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Clinical features of immune checkpoint inhibitor-related pneumonitis in older patients with lung cancer receiving immune checkpoint inhibitors-based therapy: a retrospective study

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Abstract

Background Older patients with lung cancer are underrepresented in pivotal trials of immune checkpoint inhibitors (ICIs). This study primarily retrospectively evaluated the older patients with lung cancer treated with ICIs to determine which factors are related to the occurrence and prognosis of ICI-related pneumonitis (CIP).

Methods We conducted a single-center, retrospective study of patients age ≥ 65 years diagnosed with lung cancer who received ICIs between January 2018 and June 2023 at the First Hospital of China Medical University. Clinical characteristics and blood parameters at baseline (before ICIs), at onset of pneumonitis (in the CIP group), and before the last dose of ICIs (in the non-CIP group) were collected and compared.

Results A total of 205 older patients with lung cancer were included, of which 51 (24%) patients developed CIP. Radiotherapy history, first line treatment, and the increased baseline systemic immune-inflammation index (SII), and CD4/CD8 were significantly and independently associated with the risk of CIP. Significant increase in CRP and decrease in albumin (ALB), prognostic nutritional index (PNI), and PaO_2 were observed from baseline to CIP during treatment with ICIs. The PD-L1 expression status < 50% ($P = 0.022$) was the risk factor affecting their progression free survival (PFS). ECOG PS ≥ 2 ($P = 0.031$) and high-CRP ($P = 0.007$) of older patients were significantly correlated with their overall survival (OS), and patients who experienced CIP had a better OS than non-CIP ($P = 0.001$). The older patients with interstitial lung abnormalities (ILA) showed a shorter PFS than those without ILA ($P = 0.036$), and the PD-L1 expression status < 50% ($P = 0.005$), and low ALB ($P = 0.023$) was correlated with the OS in CIP.

Conclusions Radiotherapy history, first line treatment (mostly in combination therapy), and increased baseline SII and CD4/CD8 were associated with the occurrence of CIP in older patients with lung cancer. PD-L1 expression status < 50%, ECOG PS ≥ 2 and high-CRP were associated with worse prognosis in all older patients. ILA, PD-L1 expression status < 50% and low-ALB at onset of CIP were related to poor prognosis in CIP.

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Keywords Clinical features, Checkpoint inhibitor-related pneumonitis, Immune checkpoint inhibitors, Lung cancer, Older patients

Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the therapeutic management of a number of malignancies, in particular lung cancer where they are the most promising treatments. With the increasing number of patients treated with ICIs, safety is a major concern. The reason for this is that ICIs could destroy normal tissues and organs of the human body while activating the immune system [1], thereby lead to the occurrence of immune-related adverse events (irAEs) [2]. Among the reported irAEs, ICI-related pneumonitis (CIP) is the most common pulmonary toxicity in patients receiving ICIs [3–5]. Previous studies showed that, compared with other malignancies, the incidence of CIP in patients with lung cancer is higher, and the incidence of CIP in clinical trials is about 1%~4% [6], but the incidence is higher than this level in the real world [7].

Previous studies have almost always focused on patients of general age: geriatric patients were underrepresented in clinical trials. Compared with younger patients, older patients with lung cancer have their own characteristics, such as: comorbidities [8, 9], poor physical status, immune dysfunction, and decreased metabolic rate [10]. For older patients with cancer, the risk of surgery and the toxicity of chemotherapy and radiotherapy were often increased. In particular, previous traditional chemotherapy would produce adverse effects such as myelosuppression, which many older patients could not tolerate; ICIs provided a more suitable treatment for older cancer patients. In comparison with chemotherapy-related adverse events, irAEs generally depict a delayed onset and longer duration, and effective management relies on early recognition and timely intervention, including discontinuation, immunosuppression, and/or immunomodulatory strategies [1, 4]. Therefore, the prediction and evaluation of immune adverse reactions in older patients have become a new challenge, especially in CIP. There have, at time of writing, been no studies on the incidence of CIP, risk factors, and factors affecting the survival of older patients with lung cancer.

Best clinical practices concerning diagnosis and risk stratification of CIP remain a primary barrier to ameliorate lung cancer treatment and outcomes in older patients. Thus, our study aimed to evaluate the real-world clinical features of CIP in older patients with lung cancer, and investigate potential predictors.

Materials and methods

Patients

A retrospective and observational study was performed to determine the incidence of CIP and risk factors for its development by reviewing lung cancer patients (≥ 65 years old) who received programmed death-1 (PD-1) / programmed death-ligand 1 (PD-L1) inhibitors between January 2018 and June 2023 at the First Hospital of China Medical University. Demographic, clinical, and survival data were retrieved from electronic medical records. Pulmonary tuberculosis and bacterial and fungal infections in the lungs before immunotherapy were excluded. All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the First Hospital of China Medical University (Project number: AF- SOP- 07- 1.1- 01).

Diagnosis and assessment of CIP

Patients received at least one course of PD-1/PD-L1 inhibitors developed new symptoms, such as dyspnoe, chest pain, chest tightness, fever, cough, expectoration, hypoxia and other symptoms, or the original above symptoms were aggravated. CIP is a diagnosis of exclusion. The diagnosis of CIP was established based on the results of chest computed tomography (CT) and clinical findings after the exclusion of other known etiologies, including infection, tumor progression, congestive heart failure, etc. The application of antibiotics was ineffective in treatment, while hormones had been effective. If CIP developed, meeting the aforementioned criteria, the patient was included in the CIP group for all analyses.

Based on previous reports [11], we also categorized the radiological features of CIP into five groups in chest CT images: cryptogenic organizing pneumonitis (COP), ground glass opacity (GGO), hypersensitivity pneumonitis (HP), interstitial pneumonitis and others. For all participants, the serial chest CT scans were retrospectively reviewed by the investigator, and if CIP developed met the aforementioned criteria, the patient was included in the CIP group for all analyses.

The grade of CIP was recorded according to the fifth Common Terminology Criteria for Adverse Events (CTCAE5.0). At the relevant time the date of CIP diagnosis could be recorded.

Data collection and outcome assessment

The clinical information collected from patient's electronic medical records included age-at-treatment, gender, smoking history, radiotherapy history, Eastern

Cooperative Oncology Group performance status (ECOG PS), tumor histologic type, initial cancer stage, PD-L1 expression status, therapeutic regimens, previous history of lung diseases and comorbidity. Comorbidity was commonly defined as the co-occurrence of at least two chronic conditions in the an individual [12], which main included diabetes mellitus, stroke, cancer, chronic obstructive pulmonary disease, hypertension, coronary heart disease, chronic kidney disease and heart failure in our study [9]. Baseline peripheral blood parameters included CD3, CD4, CD8, CD4/CD8, white blood cell (WBC), neutrophil (NE), lymphocyte (LY), platelet (PLT), eosinophil (EO), albumin (ALB), hemoglobin (Hb), and c-reaction protein (CRP). The NLR was calculated as NE divided by LY. The SII means systemic immune-inflammation index ratio. We also collected some relevant indicators of pulmonary function including carbon monoxide diffusing capacity (DLCO), partial pressure of carbon dioxide ($PaCO_2$), and partial pressure of oxygen (PaO_2). The values of body mass index (BMI) were also calculated. In doing so, the definitions of SII and prognostic nutritional index (PNI) were showed as follows: SII = (neutrophil count × platelet count)/lymphocyte count [13]; PNI = albumin (g/L) + 5 × total lymphocyte counts (10^9/L) [14].

In the CIP group, the time course and clinical outcomes of the CIP were also collected. The progression free survival (PFS) was calculated from the date of first administration of the ICIs until the progression of disease. The overall survival (OS) was calculated from the date of first administration of the ICIs until death or the last follow-up date (30 June 2023). Among patients with CIP, we collected peripheral blood parameters at two time points: baseline (before ICI treatment), and at the time of CIP diagnosis. In the non-CIP group, these parameters were recorded at two time points: baseline data before starting ICI treatment and the corresponding data before the last dose of ICIs.

Statistical analysis

To describe general baseline characteristics, continuous variables data were expressed as mean ± standard deviation, and independent sample *t*-test or Mann-Whitney *U*-test was applied for intergroup comparisons. Categorical variable data were summarized by frequency (%), and differences in categorical variables at baseline were assessed using chi-squared test or Fisher's exact tests. Laboratory indicators with $P < 0.05$ based on the baseline comparison results were included in the risk factor analysis. Logistic univariate analysis was used to determine which factors were associated with CIP. Multivariate logistic regression analysis was used to analyze those variables with a *P*-value < 0.1 in the univariate analysis to ascertain potential risk factors of CIP. After multivariate analysis, receiver operating characteristic (ROC) curves were applied to evaluate the diagnostic effect of statistically significant laboratory indicators and performed to determine the best cutoff value of baseline peripheral blood parameters for the prediction of CIP. We used Kaplan-Meier curve analysis to evaluate the PFS and OS with 95% confidence intervals (CIs). The Cox proportional hazards model was used to analyze prognostic factors associated with the PFS and OS in all of the older patients using multivariable survival analysis, including those variables with *P*-values < 0.05 in the univariate analysis.

Changes in peripheral blood parameters over time were assessed by a two sample *t*-test or the Wilcoxon signed-rank test. Firstly, the paired samples *t*-test was used to compare changes in blood parameters between the baseline and the CIP. Continuous variables were summarized by the median and interquartile range (IQR). For those blood parameters with significant changes over time, changes between the baseline and the last time of the medication in the non-CIP group were compared. Thus, the potential biomarkers associated with CIP can be identified. For those blood parameters that changed significantly over time, a Cox proportional hazards model was used to determine the prognostic factors associated with the PFS and OS in the older CIP population by univariate, multivariate survival analysis. The univariate and multivariate hazard ratios (HRs) were calculated. The CI value was 95%. A *P*-value < 0.05 was deemed statistically significant therein. All statistical analyses described above were conducted using SPSS, Version 26.

Results

Patient characteristics

A total of 251 older patients aged 65 years and over who were diagnosed with lung cancer and received at least one course of ICIs were initially included during the study period. Among them, we excluded 46 older patients who could not be evaluated for therapeutic reaction and 205 older patients were included in our analysis. All older patients were treated with PD-1 or PD-L1 inhibitors, with PD-1 inhibitors being more commonly used. Some 51 older patients experienced CIP (Fig. 1). The clinical characteristics of the enrolled patients are summarized in Table 1. The demographic characteristics were similar between the CIP and non-CIP groups. However, the distributions of different age, radiotherapy history and peripheral airway dysfunction among two sets of data were significantly different. The incidence of CIP was highest among patients aged 65 to 69 years (54.9%), whereas the non-CIP group was mainly distributed between the aged of 70 and 74 years (50%). Compared with the non-CIP group, the CIP group had a higher frequency of prior radiation (23.7% *v.* 33.3%; $P = 0.015$). The

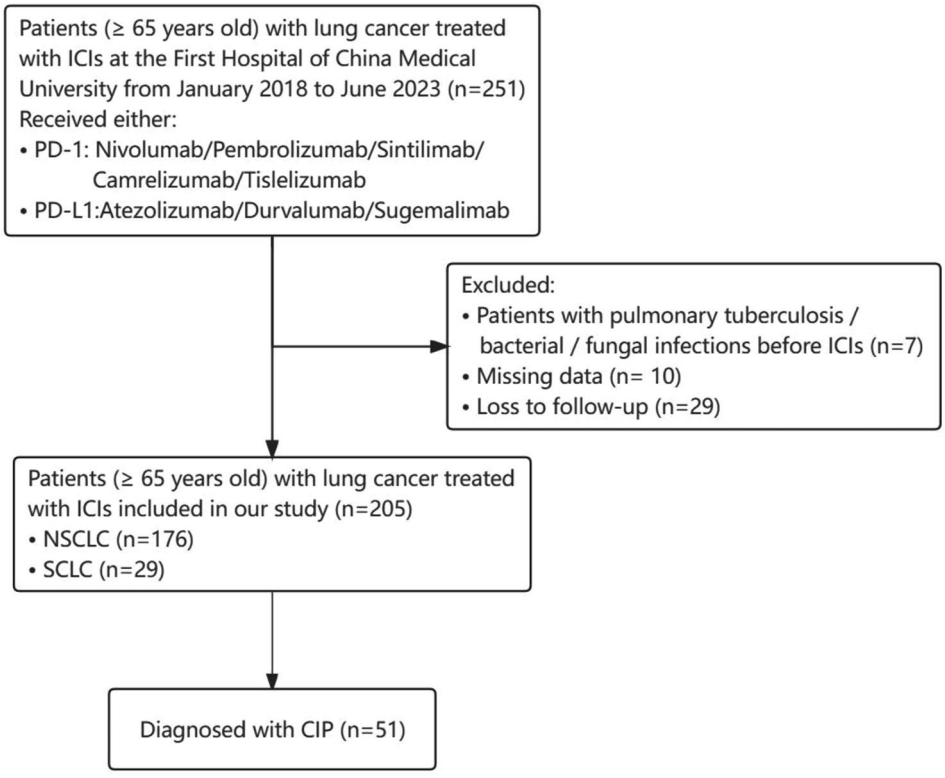

Fig. 1 Flow chart through the study design and patient inclusion. ICIs, immune checkpoint inhibitors; CIP, checkpoint inhibitor-related pneumonitis

levels of baseline NE, NLR, SII, CD4/CD8, and CRP of older patients with CIP tended to be higher than that among those without CIP ($P<0.05$); the baseline DLCO level of patients with CIP was lower than that in patients without CIP ($P=0.022$).

Clinical and radiologic characteristics of CIP

The incidence of CIP in older patients was 24% (51/205 patients). The older patients were divided into three groups based on age, such as 65 to 69 years, 70 to 74 years, and ≥ 75 years. The specific trends showed that 28 patients (35.4%) experienced CIP in the group aged from 65 to 69 years which had the highest incidence rate, 18 patients (18.9%) experienced CIP in the age group of 70 to 74 years, and five patients (16.1%) experienced CIP in the age group of 75 years over which had the lowest incidence. It could be seen that the incidence rate decreased with age (Fig. 2A). The results showed a statistically significant incidence of CIP between the age group of 65–69 years and the other two age groups ($\chi^2=6.035$, $P=0.014$; $\chi^2=3.955$, $P=0.047$). However, there was no statistical difference in CIP incidence between the age of 70–74 years and ≥ 75 years ($\chi^2=0.124$, $P=0.724$).

Among the 51 patients with CIP, almost all CIP patients (49, 96.1%) experienced Grades 1–2 pneumonitis, only two patients (3.9%) experienced Grade 3, and no participants developed to Grades 4–5 CIP in our study population during the follow-up period. The median time from the initial administration of ICIs to the occurrence of CIP was 113 days with large variability in individual times (13 days to 712 days). The median time of the developed to Grade 1 CIP was 143 days (16 days to 712 days), to the Grade 2 CIP was 112 days (14 days to 248 days). No significant difference in the occurrence time to CIP was observed when stratified by severity of CIP ($P>0.05$) (Fig. 2B).

The most common symptoms of CIP were cough (13/51, 25.5%), expectoration (10/51, 19.6%), shortness of breath (8/51, 15.7%), and fever (6/51, 11.8%). In older patients with CIP, chest discomfort (5/51, 9.8%) was less common. A total of 33 participants (33/51, 64.7%) were asymptomatic at the onset of pneumonitis during regular chest CT evaluation for the immunotherapy efficacy (Fig. 2C). The predominant radiologic features of CIP found using chest CT were COP-like (28/51, 54.9%), followed by GGO (7/51, 13.7%), interstitial pneumonitis (7/51, 13.7%), HP (4/51, 7.8%), and others (5/51, 9.8%; Fig. 2D).

Associations between baseline risk factors and CIP in older patients

In the univariate logistic regression analyses, assessing risk factors for CIP showed that age < 70 years [odds ratio (OR), 0.407; 95% confidence interval (CI): 0.213 to 0.776],

Table 1 Baseline characteristics in lung cancer older patients treated with ICIs

Variables	All ($n=205$)	CIP ($n=51$)	Non- CIP ($n=154$)	*P*-value
Age (years)	70 [65–87]	69 [65–78]	71 [65–87]	**0.018**
65–69	79 (38.5)	28 (54.9)	51 (33.1)	**0.020**
70–74	95 (46.3)	18 (35.3)	77 (50.0)	
≥ 75	31 (15.1)	5 (9.8)	26 (16.9)	
Gender				
Male	162 (79.0)	40 (78.4)	122 (79.2)	0.904
Female	43 (21.0)	11 (21.6)	32 (20.8)	
Smoking history				
Yes	76 (25.9)	19 (33.3)	57 (23.7)	0.975
No	129 (70.1)	32 (66.7)	97 (76.3)	
Radiotherapy history				
Yes	47 (25.9)	18 (33.3)	29 (23.7)	**0.015**
No	158 (70.1)	33 (66.7)	125 (76.3)	
ECOG PS				
0–1	164 (82.1)	41 (81.0)	123 (82.5)	0.936
≥ 2	41 (17.9)	10 (19.0)	31 (17.5)	
Tumor histologic type				
SCLC	29 (14.1)	6 (11.8)	23 (14.9)	0.573
NSCLC	176 (85.9)	45 (88.2)	131 (85.1)	
Initial cancer stage	201	50	151	
≤III	61 (30.3)	14 (28.0)	47 (31.1)	0.677
IV	140 (96.7)	36 (72.0)	104 (68.9)	
PD-L1 expression status	104	26	78	
< 50%	58 (55.8)	14 (53.8)	44 (56.4)	0.820
≥ 50%	46 (44.2)	12 (46.2)	34 (43.6)	
Therapeutic regimen				
Monotherapy	61 (25.9)	12 (20.6)	49 (27.5)	0.262
Combined chemotherapy	144 (74.1)	39 (79.4)	105 (72.5)	
Treatment line				
First-line	94 (45.9)	29 (56.9)	65 (42.2)	0.069
Subsequent line	111 (54.1)	22 (43.1)	89 (57.8)	
ILA				
Yes	78 (38.5)	19 (37.3)	59 (38.3)	0.895
No	127 (61.5)	32 (62.7)	95 (61.7)	
Emphysema				
Yes	109 (53.2)	27 (52.9)	82 (53.2)	0.970
No	96 (46.8)	24 (47.1)	72 (46.8)	
Comorbidity				
Yes	97 (47.1)	21 (38.1)	84 (49.8)	0.098
No	108 (52.9)	30 (61.9)	70 (50.2)	
Ventilatory Function	73	17	56	0.550
Normal results	22 (30.1)	4 (23.5)	18 (32.1)	
Restrictive	13 (17.8)	3 (17.6)	10 (17.9)	
Obstructive	4 (5.5)	2 (11.8)	2 (3.6)	
Mixed	34 (46.6)	8 (47.1)	26 (46.4)	
Peripheral Airway	73	17	56	
Normal	27 (37.0)	7 (41.2)	20 (35.7)	**< 0.001**
Dysfunction	46 (63.0)	10 (58.8)	36 (64.3)	
WBC ($\times 10^9$/L)	6.46 ± 2.05	6.81 ± 2.67	6.33 ± 1.76	0.161
NE ($\times 10^9$/L)	4.43 ± 1.71	4.88 ± 2.11	4.25 ± 1.50	**0.030**
LY ($\times 10^9$/L)	1.34 ± 0.50	1.31 ± 0.54	1.35 ± 0.49	0.679
EO ($\times 10^9$/L)	0.15 ± 0.18	0.18 ± 0.29	0.14 ± 0.10	0.172

Table 1 (continued)

Variables	All (*n* = 205)	CIP (*n* = 51)	Non- CIP (*n* = 154)	*P*-value
NLR	3.75 ± 2.23	4.58 ± 3.29	3.42 ± 1.55	**0.022**
SII	875.66 ± 539.39	1066.52 ± 705.23	800.57 ± 439.37	**0.018**
CD4/CD8	1.63 ± 0.84	1.97 ± 0.97	1.52 ± 0.77	**0.004**
ALB (g/L)	41.19 ± 2.96	41.03 ± 3.44	41.26 ± 2.74	0.682
PNI (%)	47.20 ± 4.54	47.49 ± 4.29	47.08 ± 4.65	0.603
CRP (mg/L)	11.41 ± 13.48	16.54 ± 21.47	9.07 ± 6.80	**0.045**
$PaCO_2$ (mmHg)	38.79 ± 4.26	39.37 ± 3.46	38.58 ± 4.53	0.480
PaO_2 (mmHg)	80.54 ± 13.12	80.57 ± 9.07	80.53 ± 14.38	0.990
DLCO (%)	71.44 ± 11.97	64.96 ± 11.28	73.71 ± 11.49	**0.022**

Bold values indicate $P < 0.05$; ICIs, Immune checkpoint inhibitors; CIP, checkpoint inhibitor-related pneumonitis; Non- CIP, non-checkpoint inhibitor-related pneumonitis; ECOG PS, Eastern Cooperative Oncology Group performance status; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; ILA, interstitial lung abnormality; WBC, white blood cell; NE, neutrophil; LY, lymphocyte; EO, eosinophil; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index ratio; ALB, albumin; PNI, prognostic nutritional index; CRP, c-reaction protein; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; DLCO, carbon monoxide diffusing capacity

radiotherapy history (OR, 2.351; 95% CI: 1.165 to 4.745), first line treatment (OR, 0.544; 95% CI: 0.292 to 1.051) and comorbidity (OR, 0.518; 95% CI: 0.269 to 0.997) were associated with increased risk of CIP developing. We selected the baseline of peripheral blood as deemed statistically significant (Table 1) such that: levels of SII (OR, 1.001; 95% CI:1.000 to 1.001), and CD4/CD8 (OR, 1.838; 95% CI:1.187 to 2.846) were also found to be associated with an increased risk. However, gender, smoking history, ECOG PS at initiation of ICIs, the expression status of PD-L1, treatment regimens, ILA, emphysema, and other peripheral blood biomarkers did not significantly affect the risk of CIP occurrence (Table 2). Variables with a *P*-value ≤ 0.100 in the univariate analysis were included in the multivariable analyses. Multivariate logistic regression analysis indicated that radiotherapy history (OR, 0.190; 95% CI: 0.060 to 0.602, $P = 0.005$), first line treatment (OR, 4.113; 95% CI: 1.423 to 11.885, $P = 0.009$), the increased baselines of SII (OR, 1.001; 95% CI: 1.000 to 1.002, $P = 0.033$), and CD4/CD8 (OR, 1.889; 95% CI: 1.107 to 3.223, $P = 0.020$) were significantly and independently associated with the risk of CIP developing (Table 2).

ROC curves were analyzed to evaluate the predictive performance of the levels of baseline SII and CD4/CD8 as a single predictor (Fig. 3). The optimal cutoff value of SII level to differentiate the occurrence of CIP was 1101.6 (AUC = 0.602, sensitivity = 37.5%, specificity = 81.1%), and the optimal cutoff value of CD4/CD8 level was 1.465 mg/L (AUC = 0.639, sensitivity = 53.5%, specificity = 75.7%).

Univariate and multivariate analysis of clinical characteristics for clinical outcomes was applied in all older patients with lung cancer

Among all with lung cancer older patients, we compared the PFS and OS between the CIP and non-CIP groups. The mPFS was 332 days (95%CI: 0.8231–2.231) in CIP and 245 days (95%CI: 0.4482–1.215) in non-CIP older patients, and the difference was not statistically significant ($\chi^2 = 2.288$, $P = 0.1304$) (Fig. 4A). But there was significant difference in mOS ($\chi^2 = 7.007$, $P = 0.0081$). The median survival time of the CIP group was 529 days (95%CI: 1.107–2.437), which was about 200 days longer than that in the non-CIP group (95%CI: 0.4103–0.9031) (Fig. 4B).

A univariate and multivariate Cox proportional hazards regression model of the baseline features was established. In the univariate analysis, older patients who diagnosed with stage IV cancer at the time of initial treatment had a shorter PFS and OS than those with stage < IV cancer, HR 1.838, 95% CI 1.109–3.048, $P = 0.018$]. Older patients with PD-L1 expression status ≥ 50% had a longer PFS than those with PD-L1 expression status < 50% (HR 0.384, 95% CI: 0.184–0.799, $P = 0.011$), but with no difference in OS. In the multivariate Cox proportional hazards regression model, only the PD-L1 expression status < 50% (HR 0.411, 95% CI: 0.193–0.878; $P = 0.022$) was significantly and independently correlated with the PFS in older patients (Table 3).

Furthermore, we also observed several factors that could influence OS (Table 4). Univariate analysis showed that patients with ECOG PS ≥ 2 had a shorter OS than those with ECOG PS 0–1 (HR 1.494, 95% CI 1.016–2.197, $P = 0.041$); patients with CIP during medication had a longer OS than patients without CIP (HR 0.569, 95% CI 0.381–0.849, $P = 0.006$). Those with underlying lung diseases such as emphysema could not shorten the OS (HR 0.703, 95% CI: 0.506–0.977, $P = 0.036$); those in the high-CRP group had significantly shorter OS than low-CRP group (HR 1.015, 95% CI 1.002–1.028, $P = 0.027$). In the multivariate analysis, the results showed that patients with ECOG PS ≥ 2 (HR 1.891, 95% CI: 1.061–3.372, $P = 0.031$) and high-CRP (HR 1.020, 95% CI: 1.005–1.036, $P = 0.007$) were significantly and independently correlated

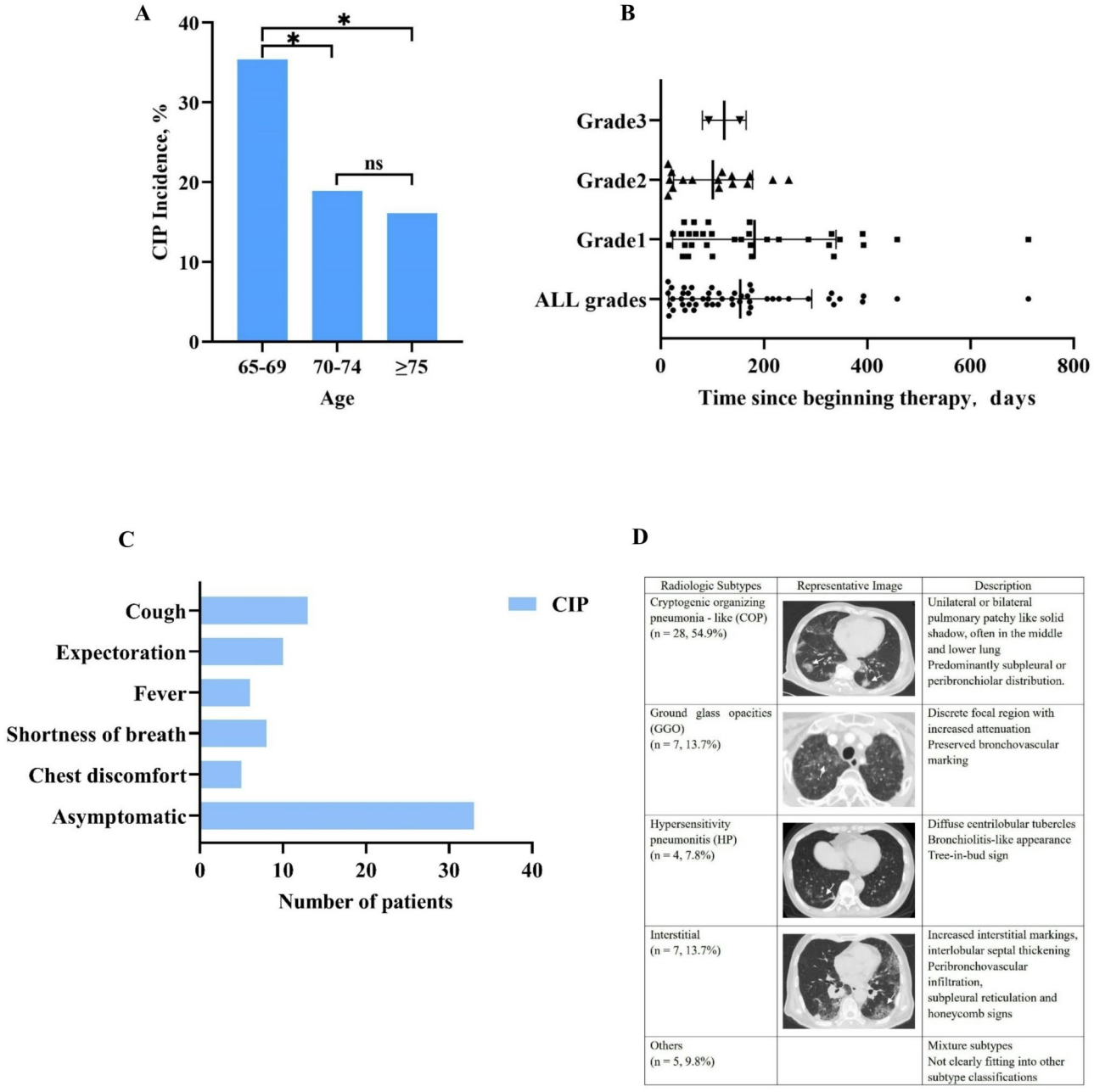

Fig. 2 Clinical and radiographic features of CIP in older patients. (**A**) Bar graphs showing the incidence of CIP in the three age groups. * represents a statistical difference between the two groups ($P \leq 0.05$). The ns means no statistical difference in CIP incidence between the two groups ($P > 0.05$). (**B**) Time from initiation of ICI therapy to date of CIP event stratified by grade, with median shown. (**C**) Symptoms occurring in older patients with CIP. (**D**) Radiological classification of older patients with CIP

with OS, and patients who experienced CIP had a better OS than those without CIP (HR 0.411, 95% CI: 0.241–0.701, $P = 0.001$).

Correlation of biomarkers with CIP

Among CIP cases, the biomarkers associated with CIP were analyzed. The results showed that CRP increased significantly from baseline to CIP [7.90 mg/L (IQR: 4.13-20.00) to 26.60 mg/L (IQR: 6.25–52.50); $P = 0.045$]. By comparison, no significant changes in CRP levels occurred over time in the non-CIP group [4.60 mg/l (IQR: 4.00–14.00) to 4.60 mg/l (IQR: 3.00–16.00); $P = 0.106$) (Fig. 5A). Similarly, we found that the median levels of ALB at baseline and CIP were 40.80 and 39.70 g/L ($P = 0.019$) respectively, and no change in ALB was observed over time in the non-CIP group ($P = 0.123$; Fig. 5B). In the CIP group, PaO_2 decreased significantly from baseline to CIP performance [78.50 mmHg

Table 2 Univariate and multivariate logistic regression analysis for the risk factors of CIP

Variables	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)				
< 70	1 (ref)	NA	1 (ref)	NA
≥ 70	0.407 (0.213–0.776)	**0.006**	1.602 (0.628–4.089)	0.324
Gender				
Male	1 (ref)	NA		
Female	1.048 (0.484–2.270)	0.904		
Smoking history				
No	1 (ref)	NA		
Yes	1.010 (0.525–1.945)	0.975		
Radiotherapy history				
No	1 (ref)	NA	1 (ref)	NA
Yes	2.351 (1.165–4.745)	**0.017**	0.190 (0.060–0.602)	**0.005**
ECOG PS				
0–1	1 (ref)	NA		
≥2	0.968 (0.437–2.144)	0.936		
PD-L1 expression status				
< 50%	1 (ref)	NA		
≥ 50%	1.048 (0.422–2.602)	0.920		
Therapeutic regimen				
Monotherapy	1 (ref)	NA		
Combined chemotherapy	1.517 (0.731–3.149)	0.264		
Treatment line				
First-line	1 (ref)	NA	1 (ref)	NA
Subsequent line	0.554 (0.292–1.051)	0.070	4.113 (1.423–11.885)	**0.009**
ILA				
No	1 (ref)	NA		
Yes	0.956 (0.497–1.839)	0.893		
Comorbidity				
No	1 (ref)	NA	1 (ref)	NA
Yes	0.518 (0.269–0.997)	**0.049**	0.930 (0.381–2.269)	0.873
Emphysema				
No	1 (ref)	NA		
Yes	0.988 (0.524–1.863)	0.970		
WBC ($\times 10^9$/L)	1.119 (0.954–1.314)	0.168		
SII	1.001 (1.000-1.001)	**0.006**	1.001 (1.000-1.002)	**0.033**
PNI (%)	1.020 (0.946–1.101)	0.601		
CD4/CD8	1.838 (1.187–2.846)	**0.006**	1.889 (1.107–3.223)	**0.020**

Bold values indicate $P < 0.05$; CIP, checkpoint inhibitor-related pneumonitis; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; ILA, interstitial lung abnormality; WBC, white blood cell; SII, systemic immune-inflammation index ratio; PNI, prognostic nutritional index; OR, odds ratio; CI, confidence interval

(IQR: 71.70–89.70) to 69.40 mmHg (IQR: 47.20–81.90); $P < 0.05$]; however, PaO_2 in the non-CIP group did not change over time [78.45 mmHg (IQR: 66.28–84.88) to 74.00 mmHg (IQR: 66.28–84.13); $P = 0.548$) (Fig. 5C). PNI gradually decreased over time from baseline to CIP [47.55% (IQR: 44.95–50.30) to 44.95% (IQR: 41.18–49.83); $P = 0.002$] in the CIP group. By contrast, PNI in the non-CIP group did not change over time [47.20% (IQR: 43.91–49.95) to 47.28% (43.61–50.15); $P = 0.577$] (Fig. 5D).

In particular, LY [1.39×10^9 /L (IQR: 0.90–1.65) to 0.95×10^9 /L (IQR: 0.68–1.42); $P = 0.041$] and Hb [129.00 g/L (IQR: 120.00-140.00) to 115.50 g/L (IQR: 104.25-124.75); $P = 0.000$] gradually decreased over time from baseline to CIP; we also observed that these two indicators changed over time from baseline to before the last dose of ICI in the non-CIP group: the specific result is LY [1.31×10^9 /L (IQR: 0.98–1.70) to 1.17×10^9 /L (IQR: 0.89–1.51); $P = 0.011$] and Hb [128.00 g/L (IQR: 114.00-140.00) to 122.00 g/L (IQR: 110.00-138.00); $P = 0.018$], which could confirm the absence of any significant changes from baseline to presentation with CIP (Supplementary Table 1; Supplementary Table 2).

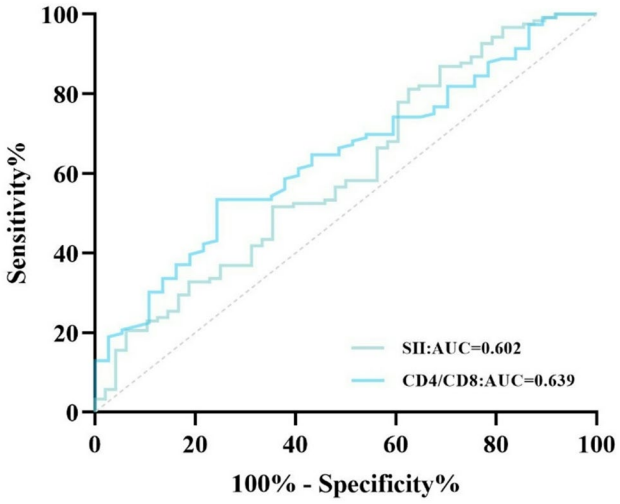

Fig. 3 The ROC curve analysis to evaluate the predictive performance of the levels of baseline. SII and CD4 / CD8 as the quantitative data

Univariate and multivariate analysis of clinical characteristics for clinical outcomes in the older CIP patients

Among all older patients with CIP, we generated a Cox proportional hazards regression model of variables measured at the time of pneumonitis diagnosis. Regarding the progression-free survival, the final analysis results showed that the patients with ILA had a shorter PFS than those without ILA (HR 2.958, 95% CI 1.074–8.147, $P=0.036$) (Table 5). For OS, we observed patients with PD-L1 expression status ≥ 50% had a longer OS than those with PD-L1 expression status < 50% (HR 0.161, 95% CI 0.043–0.595, $P=0.006$) in the univariate analysis; older patients with CIP and ECOG PS ≥ 2 (HR 2.361, 95% CI 1.058–5.268, $P=0.036$) and in combination with other therapies (HR 3.041, 95% CI 1.154–8.014, $P=0.024$), such as chemotherapy, and targeting, had shorter OS. The results also showed that ALB and PNI levels were significantly correlated with the OS (HR 0.897, 95% CI 0.835–0.964, $P=0.003$; HR 0.990, 95% CI 0.980–0.999, $P=0.039$). In the multivariate Cox proportional hazards regression analysis, the PD-L1 expression status < 50% (HR 7.999, 95% CI 1.884–33.966, $P=0.005$) and low-ALB (HR 0.852, 95% CI 0.742–0.978, $P=0.023$) were significantly and independently correlated with the OS in older patients with CIP (Table 6).

Discussion

Recently, ICIs have become a breakthrough treatment approach, its application in the population has evinced significant efficacy in clinical practice, and has been gradually expanded to older patients with malignant tumors [15, 16]. And the clinical manifestations of immune-related adverse reactions are mostly non-specific, atypical and complex, making early identification difficult. Especially in the occurrence of CIP, which clinically manifest as dyspnoe, cough, and fever [17], which causes respiratory failure in severe cases [18]. The low incidence of CIP in current clinical trials is about 3–5% [6, 19], and the restrictive entry criteria may lead to underestimation of the true incidence in clinical practice. However, real-world studies have shown that the incidence of CIP ranges between 5% and 19% [7, 20].

Currently, the effect of age on response to immunotherapy has not been studied comprehensively or systematically. Cho et al. found that, patients with CIP were usually older than 70 years (54.5% of the total studied population, $P=0.025$) [21]. Mizuho Asada et al. however observed that the risk of CIP was significantly negatively associated with age, and concluded that age ≤ 60 years was associated with increased incidence of CIP [22]. However, other research suggested that greater age did not negatively affect the toxicity rate or treatment response to ICI therapy [23, 24]. These conclusions are obviously contradictory, and aroused our interest in further exploration. In today's society, with the improvement of the lifestyle, the proportion of the older population is increasing. And the characteristics of this population are: body function decline, coexistence of multiple diseases, rapid onset, atypical clinical manifestations, poor prognosis, and so on. With the increasing use of ICIs, the treatment response of this special population should be paid more attention, and there are no separate studies in the older population. Therefore, we conducted a real-world and retrospective study, which observed the clinical case data pertaining to 205 older lung cancer patients aged ≥ 65 years and treated with ICIs. We found that incidence of CIP was about 24%, which was significantly higher than that reported in previous clinical trials [6, 19]. In general population, real-world studies have shown that its incidence ranges from 5 to 19% in lung cancer cohorts [1]. Comparisons concluded that the incidence of CIP was higher in the older population.

Meanwhile, we were more specific to the age stratification in the older population, dividing patients into three groups: 65–69 years (79 cases), 70–74 years (95 cases), ≥ 75 years (31 cases), among which we could observe that the highest incidence of CIP in the group aged 65–69 years was 35.4%, followed by 70–74 years (18.9%) and the lowest at ≥ 75 years (16.1%). This suggested a reduced incidence of CIP with increasing age in the older age population. Although not statistically significant between the baseline data of the above three groups, our data show that the main population of applied ICIs was concentrated at ages 65–74 years. For further analysis, we stratified the age groups as < 70 years and ≥ 70 years, and then the results of comparing the baseline data between the two groups suggested that the history of radiotherapy (31.6%) of the patients < 70 years was higher than that of

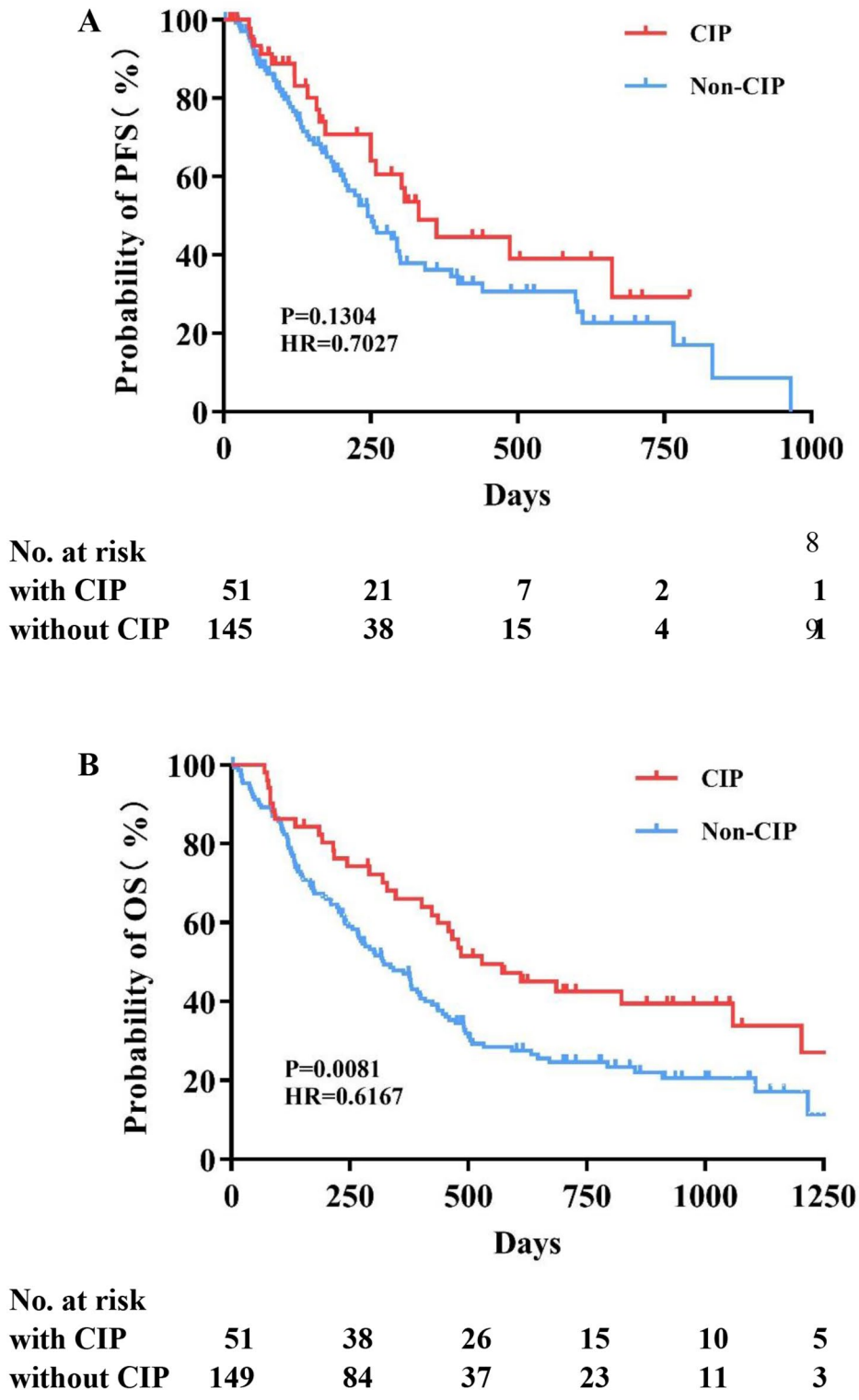

Fig. 4 Clinical outcomes of ICI therapy ($n=205$). (**A**) Among all with lung cancer older patients. The mPFS was 332 days (95%CI: 0.8231–2.231) in CIP and 245 days (95%CI: 0.4482–1.215) in non-CIP older patients, and the difference was not statistically significant ($\chi^2 = 2.288$, $P=0.1304$); (**B**) There was significant difference in mOS ($\chi^2 = 7.007$, $P=0.0081$). The median survival time of the CIP group was 529 days (95%CI: 1.107–2.437). The median survival time of the non-CIP group was 316 days (95%CI: 0.4103–0.9031)

Table 3 Cox proportional hazard regression model for the PFS in all older patients

Variables	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
< 70	1 (ref)	NA		
≥ 70	0.978 (0.630–1.518)	0.920		
Gender				
Male	1 (ref)	NA		
Female	1.200 (0.742–1.940)	0.458		
Smoking history				
No	1 (ref)	NA		
Yes	0.991 (0.624–1.573)	0.970		
Radiotherapy history				
No	1 (ref)	NA		
Yes	0.886 (0.537–1.463)	0.637		
ECOG PS				
0–1	1 (ref)	NA	1 (ref)	NA
≥ 2	1.608 (0.993–2.602)	0.053	1.379 (0.616–3.086)	0.434
CIP				
No	1 (ref)	NA		
Yes	0.683 (0.413–1.128)	0.136		
Initial cancer stage				
< IV	1 (ref)	NA	1 (ref)	NA
IV	1.838 (1.109–3.048)	**0.018**	1.392 (0.688–2.817)	0.357
PD-L1 expression status				
< 50%	1 (ref)	NA	1 (ref)	NA
≥ 50%	0.384 (0.184–0.799)	**0.011**	0.411 (0.193–0.878)	**0.022**
Therapeutic regimen				
Monotherapy	1 (ref)	NA		
Combined chemotherapy	1.367 (0.850–2.196)	0.197		
Treatment line				
First-line	1 (ref)	NA		
Subsequent line	1.245 (0.811–1.913)	0.317		
ILA				
No	1 (ref)	NA		
Yes	1.228 (0.798–1.892)	0.350		
Comorbidity				
No	1 (ref)	NA		
Yes	1.042 (0.684–1.588)	0.848		
Emphysema				
No	1 (ref)	NA	1 (ref)	NA
Yes	0.692 (0.452–1.060)	0.091	1.241 (0.641–2.403)	0.523
NE ($\times 10^9$/L)	1.031 (0.905–1.176)	0.644		
NLR	0.918 (0.823–1.025)	0.130		
SII	1.000 (0.999-1.000)	0.248		
CRP (mg/L)	1.003 (0.983–1.023)	0.773		
CD4/CD8	1.147 (0.856–1.535)	0.359		

Bold values indicate $P < 0.05$; PFS, progression free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; ILA, interstitial lung abnormality; NE, neutrophil; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index ratio; CRP, c-reaction protein; HR, hazard ratio; CI, confidence interval

≥ 70 years (17.5%). Most of patients aged < 70 years were treated above first-line (63.3%), and their comorbidity (36.7%) was significantly lower than that of those ≥ 70 years old. Although ECOG PS and combination therapy were not statistically significant between the data of two groups, 84.8% of < 70-year-old patients had ECOG PS of 0–1, and 75.9% of them received the combination regimen (Supplementary Table 3). This reflected the fact that clinicians choose to apply ICIs. We usually choose relatively young older patients because of their fewer

Table 4 Cox proportional hazard regression model for the OS in all older patients

Variables	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
< 70	1 (ref)	NA		
≥ 70	1.379 (0.972–1.956)	0.072		
Gender				
Male	1 (ref)	NA		
Female	1.180 (0.796–1.749)	0.409		
Smoking history				
No	1 (ref)	NA		
Yes	1.339 (0.954–1.879)	0.091		
Radiotherapy history				
No	1 (ref)	NA		
Yes	0.835 (0.568–1.229)	0.361		
ECOG PS				
0–1	1 (ref)	NA	1 (ref)	NA
≥ 2	1.494 (1.016–2.197)	**0.041**	1.891 (1.061–3.372)	**0.031**
CIP				
No	1 (ref)	NA	1 (ref)	NA
Yes	0.569 (0.381–0.849)	**0.006**	0.411 (0.241–0.701)	**0.001**
Initial cancer stage				
< IV	1 (ref)	NA		
IV	1.498 (1.026–2.188)	**0.036**		
PD-L1 expression status				
< 50%	1 (ref)	NA		
≥ 50%	0.747 (0.455–1.226)	0.248		
Therapeutic regimen				
Monotherapy	1 (ref)	NA		
Combined chemotherapy	1.146 (0.798–1.644)	0.461		
Treatment line				
First-line	1 (ref)	NA		
Subsequent line	0.966 (0.695–1.342)	0.837		
ILA				
No	1 (ref)	NA		
Yes	0.953 (0.678–1.340)	0.780		
Comorbidity				
No	1 (ref)	NA		
Yes	1.138 (0.821–1.579)	0.438		
Emphysema				
No	1 (ref)	NA		
Yes	0.703 (0.506–0.977)	**0.036**		
NE ($\times 10^9$/L)	1.050 (0.962–1.146)	0.278		
NLR	1.005 (0.932–1.083)	0.906		
SII	1.000 (1.000–1.000)	0.653		
CRP (mg/L)	1.015 (1.002–1.028)	**0.027**	1.020 (1.005–1.036)	**0.007**
CD4/CD8	1.015 (0.806–1.279)	0.896		

Bold values indicate $P < 0.05$; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; ILA, interstitial lung abnormality; NE, neutrophil; NLR, neutrophil to lymphocyte ratio; SII, systemic immune-inflammation index ratio; CRP, c-reaction protein; HR, hazard ratio; CI, confidence interval

comorbidities and better physical condition, but due to these advantages, clinicians usually choose combination therapy, especially in the first-line or second-line chemoradiotherapy and targeted therapy is not effective, combined ICIs has become a better treatment regimen. For patients aged ≥ 75 years, clinicians would be more cautious, because of patient age and increased comorbidities, often choosing patients with better basic conditions. To ensure efficacy and reduce the occurrence of adverse reactions, the choice of treatment regimen was more

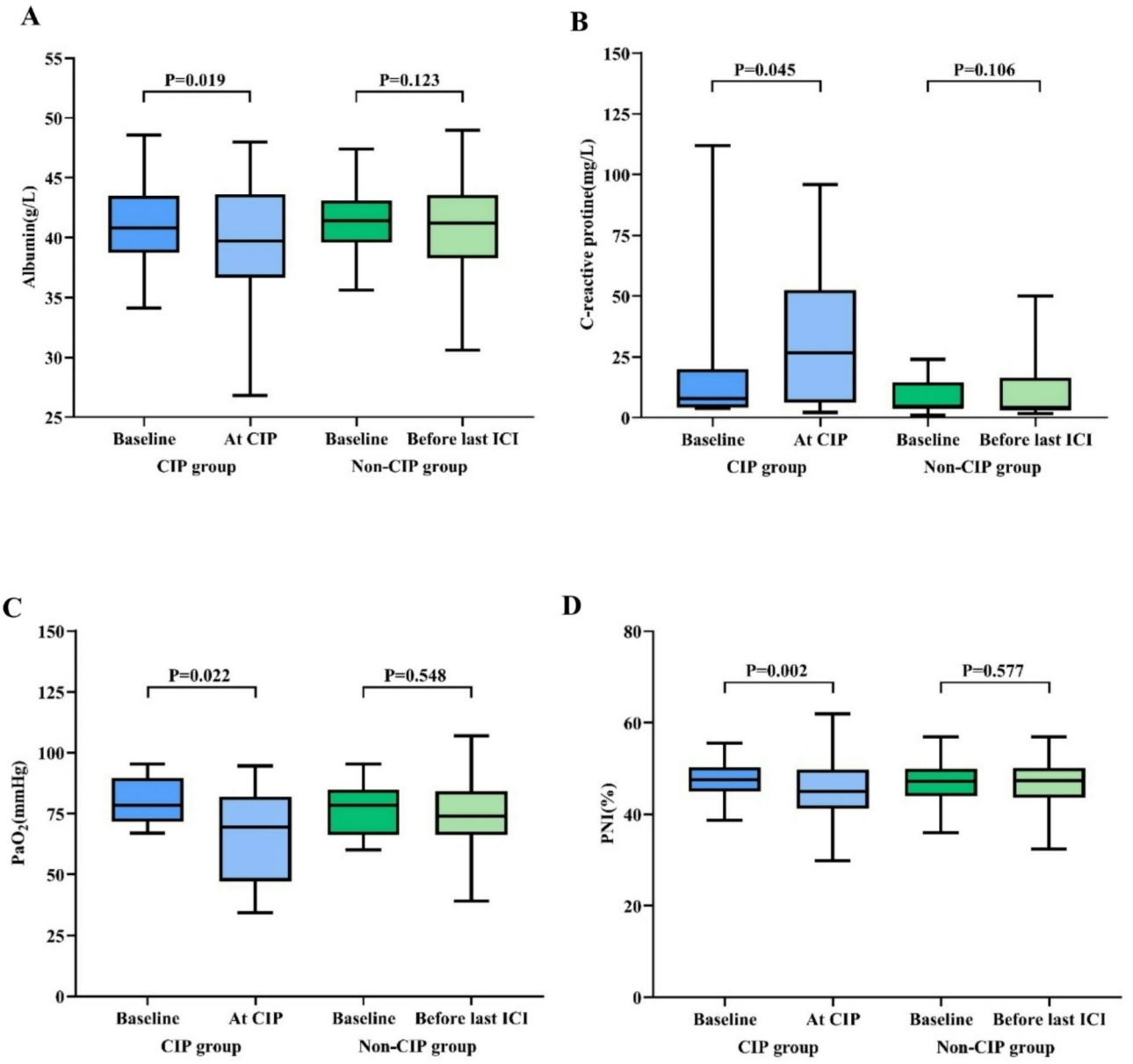

Fig. 5 Bar plots of laboratory indicators in older patients with CIP and non-CIP at different times. (**A**) C-reactive protein. (**B**) Albumin. (**C**) PaO_2. (**D**) PNI

conservative. Our results showed that age and comorbidity are not risk factors for the occurrence and development of CIP in the application of ICIs.

It was found that the median occurrence time of CIP was about 3 months [25], most of which occurred early in the immunotherapy process. We analyzed the time to onset of CIP according to the data collected, and the results showed that the individual onset time of CIP showed large variability (13 days to 23.7 months), consistent with previous study (several days to more than 1 year) [11, 26–28]. Our results suggested that most cases of CIP, regardless of grade, also tend to occur early (within 6 months after initiation of ICIs). We also noted that Grade 1–2 CIP (49/51, 96.1%) mainly occurred in older CIP patients, mostly mild, and only two cases had Grade 3 CIP. In our study, the most common symptoms of patients with CIP were cough (25.5%) and expectoration (19.6%), which were not specific symptoms. When patients have other lung diseases, such as chronic bronchitis, COPD and others, the same symptoms will also appear, which are easy to be ignored. The most common symptoms of CIP in general population were shortness of breath [27]. However, about 65% of cases had no clinical symptoms in older patients, but were diagnosed through routine chest CT. We can conclude that the time to onset of CIP was not fixed, and most asymptomatic patients need to rely on imaging diagnosis, which indicates that we should be vigilant for signs and symptoms in the

Table 5 Cox proportional hazards regression analysis of clinical factors associated with the PFS of CIP

Variables	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
< 70	1 (ref)	NA		
≥ 70	0.715 (0.294–1.739)	0.459		
Gender				
Male	1 (ref)	NA		
Female	0.804 (0.289–2.237)	0.676		
Smoking history				
No	1 (ref)	NA		
Yes	1.001 (0.380–2.634)	0.999		
Radiotherapy history				
No	1 (ref)	NA		
Yes	0.715 (0.274–1.868)	0.494		
ECOG PS				
0–1	1 (ref)	NA	1 (ref)	NA
≥ 2	2.411 (0.911–6.381)	0.076	1.610 (0.572–4.536)	0.367
Grade of CIP				
1	1 (ref)	NA		
≥ 2	1.055 (0.373–2.984)	0.920		
Initial cancer stage				
< IV	1 (ref)	NA		
IV	1.661 (0.590–4.675)	0.336		
PD-L1 expression status				
< 50%	1 (ref)	NA		
≥ 50%	0.502 (0.158–1.598)	0.243		
Therapeutic regimen				
Monotherapy	1 (ref)	NA		
Combined chemotherapy	2.075 (0.688–6.259)	0.195		
Treatment line				
First-line	1 (ref)	NA		
Subsequent line	0.689 (0.273–1.735)	0.429		
ILA				
No	1 (ref)	NA	1 (ref)	NA
Yes	3.389 (1.300-8.885)	**0.013**	2.958 (1.074–8.147)	**0.036**
Emphysema				
No	1 (ref)	NA		
Yes	0.564 (0.229–1.392)	0.214		
Comorbidity				
No	1 (ref)	NA		
Yes	0.645 (0.253–1.645)	0.359		
CRP (mg/L)	1.004 (0.993–1.015)	0.486		
PaO_2 (mmHg)	1.010 (0.977–1.044)	0.564		
ALB (g/L)	0.990 (0.882–1.112)	0.864		
PNI (%)	0.998 (0.984–1.013)	0.836		

Bold values indicate $P<0.05$; PFS, progression free survival; CIP, checkpoint inhibitor-related pneumonitis; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; ILA, interstitial lung abnormality; CRP, c-reaction protein; PaO_2, partial pressure of oxygen; ALB, albumin; PNI, prognostic nutritional index; HR, hazard ratio; CI, confidence interval

application of immunotherapy, regular imaging examination and before-after comparison should not be ignored.

To explore risk factors of CIP, domestic and foreign reports had discussed many potential risk factors of CIP. The influences of age, gender, smoking history, chest radiotherapy history, pathological type, and pulmonary chronic disease on the occurrence of CIP were found [29–31]. However, the predictive value of CIP is not uniform in most clinical studies, which requires further validation. In our study, a previous history of thoracic radiotherapy and first-line therapy were risk factors for CIP in older patients. A previous study showed that

Table 6 Cox proportional hazards regression analysis of clinical factors associated with the OS of CIP

Variables	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
< 70	1 (ref)	NA		
≥ 70	1.372 (0.680–2.767)	0.377		
Gender				
Male	1 (ref)	NA		
Female	1.384 (0.619–3.093)	0.428		
Smoking history				
No	1 (ref)	NA		
Yes	0.939 (0.440–2.004)	0.871		
Radiotherapy history				
No	1 (ref)	NA		
Yes	0.959 (0.463–1.985)	0.909		
ECOG PS				
0–1	1 (ref)	NA		
≥ 2	2.361 (1.058–5.268)	**0.036**		
Grade of CIP				
1	1 (ref)	NA		
≥ 2	1.632 (0.808–3.297)	0.172		
Initial cancer stage				
< IV	1 (ref)	NA		
IV	1.557 (0.695–3.489)	0.282		
PD-L1 expression status				
< 50%	1 (ref)	NA	1 (ref)	NA
≥ 50%	0.161 (0.043–0.595)	**0.006**	7.999 (1.884–33.966)	**0.005**
Therapeutic regimen				
Monotherapy	1 (ref)	NA		
Combined therapy	3.041 (1.154–8.014)	**0.024**		
Treatment line				
First-line	1 (ref)	NA		
Subsequent line	0.715 (0.241–2.119)	0.677		
ILA				
No	1 (ref)	NA		
Yes	1.164 (0.567–2.387)	0.680		
Emphysema				
No	1 (ref)	NA		
Yes	0.646 (0.320–1.305)	0.224		
Comorbidity				
No	1 (ref)	NA		
Yes	0.783 (0.368–1.663)	0.524		
CRP (mg/L)	1.002 (0.994–1.009)	0.688		
PaO_2 (mmHg)	0.995 (0.966–1.026)	0.755		
ALB (g/L)	0.897 (0.835–0.964)	**0.003**	0.852 (0.742–0.978)	**0.023**
PNI (%)	0.990 (0.980–0.999)	**0.039**		

Bold values indicate $P < 0.05$; OS, overall survival; CIP, checkpoint inhibitor-related pneumonitis; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1; ILA, interstitial lung abnormality; CRP, c-reaction protein; PaO_2, partial pressure of oxygen; ALB, albumin; PNI, prognostic nutritional index; HR, hazard ratio; CI, confidence interval

history of radiotherapy may increase the risk of developing CIP [30], which is consistent with our findings. The main mechanism is that the continuous low-level release of inflammatory factors caused by radiotherapy, which leads to lung damage after a certain dose of lung radiotherapy [32]. However, previous studies not clearly suggested that the treatment line is related to the occurrence of CIP. In our data, there were 29 patients applying the first-line therapy in the 51 older CIP patients, and the patients aged ≥ 70 years represented about 59%. This coincides with the fact that clinicians consider their aging, more comorbidities, relatively poor basic conditions

and insidious onset, and to ensure the safety and maximize their benefits, they usually choose ICIs alone or in combination with other treatments as the first-line treatment plan. And the comorbidities among older patients also give rise to several unique concerns. With increasing age, changes in functional status, cognition, and comorbidity may affect the life expectancy, subsequent function decline risk, and other complications [33, 34]. These age-related changes will affect the tolerance of cancer treatment, and the degree of benefit from cancer treatment. Our results showed that comorbidity is not a risk factor for the occurrence of CIP, which has a certain guiding role in clinical work. While relaxing the restrictions on clinicians when choosing ICI therapy, it provides more options for older patients with lung cancer.

Furthermore, we also observed that elevated levels of baseline SII and CD4/CD8 were relevant risk factors of the development of CIP. Although the specific mechanism of CIP remains unknown, it is obvious that immunological suppression plays an important role in the development of irAEs. We learned that peripheral blood NE reflects the immune status of the body, and its elevation is considered to be associated with autoimmune suppression in tumor patients. The current study shows that a tumor produces growth factors including granulocyte colony-stimulating factors, tumor necrosis factors, and other growth factors, which can increase the number of NEs inside the body. After remodeling the extracellular matrix, NE acts to promote tumor growth and release reactive oxygen species, nitric oxide and arginase. It then suppresses lymphocyte activity, leading to immunosuppression [35]. Interference with the immune checkpoint pathway is the main mechanism for enhancing the immune response against tumor cells, but this pathway has also been implicated in the emergence of various irAEs. This enhanced immune activity culminates in reactions that resemble autoimmune responses [1]. If the lung tissue is damaged, it means that CIP occurs. The development of CIP may also be related to the increased activity of T cells against cross-antigens expressed in tumor and normal tissues. Suresh et al. found that bronchoalveolar lavage samples from patients with CIP showed increased lymphocytes, mainly constituted of $CD4^+$ T cells, and also observed that PD-1 and CTLA-4 Tregs negatively regulated the $CD8^+$ T cells, conventional T cells, and macrophage proinflammatory responses [36, 37]. This explains the increase of the CD4/CD8 ratio. Meanwhile, the increased levels of inflammatory cytokines may also be related to the appearance of CIP. As report goes, a NSCLC patient with CIP after Atilizumab treatment had elevated CRP levels compared to baseline [38], consistent with our findings. We also included inflammatory cytokines such as IL-6 at the beginning of the data collection, but the data were excluded due to the small sample size.

To identify factors that may also need to enhance CIP monitoring in older lung cancer patients during the application of ICIs, indicators of significant dynamic changes with progression of treatment were identified. The results indicated that the CRP level was significantly higher at CIP onset compared to baseline, while levels of ALB, PNI, and PaO_2 were reduced, and that non-CIP patients did not change over time with treatment. On this basis, our study analyzed the factors affecting the clinical outcomes of the older CIP population, and the results showed that for older lung cancer patients, previous ILA history was the risk factor affecting their PFS. For ILA, the most common type is idiopathic interstitial pneumonia, which occurs frequently in the older patients. Previous studies indicated senility is a risk factor for ILA [39, 40], smoking also increases the risk of ILA. And the incidence of ILA is higher in the males than females [41]. Combined with our clinical study data, the majority of older people is male, and most of the male patients have a history of smoking, furthermore, the incidence of CIP was found in previous study to be associated with ILA [42]. And ILA as an age-increasing disease will affect lung function [43]. Reduced diffusion function is a sensitive indicator of early change of ILA, which can also be used to evaluate disease progression and treatment effect in practice [44, 45]. Statistical analysis showed that the DLCO of patients with CIP was significantly lower than that of patients without CIP at baseline, with statistical significance ($P = 0.022$). Since only 18 patients were subjected to lung function tests at the time of CIP, the numbers of data in our study were lower, but 14 of them (77.8%) had different degrees of reduction in diffusion function. On the other hand, ventilation function of ILA is characterized by restrictive ventilatory disorder, but small airway obstruction is an earlier impairment of lung function in ILA, so changes in indicators of small airway function are more sensitive than ventilatory function. In the 17 sets of data we collected, there were 13 (76.5%) patients with small airway dysfunction. In conclusion, the effects of reduced diffusion function and small airway dysfunction on the development of CIP in older lung cancer patients are worth of further studied by expanding the sample size. The indirect assessment of the effect of ILA on clinical outcomes in CIP among the older population through lung function also reminds us that the assessment of baseline lung function and the monitoring of its dynamic changes in clinical work are meaningful, and its importance cannot be ignored.

In our results, for older patients, low levels of ALB and PD-L1 < 50% were risk factors affecting their OS and their clinical survival was shortened. There are several studies of community-dwelling older people that have identified

the association between low BMI and increased risk of mortality and also highlighted the importance of adequate nutrition [46, 47]. Poor clinical outcomes in cancer patients with concomitant weight loss were also observed in disease-specific studies of patients with small cell lung cancer and gastrointestinal malignancies [48, 49]. Therefore, we included the nutritional situation of older patients in the study of lung cancer patients, such as ALB and PNI, to clarify whether poor nutritional status in the natural or diseased state will affect the occurrence of CIP and clinical outcomes in the older population. The results showed that in retrospective analysis, no influence of nutritional status on the occurrence of CIP, however, in the older CIP population, low ALB and low PNI will change dynamically with CIP, and low ALB will reduce the survival time of the older lung cancer CIP population. Previous studies have suggested that low ALB level is a risk factor for CIP [50], and a predictor of poor OS [51], which matches our findings. As CIP may lead to proinflammatory and inflammatory cytokines release, increased capillary permeability and promotion of solutes in cells and plasma (such as ALB) into diseased tissues, ultimately reduced serum albumin [52]. This makes us alert to the need for assessment of nutritional status and changes in the older CIP population. Moreover, since the nutritional status of the elderly is one aspect of the comprehensive assessment of frailty, we have paid attention thereto. Frailty is a non-specific state that the decline of physiological reserve because of various reasons in the older leads to the increase of body vulnerability and the decrease of stress resistance. The main manifestations are weakness, fatigue, malnutrition, etc. Frailty is also an important geriatric syndrome, which is a multisystem dysfunction that changes dynamically over time. The pre-frail phase is a transition phase between the healthy and debilitating periods. Previous studies have shown that the early frailty is reversible, and earlier intervention in older patients in the early frailty can improve their health-reversal rate.

There is no retrospective study for frailty and older patients with lung cancer occurrence of CIP and explore the relationship between clinical outcomes, the future can prospectively study the influence of the older patients with tumor treatment process, especially for the early recognition of weak, it is likely to provide an effective management of frailty and improve the clinical outcome of cancer patients.

In the overall age older population, PD-L1 < 50% was the risk factors affecting their PFS, and the risk factors affecting their OS were ECOG ≥ 2 and higher CRP, which matches previous studies [53, 54]. In particular, the older lung cancer patients with CIP are not a risk factor for OS. Some previous research has investigated the relationship between the occurrence of irAEs and better prognosis, whereas there was no significant correlation between CIP and the efficacy of immunotherapy in subgroup analysis [55–58]. However, there have been reports in recent years showing a relationship between the occurrence of CIP and good prognosis [59–61]. For example, Ono et al. reported that patients who had CIP had significantly longer PFS (18.9 months vs. 3.9 months, $p < 0.01$) and OS (27.4 months vs. 14.8 months, $p = 0.003$) [60]. Tone et al. observed improved ICI efficacy of grade 1–2 CIP, whereas no correlation was observed between grade 3–4 CIP and the efficacy of ICIs [62]. Our study shows that Grade 1–2 CIP (49/51, 96.1%) mainly occurred in older CIP patients, mostly mild, and only two cases had Grade 3 CIP. We also noted that both the median PFS and median OS in the CIP group are longer than those of older patients in the non-CIP group. Thus, it can be concluded that CIP is not limited to older lung cancer patients when choosing ICIs, but at the same time in clinical treatment, the more holistic assessment of older patients is essential, especially in terms of their nutritional status, physical status, and the expression of PD-L1, when we can screen before treatment, as older lung-cancer patients with ICI treatment its benefits will far outweigh its adverse consequences.

Study limitations

The present study had some limitations. First, this study was a real-world and single-center retrospective study that possibly has information bias. Secondly, peripheral blood parameters also needed to be verified in prospective studies, along with IL-6, pulmonary function indicators, etc. Due to insufficient previous attention, the baseline assessment data were too little to conduct a statistical data analysis. Additionally, the occurrence of CIP was mostly diagnosed by imaging, and almost rarely a histopathologically definite diagnosis.

Conclusions

Our study indicated a history of previous thoracic radiotherapy, ICIs as first-line therapy (75.9% for combination therapy), and high baseline NE, CRP, and CD4/CD8 were risk factors for the older lung cancer patients with CIP. Higher CRP levels or decreased levels of ALB, PNI, and PaO_2 during treatment with ICIs may also serve as biomarkers for early diagnosis of CIP. At the initial onset of CIP symptoms, levels of ILA, PD-L1 < 50%, and reduced ALB were indicators affecting the clinical outcome in the older CIP patients. These findings could facilitate the identification of older patients with lung cancer at high risk of CIP and reveal that age is not a reason to refrain from administering ICIs.

Abbreviations

ICIs	Immune Checkpoint Inhibitors
irAEs	Immune-related Adverse Events
LC	Lung Cancer

CIP	Immune Checkpoint Inhibitor-related Pneumonitis
PD-1	Programmed Death-1 Inhibitors
PD-L1	Programmed Death-ligand 1 Inhibitors
ECOG PS	Eastern Cooperative Oncology Group Performance Status
WBC	White Blood Cell
NE	Neutrophile Granulocyte
LY	Lymphocyte
EO	Eosinophil
Hb	Hemoglobin
PLT	Platelet
CRP	C-reactive Protein
ALB	Albumin
PNI	Prognostic Nutritional Index
DLCO	Carbon Monoxide Diffusing Capacity
PaO_2	Partial Pressure of Oxygen
$PaCO_2$	Partial Pressure of Carbon Dioxide
BMI	Body Mass Index
PFS	Progression Free Survival
OS	Overall Survival
CT	Computed Tomography
ILA	Interstitial Lung Abnormalities
GGO	Ground Glass Opacity
COP	Cryptogenic Organizing Pneumonitis
HP	Hypersensitivity Pneumonitis
Pneumonitis-NOS	Pneumonitis Not Otherwise Specified
OR	Odds Ratio
HR	Hazard Ratio
IQR	Interquartile Range
CI	Confidence Intervals

Supplementary Information

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Supplementary Material 1

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Author contributions
The study was conceived and designed by Xiaonan Wang. The data was acquired, analyzed, and interpreted by Jiafan Liu. Dongmei Zhou. and Na Wu. The initial draft of the manuscript was prepared by Jiafan Liu. and Jia Liu., while Xiaonan Wang. provided critical revisions. All authors have given their final approval and have agreed to take responsibility for the integrity and accuracy of the work.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the First Hospital of China Medical University.

Declarations

Ethics approval and consent to participate
This study protocol (Reference No.: AF- SOP- 07- 1.1- 01) was approved by Medical Science Research Ethics Committee of the First Hospital of China Medical University. The need for informed consent was waived by the Medical Science Research Ethics Committee of the First Hospital of China Medical University due to the retrospective nature of data gathering in this study. Prior to analysis, all patient data were anonymized to protect privacy.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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