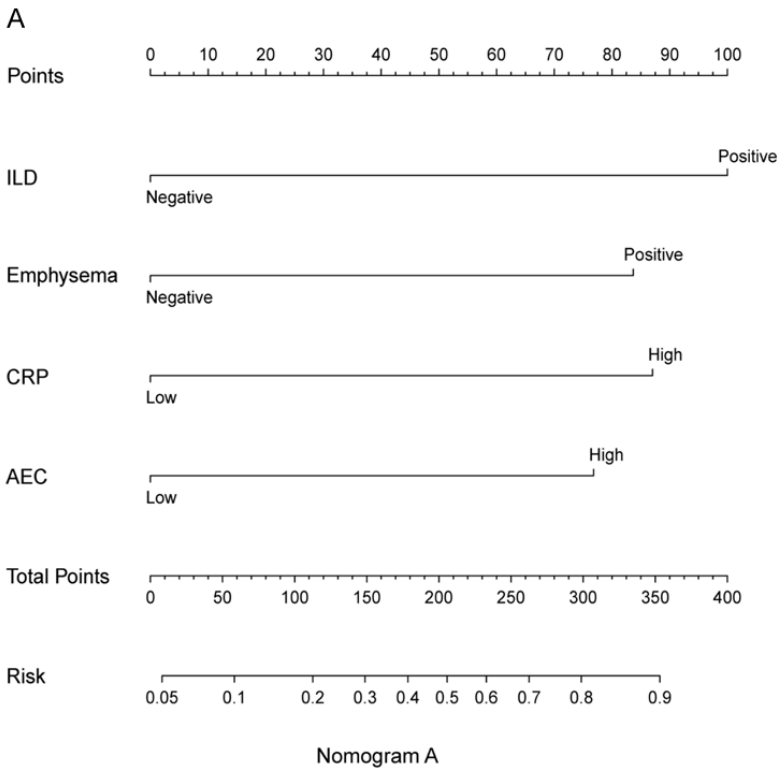
Table 4. Univariate and multivariate regression of any grade CIP cohort, Grade ≥2 CIP cohort and Grade ≥3 CIP cohort

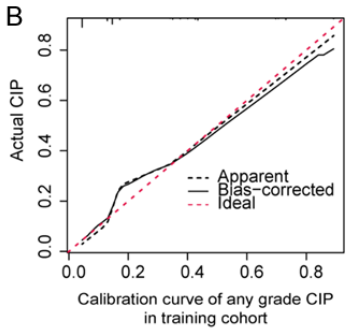
	Any grade CIP cohort								Grade ≥2 CIP cohort								Grade ≥3 CIP cohort							
	Univariate analysis				Multivariate analysis				Univariate analysis				Multivariate analysis				Univariate analysis				Multivariate analysis			
			95% CI				95% CI				95% CI				95% CI				95% CI				95% CI	
	P value	OR	Upper limit	Lower limit	*P* value	OR	Upper limit	Lower limit	*P* value	OR	Upper limit	Lower limit	*P* value	OR	Upper limit	Lower limit	*P* value	OR	Upper limit	Lower limit	*P* value	OR	Upper limit	Lower limit
Sex																								
Female																								
Male	0.024	0.846	0.752	0.951	0.469	0.646	0.198	2.108	0.020	0.876	0.808	0.950	0.140	0.262	0.044	1.553	0.527	0.980	0.927	1.036	0.277	4.135	0.320	53.402
Age																								
<75																								
≥75	0.079	1.268	0.902	1.784	0.517	1.473	0.456	4.757	0.056	1.213	0.922	1.595	0.270	2.109	0.560	7.949	0.973	0.998	0.904	1.102	0.716	0.621	0.048	8.106
ECOG																								
0																								
1																								
2	0.306	0.937	0.529	1.661	0.781	0.895	0.409	1.959	0.282	1.562	0.782	3.118	0.114	0.453	0.170	1.208	0.348	1.823	0.520	6.387	0.116	0.460	0.174	1.212
History of smoking																								
Never																								
Smoker	0.067	1.121	0.995	1.262	0.852	0.922	0.393	2.165	0.107	1.079	0.986	1.181	0.417	0.651	0.231	1.835	0.191	1.035	0.985	1.087	0.277	2.860	0.430	19.036
NMS																								
<2																								
≥2	0.018	1.160	1.023	1.315	0.815	1.167	0.321	4.245	0.654	1.021	0.931	1.121	0.137	0.307	0.065	1.457	0.986	1.000	0.950	1.052	0.990	1.016	0.092	11.156
Cancer type																								
Non-lung cancer																								
Lung cancer	0.029	1.206	1.072	1.358	0.601	1.409	0.389	5.099	0.134	1.103	1.001	1.215	0.810	0.824	0.169	4.005	0.108	1.061	1.030	1.093	0.805	0.820	0.170	3.963
Pulmonary metastasis																								
No																								
Yes	0.161	1.101	0.955	1.269	0.461	1.412	0.564	3.539	0.225	1.065	0.955	1.186	0.037	2.673	1.291	8.026	0.430	1.023	0.963	1.086	0.681	1.407	0.276	7.162
Lymphatic metastasis																								
No																								
Yes	0.118	1.102	0.976	1.244	0.857	0.925	0.395	2.164	0.416	1.039	0.948	1.139	0.442	1.490	0.539	4.115	0.862	1.005	0.955	1.057	0.586	0.636	0.125	3.237
Bone metastasis																								
No																								
Yes	0.004	1.219	1.048	1.419	0.182	1.873	0.746	4.705	0.090	1.091	0.978	1.217	0.413	1.634	0.504	5.297	0.919	1.003	0.949	1.060	0.805	0.796	0.129	4.902
Hepatic metastases																								
No																								
Yes	0.799	1.022	0.863	1.210	0.739	1.174	0.456	3.020	0.593	0.967	0.862	1.084	0.797	1.169	0.357	3.831	0.743	0.989	0.928	1.053	0.697	1.429	0.237	8.599

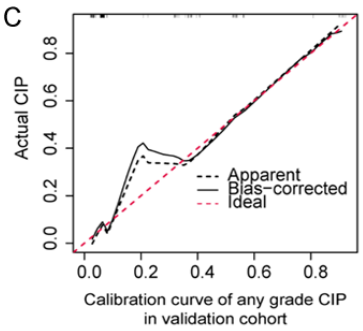
Brain metastases																							
No																							
Yes	0.747	0.973	0.830	1.142	0.665	1.256	0.448	3.521	0.389	0.947	0.849	1.056	0.583	1.441	0.390	5.323	0.793	0.991	0.928	1.058	0.637	1.631	0.213	12.472
Adrenal metastasis																							
No																							
Yes	0.140	1.178	0.908	1.529	0.264	1.922	0.611	6.043	0.360	1.077	0.895	1.296	0.196	2.527	0.619	10.309	0.641	1.021	0.924	1.127	0.617	1.663	0.227	12.193
Combined treatment																							
IO monotherapy																							
Combined IO	0.794	1.028	0.844	1.251	0.452	1.577	0.482	5.160	0.511	1.053	0.922	1.203	0.203	3.278	0.528	20.356	0.700	1.017	0.945	1.095	0.538	2.319	0.159	33.806
Baseline ILD																							
No																							
Yes	<0.001	1.749	1.416	2.160	<0.001	4.870	2.301	10.308	<0.001	1.380	1.189	1.602	0.008	3.589	1.402	9.188	0.007	1.082	1.005	1.164	0.295	2.245	0.494	10.197
Baseline emphysema																							
No																							
Yes	<0.001	1.673	1.313	2.130	0.001	4.227	1.773	10.073	<0.001	1.511	1.244	1.834	<0.001	5.905	2.234	15.610	0.003	1.102	1.006	1.207	0.184	2.996	0.593	15.136
History of radiation therapy																							
No																							
Yes	0.352	0.927	0.803	1.071	0.560	0.740	0.269	2.038	0.303	0.938	0.845	1.042	0.430	0.582	0.152	2.228	0.285	0.964	0.918	1.012	0.380	0.334	0.029	3.863
History of EGFR-TKI drug therapy																							
No																							
Yes	0.951	0.994	0.825	1.198	0.059	3.300	0.756	10.367	0.547	0.958	0.844	1.086	0.488	1.723	0.370	8.014	0.146	0.944	0.917	0.972	0.986	1.003	0.011	9.462
History of AVEGFR/AVEGF drug therapy																							
No																							
Yes	0.819	1.017	0.879	1.176	0.536	0.757	0.313	1.828	0.536	1.035	0.922	1.162	0.445	1.524	0.516	4.501	0.736	0.990	0.935	1.047	0.895	1.113	0.228	5.420
HBP																							
No																							
Yes	0.073	1.161	0.963	1.400	0.079	2.291	0.909	5.778	0.246	1.074	0.938	1.231	0.239	1.856	0.663	5.198	0.416	1.028	0.952	1.109	0.215	2.566	0.579	11.364
Diabetes																							
No																							
Yes	0.990	1.001	0.792	1.267	0.666	0.732	0.177	3.023	0.913	0.990	0.833	1.177	0.831	0.828	0.146	4.699	0.933	0.996	0.906	1.095	0.777	1.413	0.129	15.430
Baseline CRP*																							
0																							
1	<0.001	1.370	1.179	1.594	<0.001	3.929	1.859	8.306	<0.001	1.197	1.076	1.332	0.014	3.038	1.255	7.358	0.118	1.043	0.986	1.103	0.291	1.984	0.556	7.084

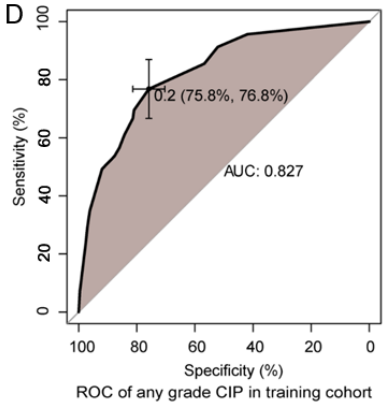
Baseline NEUT*																							
0																							
1	0.076	1.140	1.007	1.290	0.904	0.944	0.368	2.418	0.072	1.091	0.987	1.206	0.439	0.695	0.277	1.745	0.280	1.029	0.974	1.088	0.181	4.610	0.491	43.262
Baseline ALC*																							
0																							
1	0.093	1.171	0.943	1.455	0.158	2.129	0.745	6.082	0.134	1.090	0.993	1.197	0.116	2.927	0.767	11.171	0.194	1.043	0.997	1.091	0.059	8.769	0.924	83.203
Baseline AEC*																							
0																							
1	0.003	1.276	1.048	1.553	0.006	3.193	1.399	7.285	<0.001	1.250	1.063	1.470	0.004	4.116	1.590	10.655	0.001	1.112	1.010	1.225	0.062	4.278	0.237	16.089
Baseline PLR*																							
0																							
1	0.053	1.132	0.993	1.290	0.152	1.908	0.787	4.625	0.071	1.098	0.982	1.227	0.260	1.759	0.659	4.700							
Baseline SII*																							
0																							
1	0.031	1.179	0.994	1.399	0.804	1.132	0.425	3.014	0.018	1.143	1.055	1.238	0.041	4.917	1.066	22.673							

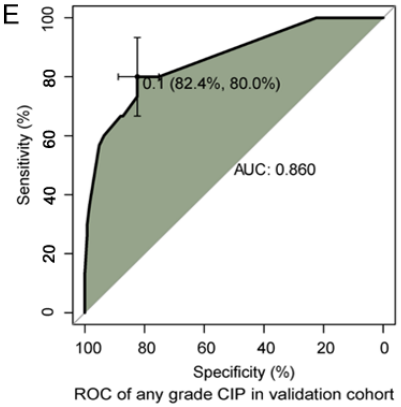
*Represents the cutoff value of different peripheral blood indicators for any grade CIP cohort and Grade ≥2 CIP cohort. Lower than the cut-off value is defined as low level, otherwise it is considered as high level. For any grade cohort, the cut-off values of individual indicator are as follows: CRP=16.25 g/L; NEUT=3.39 × 10^9 cells/L; ALC=2.145 × 10^9 cells/L; AEC=0.215 × 10^9 cells/L; PLR=191.96; SII=1592.97. For grade ≥2 CIP, the cut-off values of individual indicator are as follows: CRP=12.65 g/L; NEUT=5.68 × 10^9 cells/L; ALC=0.87 × 10^9 cells/L; AEC=0.22 × 10^9 cells/L; PLR=191.96; SII=411.14. For grade ≥3 CIP, the cut-off values of individual indicator are as follows: CRP=12.65 g/L; NEUT=4.0 × 10^9 cells/L; ALC=1.15 × 10^9 cells/L; AEC=0.22 × 10^9 cells/L. CIP, checkpoint inhibitor pneumonitis; NMS, number of metastatic sites; IO, immunotherapy; ILD, interstitial pulmonary disease; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; AVEGFR, anti-vascular endothelial growth factor receptor; AVEGF, anti-vascular endothelial growth factor; HBP, high blood pressure; CRP, C reactive protein; NEUT, neutrophil count; ALC, absolute lymphocyte count; AEC, absolute eosinophil count; PLR, the platelet/lymphocyte ratio; SII, systemic immune-inflammation index; CI, confidence interval.

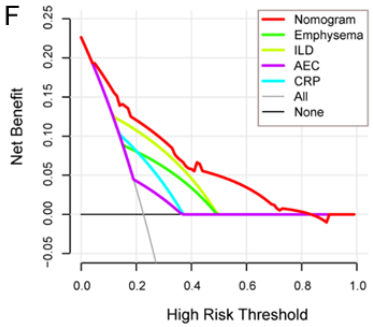


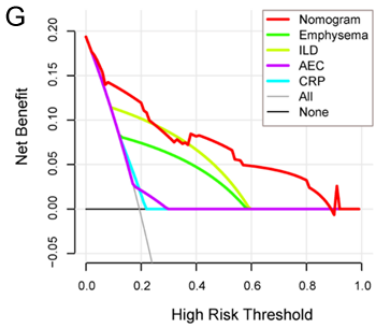


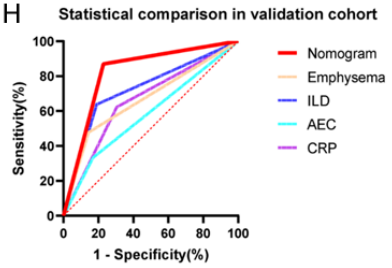




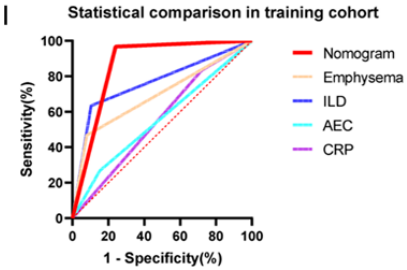








Any grade CIP			
Variable	AUC	95%CI	*p* value
Nomogram	0.827	0.764-0.876	<0.001
Emphysema	0.667	0.589-0.746	<0.001
ILD	0.724	0.651-0.797	<0.001
AEC	0.582	0.502-0.662	0.038
CRP	0.659	0.584-0.733	<0.001



Any grade CIP			
Variable	AUC	95%CI	*p* value
Nomogram	0.863	0.801-0.925	<0.001
Emphysema	0.693	0.574-0.812	0.001
ILD	0.765	0.656-0.874	<0.001
AEC	0.557	0.438-0.677	0.330
CRP	0.557	0.447-0.667	0.336

Figure 3. Nomogram A, calibration, ROC, DCA and statistical comparison of training cohort and validation cohort of any grade CIP cohort. A. Nomogram A of any grade CIP cohort. B, C. The calibration curves of training cohort and validation cohort, respectively. D, E. The ROC of training cohort and validation cohort, respectively. F, G. The DCA curve of training cohort and validation cohort, respectively. H, I. The ROC curves of each individual predictor and nomogram for training cohort and validation cohort, respectively. ROC, receiver operating characteristic; AUC, the area under curve; ILD, interstitial lung disease; CRP, C reactive protein; AEC, absolute eosinophil count.

tively). ROC curve was also used to compare the value of combining the nomogram model and single predictors in forecasting CIP occurrence. Our results indicate that the combined nomogram had the highest AUC for both cohorts, further validating the predictive power of the Nomogram A (**Figure 3H**, **3I**, respectively).

Based on the independent risk factors for grade 2 or higher CIP, we constructed another nomogram to predict the occurrence of grade 2 or higher CIP, named Nomogram B (**Figure 4A**). After internal verification, the calibration curve showed a small difference between the predicted and actual incidence, underlining the consistence of Nomogram B with actual observations (**Figure 4B**, **4C**, respectively). The C indexes of the training and validation cohorts were 0.873 (95% CI=0.826-0.921) and 0.904 (95% CI=0.804-0.973), respectively, which demonstrates the potential of Nomogram B in effectively predicting grade 2 or higher CIP (**Figure 4D**, **4E**, respectively). DCA curve also found a stronger clinical prediction power for Nomogram B than the single factor (**Figure 4F**, **4G**, respectively). Moreover, the AUC of the nomogram was the highest compared to all other single indicators, again supporting the high predictive power of Nomogram B for predicting grade 2 or higher CIP (**Figure 4H**, **4I**, respectively).

The predictive power of the nomogram model scoring system

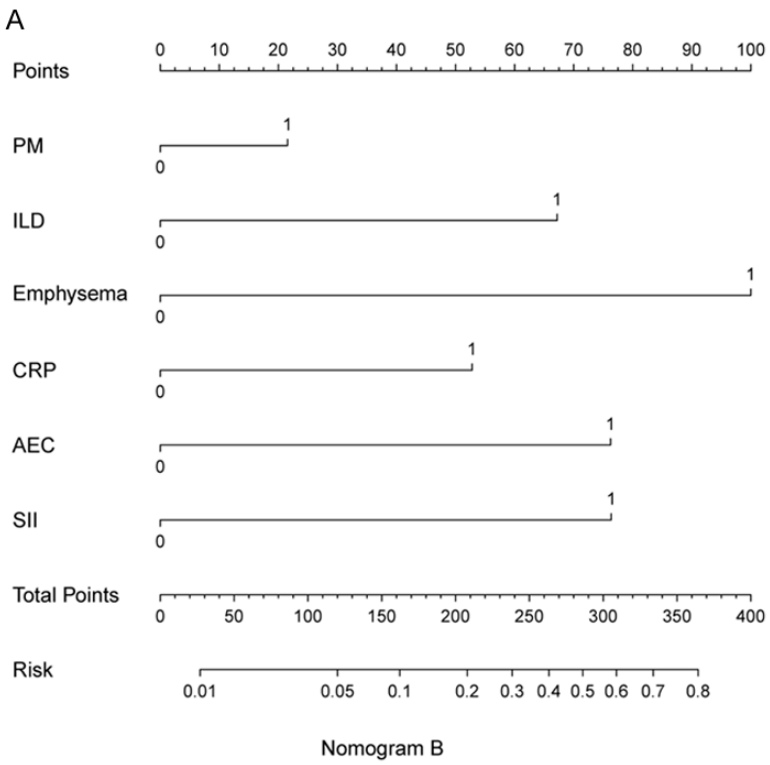
To further evaluate the predictive power of the nomogram prediction system, we divided the patients into high- and low-risk groups according to the cut-off value of the nomogram's total score. For Nomogram A, the cut-off value of the total score was 93 points. Patients with total points of ≥93 points were therefore assigned to the high-risk group and the remainder to the low-risk group. In the training cohort, univariate analysis showed a statistically significant difference in the occurrence of any grade CIP between the two risk groups (P<0.001, OR=10.402, 95% CI=5.520-19.602), which is consistent with the result from the validation cohort (P<0.001, OR=9.963, 95% CI=3.898-25.465) (**Table 5**).

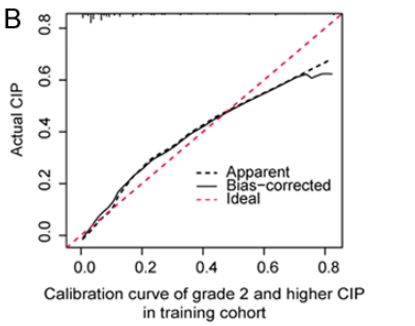
For Nomogram B, patients were similarly divided into high and low-risk groups using 175 points as the cut-off value. Univariate logistic regression analysis both found statistically significant differences in the training cohort and validation cohort (training cohort: P<0.001, OR=17.707, 95% CI=7.501-41.751; validation cohort: P=0.006, OR=6.125, 95% CI=1.686-22.246, respectively) (**Table 5**).

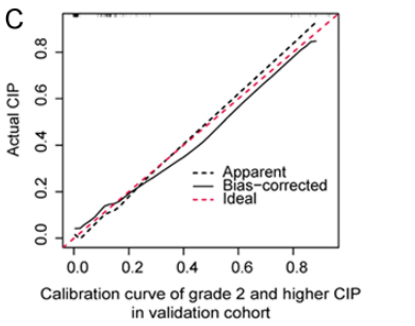
Discussion

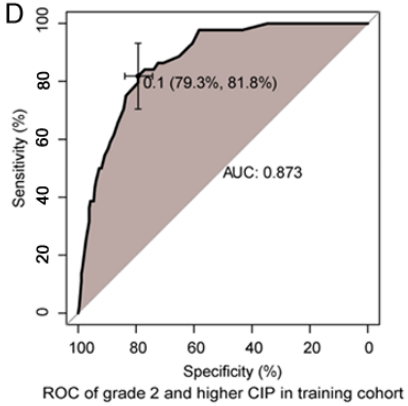
To the best of our knowledge, this is the first study to construct a visual and efficient nomogram model to prospectively predict the occurrence of CIP in patients treated with ICI, aiming to aid in clinical screening of patients who could benefit the most from ICI treatment and identifying high-risk patients who may develop CIP. Our study singled out ILD and emphysema at baseline and higher CRP and AEC at baseline as closely associated with any grade of CIP. In addition, PM, ILD and emphysema at baseline, and higher CRP, AEC, and SII at baseline were also independent risk factors for grade ≥2 CIP. We then constructed two novel predictive nomograms that could distinguish high-risk vs. low-risk patients, demonstrating the potential of these nomogram models of in clinical practice. For patients who will be treated with ICI and are classified as high risk based on our nomogram models, clinicians should be vigilant about the development of severe CIP and consider carefully whether to continue taking the ICI. Nomograms A and B cover the majority of typical solid tumor types. As a result, the application of these models can be expanded to wider patient populations and become more universal. We believe our nomogram models can be adopted as more efficient and convenient CIP prediction tools in clinical practice.

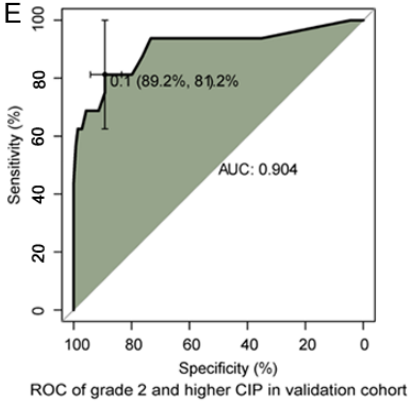
Several studies have confirmed that CIP incidence in the real world to be much higher than

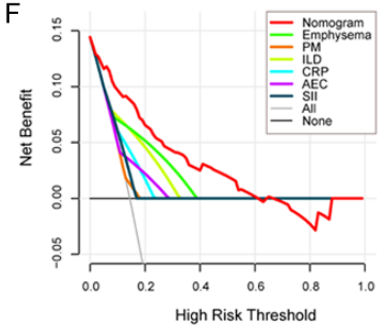


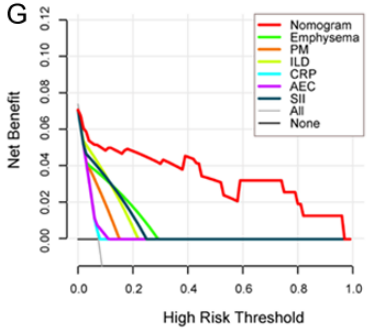


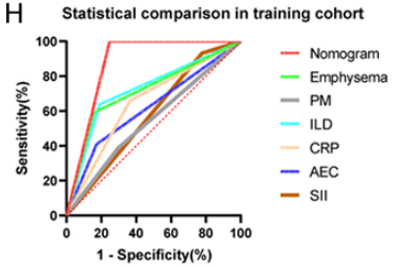




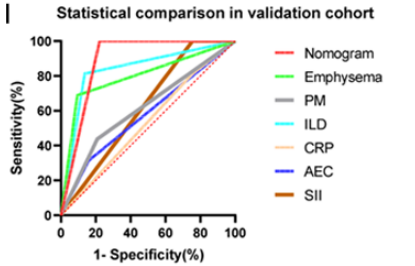








Grade 2 and higher CIP			
Variable	AUC	95%CI	*p* value
Nomogram	0.873	0.824-0.929	<0.001
Emphysema	0.717	0.626-0.808	<0.001
ILD	0.715	0.628-0.801	<0.001
PM	0.546	0.452-0.640	0.332
CRP	0.648	0.560-0.735	0.002
AEC	0.618	0.522-0.714	0.012
SII	0.577	0.493-0.661	0.102



Grade 2 and higher CIP			
Variable	AUC	95%CI	*p* value
Nomogram	0.904	0.833-0.945	<0.001
Emphysema	0.797	0.659-0.935	<0.001
ILD	0.838	0.722-0.954	<0.001
PM	0.614	0.459-0.770	0.135
CRP	0.529	0.33-0.674	0.709
AEC	0.577	0.420-0.735	0.313
SII	0.622	0.502-0.743	0.110

Figure 4. Nomogram B, calibration, ROC, DCA and statistical comparison of training cohort and validation cohort of grade 2 or higher CIP. A. Nomogram B of Grade ≥2 CIP cohort. B, C. The calibration curves of training cohort and validation cohort, respectively. D, E. The ROC of training cohort and validation cohort, respectively. F, G. The DCA curve of training cohort and validation cohort, respectively. H, I. The ROC curves of each individual predictor and nomogram for training cohort and validation cohort, respectively. ROC, receiver operating characteristic; AUC, the area under curve; PM, pulmonary metastasis; ILD, interstitial lung disease; CRP, C reactive protein; AEC, absolute eosinophil count; SII, systemic immune-inflammation index.

Table 5. Univariate logistic regression analysis of total points of nomogram model in predicting any grade CIP and grade 2 or higher CIP in the training and validation cohorts

		Any grade CIP cohort			Grade ≥2 CIP cohort		
		P value	OR	95% CI	*P value*	OR	95% CI
Training cohort	Low risk		Ref.	Ref.		Ref.	Ref.
	High risk	<0.001	10.402	5.520-19.602	<0.001	17.707	7.501-41.751
Validation cohort	Low risk		Ref.	Ref.		Ref.	Ref.
	High risk	<0.001	9.963	3.898-25.465	0.006	6.125	1.686-22.246

CIP, checkpoint inhibitor pneumonitis; Ref., reference.

the 3-5% rate reported in clinical trials [7, 8]. Indeed, in our study, the incidence of CIP was 19.35% with severe CIP incidence at 4.13%, both of which are similar to other reports [9, 22]. Furthermore, the mean time to the occurrence of grade 1-2 CIP was 93 days after immunotherapy initiation, and 99 days for grade 3 or higher CIP. The latter was slightly longer than the mean time for grade 1-2 CIP, but the difference was not statistically significant (P=0.791). Therefore, we found no difference in the time to CIP when stratified by CIP severity, a result consistent with previous studies [23].

Previous studies indicated that patients with baseline ILD [12, 13, 24] and emphysema [24] had a higher incidence of CIP. We saw similar results in our study. This may be related to the long-term inflammatory state of lung tissue caused by ILD and emphysema [25]. Chronic pulmonary inflammation and irreversible lung parenchyma damage are risk factors for multidrug pneumonitis, including CIP [13]. In addition, the presence of lung metastasis has also been shown to be an independent risk factor for grade ≥2 CIP, as it can result in poor basal lung conditions, higher tumor burden, and stronger tumor-associated inflammation. Importantly, this study is the first to show that patients with fewer than two distant metastases are more likely to develop CIP. Although there was no statistical difference in multivariate regression analysis, there are important implications in this observation. We hypothesize that this phenomenon may be explained by the fact that effective and lasting anti-tumor effects of immunotherapy depend on the patients having a sound immune system and good physical conditions [26]. It is likely that having fewer metastatic sites is a reflection of the patients' lower systemic tumor burden and better physical status [14], which can lead to better ICI efficacy but higher CIP risk [10, 11].

In our nomogram models, higher baseline AEC and CRP are independent risk factors for CIP, applicable for the any grade CIP cohort and the Grade ≥2 CIP cohort. More importantly, the optimal cut-off values of AEC and CRP were within the normal range, which suggests that clinicians should be vigilant regarding CIP occurrence in patients with normal AEC and CRP levels that exceed the cut-off value. Previous retrospective studies supported that a higher baseline AEC level was closely related to the incidence of CIP [18]. Our previous study also found that AEC was a satisfactory biomarker that can predict CIP earlier than conventional CT diagnosis [27]. AEC infiltration was found in lung biopsies of patients with CIP [15] and results from animal experiments also demonstrated the involvement of AEC in the response of pulmonary T cells [28]. The underlying mechanism is that AEC, as regulatory or effector cells, participates in a variety of immune responses, such as activating T cells and attracting tumor-specific CD8+ T cells by presenting the antigen, leading to inflammatory infiltration in the lung [29-31]. CRP has been reported to be associated with many irAEs, such as

immune-associated hypophysitis and colitis [32]. Elevated CRP reflects the presence of systemic inflammation in the host, including pulmonary inflammatory responses [33]. High baseline CRP levels were positively correlated with the infiltration of CD8+ and regulatory T cells [34], which played an important role in the development of CIP [35]. In addition, we observed that higher SII was an independent risk factor for CIP. SII is a comprehensive parameter of ALC, ANC and platelets, and believed to more objectively reflect the balance between inflammatory and immune responses in the body [36, 37]. A higher SII indicates higher tumor burden and stronger inflammatory response [38], which supports our conclusion. However, some studies have pointed out that higher SII is associated with worse OS in renal cancer patients treated with nivolumab [39], which contradicts with the previous findings that irAEs are positively correlated with a good prognosis of ICI therapy [10, 11]. The specific mechanisms and the reasons for such different findings warrant further investigation.

There are many limitations in our study. As a retrospective study, many interference factors might have caused unintentional biases. The number of patients included in this study is still relatively small. Larger patient cohorts and prospective studies are expected to verify the effectiveness of our models. Finally, PD-L1 is considered an indicator of immunotherapy benefit screening in patients with lung cancer, but not in all patients with other tumor species, resulting in a lack of PD-L1 expression level in some non-lung cancer patients. Additionally, the role of TMB and sequencing data in predicting CIP risks in tumor immunotherapy is not solid or sufficient at present. In this retrospective study, we were unable to accurately extract TMB and sequencing data reflecting genetic characteristics from all patients. A lack of these important data could have led to the failure to fully consider all specific characteristics of the tumor itself and the tumor microenvironment in our construction of prediction models of CIP. In addition, the study of the pathogenesis of CIP is still in its infancy. Comprehensive pathophysiological characterization, recognition of dynamic disease development stages, and in-depth exploration of molecular mechanisms are urgently needed. With additional research on the mechanism of CIP development, a more comprehensive and efficient CIP prediction model may be built and employed in clinical practice.

Conclusion

We have established novel nomograms A and B to predict any grade CIP and grade 2 or higher CIP, respectively. The models have shown good clinical predictive ability after repeated internal and external verification, and are expected to be a convenient, visual, and personalized clinical tool for assessing the risk of CIP development in patients receiving ICI treatment.

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Disclosure of conflict of interest

None.

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